NOVEL FERROPORTIN INHIBITORS

DESCRIPTION

INTRODUCTION

The invention relates to novel compounds of the general formula (A-I), pharmaceutical compositions comprising them and the use thereof as medicaments, in particular for the use as ferroportin inhibitors, more particularly for the use in the prophylaxis and/or treatment of diseases caused by a lack of hepcidin or iron metabolism disorders, such as particularly iron overload states such as in particular thalassemia and hemochromatosis.

BACKGROUND AND PRIOR ART

Iron is an essential trace element for almost all organisms and is relevant in particular with respect to growth and the formation of blood. The balance of the iron metabolism is in this case primarily regulated on the level of iron recovery from haemoglobin of ageing erythrocytes and the duodenal absorption of dietary iron. The released iron is taken up via the intestine, in particular via specific transport systems (DMT-1, ferroportin), transferred into the blood circulation and thereby conveyed to the appropriate tissues and organs (transferrin, transferrin receptors).

In the human body, the element iron is of great importance, *inter alia* for oxygen transport, oxygen uptake, cell functions such as mitochondrial electron transport, cognitive functions, etc. and ultimately for the entire energy metabolism.

On average, the human body contains 4 to 5 g iron, with it being present in enzymes, in haemoglobin and myoglobin, as well as depot or reserve iron in the form of ferritin and hemosiderin. Approximately half of this iron, about 2 g, is present as heme iron, bound in the haemoglobin of the erythrocytes. Since these erythrocytes have only a limited lifespan (75-150 days), new ones have to be formed continuously and old ones degraded (over 2 million erythrocytes are being formed per second). This high regeneration capacity is achieved by macrophages phagocytizing the ageing erythrocytes, lysing them and thus recycling the iron thus obtained for the iron metabolism. The majority of the iron required for erythropoiesis, about 25 mg per day, is provided in this way.

The daily iron requirement of a human adult is between 0.5 to 1.5 mg per day, infants and women during pregnancy require 2 to 5 mg of iron per day. The daily iron loss, e.g. by desquamation of skin and epithelial cells, is low. Increased iron loss occurs, for example, during menstrual hemorrhage in women. Generally, blood loss can significantly reduce the iron level since about 1 mg iron is lost per 2 ml blood. In a healthy human adult, the normal daily loss of iron of about 1 mg is usually replaced via the daily food intake thus rebalancing the daily iron requirement to the adequate level

The iron level is regulated by absorption, with the absorption rate of the iron present in food being between 6 and 12 %, and up to 25 % in the case of iron deficiency. The absorption rate is regulated by the organism depending on the iron requirement and the size of the iron store. In the process, the human organism utilizes both divalent as well as trivalent iron ions. Usually, iron(III) compounds are dissolved in the stomach at a sufficiently acid pH value and thus made available for absorption. The absorption of the iron is carried out in the upper small intestine by mucosal cells. In the process, trivalent non-heme iron is first reduced in the intestinal cell membrane to Fe(II) for absorption, for example by ferric reductase (membrane-bound duodenal cytochrome b), so that it can then be transported into the intestinal cells by means of the transport protein DMT1 (divalent metal transporter 1). In contrast, heme iron enters the enterocytes through the cell membrane without any change. In the enterocytes, iron is either stored in ferritin as depot iron, or released into the blood by the transport protein ferroportin. Hepcidin plays a central role in this process because it is the essential regulating factor of iron absorption. The divalent iron transported into the blood by ferroportin is converted into trivalent iron by oxidases (ceruloplasmin, hephaestin), the trivalent iron then being transported to the relevant places in the organism by transferrin

(see for example "Balancing acts: molecular control of mammalian iron metabolism". M.W. Hentze, Cell 117,2004,285-297.).

Mammalian organisms are unable to actively discharge iron. The iron metabolism is substantially controlled by hepcidin via the cellular release of iron from macrophages, hepatocytes and enterocytes.

Hepcidin is a peptide hormone produced in the liver. The predominant active form has 25 amino acids (see for example: "Hepcidin, a key regulator of iron metabolism and mediator of anaemia of inflammation". T. Ganz, Blood, 102, 2003, 783-8), although two forms which are shortened at the amino end, hepcidin-22 and hepcidin-20, have been found. Hepcidin acts on the absorption of iron via the intestine and via the placenta and on the release of iron from the reticuloendothelial system. In the body, hepcidin is synthesized in the liver from what is known as pro-hepcidin, pro-hepcidin being coded by the gene known as the HAMP gene. The formation of hepcidin is regulated in direct correlation to the organisms iron level, i.e. if the organism is supplied with sufficient iron and oxygen, more hepcidin is formed, if iron and oxygen levels are low, or in case of increased erythropoiesis less hepcidin is formed. In the small intestinal mucosal cells and in the macrophages hepcidin binds with the transport protein ferroportin, which conventionally transports the phagocytotically recycled iron from the interior of the cell into the blood.

The transport protein ferroportin is a transmembrane protein consisting of 571 amino acids which is formed in the liver, spleen, kidneys, heart, intestine and placenta. In particular, ferroportin is localized in the basolateral membrane of intestinal epithelial cells. Ferroportin bound in this way thusacts to export the iron into the blood. In this case, it is most probable that ferroportin transports iron as Fe^{2+}. If hepcidin binds to ferroportin, ferroportin is transported into the interior of the cell, where its breakdown takes place so that the release of the phagocytotically recycled iron from the cells is then almost completely blocked. If the ferroportin is inactivated, for example by hepcidin, so that it is unable to export the iron which is stored in the mucosal cells, the stored iron is lost with the natural shedding of cells via the stools. The absorption of iron in the intestine is therefore reduced, when ferroportin is inactivated or inhibited, for example by hepcidin. In addition, ferroportin is markedly localized in the reticuloendothelial system (RES), to which the macrophages also belong. Hepcidin plays an important part here when iron metabolism is impaired by chronic inflammation. In case of inflammation in particular interleukin-6 is increased, triggering an increase in hepcidin levels. As a result, more hepcidin is bound to the ferroportin of the macrophages, thus blocking the release of stored iron, which ultimately leads to anemia of inflammation (ACD or AI).

On the other hand, if the serum iron level decreases, hepcidin production in the hepatocytes of the liver is reduced so that less hepcidin is released and accordingly less ferroportin is inactivated, allowing a larger amount of stored iron to be transported into the serum.

Therefrom it becomes apparent that the hepcidin-ferroportin system directly regulates the iron metabolism and that a disorder of the hepcidin regulation mechanism therefore has a direct effect on iron metabolism in the organism. In principle the hepcidin-ferroportin regulation mechanism acts via the two following opposite principles:

On the one hand, an increase of hepcidin leads to inactivation of ferroportin, thus blocking the release of stored iron from the cells into the serum, thus decreasing the serum iron level. In pathological cases a decreased serum iron level leads to a reduced hemoglobin level, reduced erythrocyte production and thus to iron deficiency anemia.

On the other hand, a decrease of hepcidin results in an increase of activeferroportin, thus allowing an enhanced release of stored iron and an enhanced iron uptake e.g. from the food, thus increasing the serum iron level. In pathological cases an increased iron level leads to iron overload.

Iron overload states and diseases are characterized by excess iron levels. Therein, the problems arise from excess serum iron level which lead to non-transferrin bound iron (NTBI). The NTBI is rapidly taken up unspecifically by the organs, leading to an accumulation of iron in tissue and organs. Iron overload causes many diseases and undesired medical conditions, including cardiac, liver and endocrine

damage. Further, iron accumulation in brain has been observed in patients suffering from neurodegenerative diseases such as for example Alzheimer's disease and Parkinson's disease. As a particular detrimental aspect of excess free iron the undesired formation of radicals must be mentioned. In particular iron(II) ions catalyze the formation (inter alia via Fenton reaction) of reactive oxygen species (ROS). These ROS cause damage to DNA, lipids, proteins and carbohydrates which has far-reaching effects in cells, tissue and organs. The formation of ROS is well known and described in the literature to cause the so-called oxidative stress.

A well-established hitherto existing method for treating iron overload is based on the concept to reduce the amount of iron in the serum by increased removal of the iron from the body. The eldest known and still routine treatment method in an otherwise-healthy person consists of regularly scheduled phlebotomies (bloodletting). When first diagnosed, the phlebotomies are usually scheduled fairly frequent, e.g. once a week, until iron levels are brought to within normal range, followed by phlebotomies which are then scheduled once a month or every three months depending upon the patient's rate of iron loading.

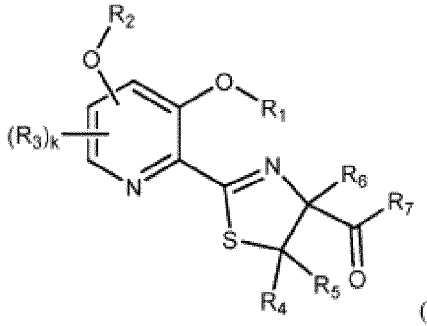
For patients unable to tolerate routine blood draws, there are chelating agents available for use. For example, deferoxamine (also known as desferrioxamine B, N'-{5-[acetyl(hydroxy)amino]pentyl}-N-[5-({4-[(5-aminopentyl)(hydroxy)amino]-4-oxobutanoyl} amino)pentyl]-N-hydroxysuccinamide or Desferal®), which is a bacterial siderophore, is an established drug used in chelation therapy. Deferoxamine binds iron in the bloodstream as an chelator and enhances its elimination via urine and faeces. Typical treatment of chronic iron overload requires subcutaneous injection over a period of 8 – 12 hours daily. Parenterally injectable compositions of desferrioxamine-B salts are described for example in WO 1998/25887.

Two newer drugs, licensed for use in patients receiving regular blood transfusions to treat thalassemia, resulting in the development of iron overload, are deferasirox and deferiprone.

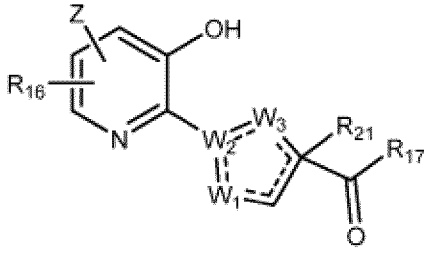
Deferasirox (Exjade®, 4-(3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl)benzoic acid), being described for example in WO 1997/49395 and deferiprone (Ferriprox®, 3-hydroxy-1,2-dimethylpyridin-4(1H)-one) are similarly acting as an iron chelating agent, thus being suitable as a drug for iron chelation therapy.

Further compounds acting as iron chelator for use in the treatment of iron overload have been described. For example WO 2013/142258 relates to encapsulated particles of diethylenetriaminepentaacetate (DTPA) and a zinc salt. WO 2003/041709 relates to 4-hydroxy-2-alkylquniolines such as 4-hydroxy-2-nonylqunioline as an iron chelator. WO 1998/09626 relates to chelating agents for treating iron overload states on the basis of dithiocarbamate-containing compositions.

WO 2015/077655 relates to desferrithiocin derivatives of the formula (A) or (J)



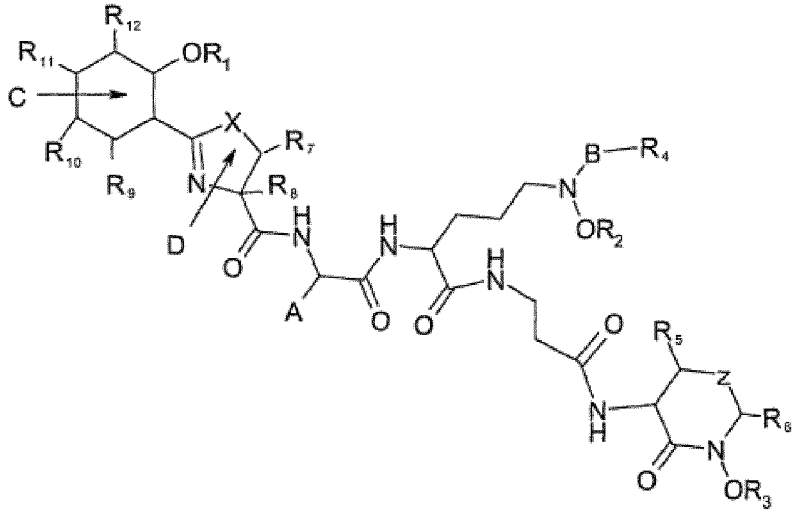
(A),



(J),

for the use in the treatment of iron overload diseases. According to WO 2015/077655 said desferrithiocin derivatives have been found to act as iron chelating agents.

WO 2005/051411 relates to novel antibiotics or antimycotics on the basis of oxachelin and derivatives thereof according to formula



which are described to act as an iron chelator and to be used in the treatment of iron overload diseases.

The disadvantage in the treatment of iron overload by chelation therapy is the removal of the chelated iron from the body when the iron overload has already occurred instead of preventing the occurrence of the disorder. Further, the established drugs for iron chelation therapy are known to exhibit a toxic potential.

Modern approaches can be expected to supersede this method increasingly, in particular with increasing knowledge about the underlying mechanisms and development of appropriate treating methods on the basis of such knowledge. Hepcidin agonists or compounds which have an inhibiting or supporting effect on the biochemical regulatory pathways in the iron metabolism are basically known from the prior art.

Iron overload may occur, for example, if hepcidin expression is prevented, for example due to a genetic defect, such as in the known iron overload disease haemochromatosis. Hemochromatosis is a disease of iron overload caused by mutations in genes that control hepcidin synthesis or in the hepcidin gene itself. Low or absent levels of hepcidin in these patients result in enhanced amounts of active ferroportin, allowing increased absorption of dietary iron, leading to severe iron overload, which causes cardiac, liver and endocrine damages. Hepcidin mimetic peptides, i.e. peptides which similarly bind and inactivate ferroportin, have been shown to effectively reverse the accumulation of tissue iron in the hepcidin knockout mouse, a model of Type 2 (juvenile) hemochromatosis. (Ramos et al, Blood 2012).

In the known iron overload disease beta-thalassemia a mutation in the beta globin gene causes a reduction in hemoglobin production and ineffective erythropoiesis, the inability to produce adequate numbers of red cells because of damage to and death of developing red cells in the bone marrow. This causes upregulation of the rate of erythropoiesis and a reduction in hepcidin level to make more iron available for increased erythropoietic activity. This maladaptive response results in iron overloaddue to the reduced hepcidin levels, which lead to enhanced amounts of active ferroportin, allowing increased absorption of dietary iron, as described above. Red cells in thalassemia have a shortened half-life because of the toxicity of an imbalanced ratio of alpha- and beta- hemoglobin-subunits. Also in the treatment of beta-thalassemia the use of hepcidin mimetic peptides has been described, the therapeutic rationale being based on the increase of hepcidin activity leading to iron restriction and reduction of iron mediated damage in red cells. Administration of hepcidin mimetic peptides to the th3/+ mouse, a model of non-transfusion dependent beta-thalassemia resulted in relief of ineffective erythropoiesis, increased red cell survival time and improvement of anemia. In this model the prevention of iron overload due to reduction in the absorption of dietary iron turned out as an additional benefit of the hepcidin mimetic therapy (Gardenghi et al, 2010; Casu et al 2013).

The described therapeutic approaches are based on a direct involvement into the disturbed iron metabolism pathway by directly acting via the primary regulator hepcidin by providing a hepcidin mimeticor a hepcidin agonist, i.e. acting in the sense of a kind of hepcidin substitute or supply. The approach is

based on the therapeutic rationale to treat iron overload, i.e. excess serum iron level, by inhibiting ferroportin, via the hepcidin-inactivation mechanism, thus blocking excessive iron absorption.

Further known iron overload related diseases are diseases associated with ineffective erythropoiesis such as the myelodysplastic syndromes (also known as MDS or myelodysplasia), polycythemia vera, etc.

Further, mutations in genes involved in sensing the systemic iron stores, such as hepcidin (Hamp1), hemochromatosis protein (HFE), hemojuvelin (HJV) and transferrin receptor 2 (TFR2) cause iron overload in mice and men. Accordingly, diseases related to HFE and gene mutations, chronic hemolysis associated diseases, sickle cell diseases, red cell membrane disorders, as well as Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), erythrpoietic porphyria and Friedrich`s Ataxia can be mentioned. Further, subgroups of iron overload comprise transfusional iron overload, iron intoxication, pulmonary hemosiderosis, osteopenia, insulin resistense, African iron overload, Hallervordan Spatz disease, hyperferritinemia, ceruloplasmin deficiency, neonatal hemochromatosis and red blood cell disorders comprising thalassemia, alpha thalassemia, thalassemia intermedia, sickle cell disease and myelodyplastic syndrome are included.

Further disease and/or disorders and/or diseased conditions associated with elevated iron levels include, but are not limited to, diseases with elevated iron level, comprising ataxia, Friedrich's ataxia, age-related macular degeneration, age-related cataract, age-related retinal diseases and neurodegenrative disease, whereby such neurodegenrative disease comprises Alzheimer's disease, Parkinson's disease, pantothenate kinase-associated neurodegeneration, restless leg syndrom and Huntington's disease,

Hepcidin is a host defense peptide, representing a component of the innate immune system that responds to invading organisms.

It has been described that many bacteria are highly dependent on a supply of iron from the host (so-called siderophilic organisms) and have evolved mechanisms to capture iron from the local tissues. The ability to limit the amount of iron available to such organisms by ferroportin-inhibitors may represent effective adjunctive therapy. One such siderophilic organism is *Vibrio vulnificus*, which causes rare but extremely severe infections in coastal communities, often in subjects with undiagnosed iron overload. Studies in animals that have been inoculated with a lethal dose of *Vibrio vulnificus* have demonstrated nearly 100% survival in response to treatment with hepcidin mimetic peptides, inactivating ferroportin, regardless of whether treatment is started before or after the infection is initiated (Arezes et al 2015).

As known hepcidin mimetics the so-called minihepcidins can be mentioned, described for example in WO 2013/086143. Minihepcidins are small-sized synthetic peptide analogues of the hepcidin N-terminus which is crucial for hepcidin interaction with ferroportin. Minihepcidins have been developed on the basis that the first 9 amino acids of hepcidin (DTHFPICIF) have been found to be sufficient for in vitro activity (measured as ferroportin-GFP degradation). Minihepcidins have a modified hepcidin-9 amino acid sequence to exhibit improved resistance to proteolysis and enhanced biophysical interaction with ferroportin. Minihepcidins are described to be useful for the treatment of human iron overload conditions caused by hepcidin deficiency.

WO 2015/069660 describes methods for increasing hepcidin expression for treating iron overload disorders by decreasing non-transferrin bound iron (NTBI) by administering a modified iron binding/releasing transferrin.

All the described compounds which act as hepcidin agonists, hepcidin mimetics or ferroportin inhibitor etc. are relatively high molecular weight compounds, in particular those which are obtainable predominantly by genetic engineering. Various further approaches on the basis of biomolecular interactions and biomolecules have been described. The disadvantage is the complex preparation and high sensitivity of such biomolecular compounds. In particular methods on the basis of ferroportin antibodies are not sufficiently efficient as the antibody-inhibited ferroportin is permanently reproduced by the organism and the inhibition is thus not sufficiently long-lasting to achieve the desired therapeutic effect

Low molecular weight compounds which play a part in iron metabolism and can have an inhibiting or promoting effect are also known.

For example WO 2008/151288, WO 2008/118790, WO 2008/115999, and WO 2008/109840 describe compounds acting as divalent metal transporter-1 (DMT1) inhibitors and their use for the treatment of iron disorders such as thalassemia or hemochromatosis.

WO 2008/123093 relates to an agent for prevention or treatment of iron overload disorders, comprising 22 beta-methoxyolean-12-ene-3 beta,24(4 beta)-diol.

EP 1074254 and EP1072265 relate to the use of catechic- and flavonoid-structure plant polyphenols for treating iron overload.

WO 2011/029832 relates to thiazol and oxazol compounds which act as hepcidin antagonists and are thus described to be suitable in the use for the treatment of iron deficiency diseases. Therein, hepcidin antagonistic activity is described to inhibit the inhibition of ferroportin by hepcidin, which is the opposite effect as has been found by the inventors of the present invention for the novel thiazol and oxazol compounds as described herein.

Chemical compounds based on the structures of the general formulae of the present invention have hitherto not been disclosed in connection with their activity as ferroportin inhibitors or for the use in the prophylaxis and treatment of iron metabolism disorders which are associated with increased iron levels such as iron overload.

US 2004/0138268 A1, US 2011/0224136 A1, CN 103508957, WO 2006/062224 A1, WO 2015/051362 A1, EP 1953145 A1, WO 2009/154739 A2, GB 937878 A, WO 2011/023722 A1, WO 2010/020556 A1, WO 2005/011685 A1, WO 00/56724 A1, WO 2010/036632 A1, WO 2005/014576 A1, WO 2013/067578 A1, WO 2005/116355 A1 or in Zou Yiquan et al. "Discovery of pyrazole as C-terminus of selective BACE1 inhibitors"; Eur. J. of Medicinal Chemistry 68 (2013) 270-283, Tussing-Humphreys et al. "Rethinking Iron Regulation and Assessment in Iron Deficiency, Anemia of Chronic Disease, and Obesity: Introducing Hepcidin" J. Academy of Nutrition and Dietetics (2012), Vol. 122, No. 3, 391-400, Riordan et al. "Bleomycin analogs. Synthesis and proton NMR spectral assignments of thiazole amides related to bleomycin A2 (1)"; J. Heterocyclic Chem. 18, 1213 (1981), Hideaki Sasaki "Synthesis of a novel bis(2,4'-bithiazole) derivative as a Co(II)-activated DNA cleaving agent"; Chem. Pharm. Bull. 42(8) 1685-1687 (1994), and Ballell et al. "Fueling open-source drug discovery. 177 small-molecule leads against tuberculosis"; ChemMedChem 2013, 8, 313-321 describe compounds for different medical uses and mechanisms of action.

OBJECT

The object of the present invention was to provide, in particular, new therapeutically effective compounds that can be used for an effective therapy for the prophylaxis and treatment of iron metabolism disorders which are associated with increased iron levels, such as in particular iron overload. In a further object, the new compounds should exhibit few side effects and have a very low toxicity and good bioavailability and compatibility. Moreover, these new compounds, in contrast to the known iron chelating compounds, should be suitable to prevent the occurrence of increased iron levels and thus the related disorders, instead of removing excess iron from the body when the iron overload has already occurred. In a further object the new compounds should have a defined structure (stoichiometry) and should be preparable by simple synthesis processes, exhibit less sensitivity and improved long-lasting efficiency as compared to the known biomolecular compounds, such as antibodies.

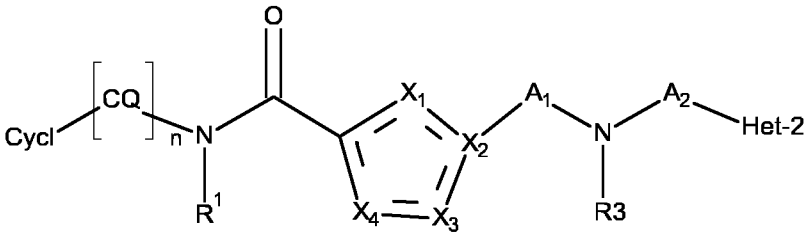
This goal was achieved by the development of the novel compounds according to the formulae as defined herein, such as in particular formula (A-I), which have been found to act as ferroportin inhibitors, thus being suitable for the use in the inhibition of iron transport, and thus being effective in the prophylaxis and treatment of iron metabolism disorders which are associated with increased iron levels, such as in particular iron overload, as well as in in the prophylaxis and treatment of diseases caused by a lack of

hepcidin, diseases related to or caused by increased iron levels or iron overload and diseases associated with ineffective erythropoiesis.

DESCRIPTION OF THE INVENTION

The inventors have surprisingly found that specific compounds having the general structural formula (A-I) as defined herein, act as ferroportin inhibitors, thus effectively inhibiting iron transport and accordingly being particularly suitable for the use as medicaments, in particular for the use in the treatment and/or prophylaxis of diseases caused by a lack of hepcidin, diseases associated with ineffective erythropoiesis or iron metabolism disorders leading to increased iron levels, such as particularly iron overload states such as in particular thalassemia and hemochromatosis. Very particularly the new compounds turned out to be suitable for treating thalassemia and hemochromatosis. The new compounds are also suitable for the treatment of diseases caused by pathologically low hepcidin-levels and for the use in the inhibition of iron transport.

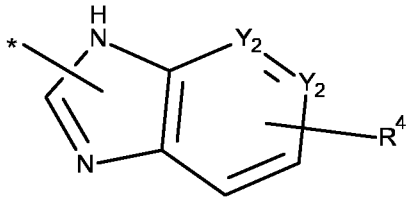
Accordingly, the invention relates to novel compounds of general formula (A-I)



(A-I)

wherein

Het-2 is an optionally substituted bicyclic heteroaryl of the formula



wherein * indicates the binding site to A^2 and

R^4 indicates 1, 2 or 3 optional substituents, which may independently be selected from the group consisting of

- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted alkoxy, and
- a carboxyl group;

X^1 is C, N, S or O;

X^2 is C or N;

X^3 is C, N, S or O; and

X^4 is C, N, or S

with the proviso that 1 to 3 heteroatoms X are present,

and wherein X^1, X^3 and X^4, when having the meaning of C or N, may carry a further substituent, such as preferably hydrogen or a substituent as defined above for substituted heteroaryl;

R^1 is selected from the group consisting of
- hydrogen and
- optionally substituted alkyl;

Cycl is selected from the group consisting of
- substituted aryl and
- substituted or unsubstituted heteroaryl;

Q is
- hydrogen or
- C_1-C_4-alkyl, which may form a fused 5- or 6-membered ring with Cycl;

n is 0 or an integer of 1 to 8, preferably n is 0 or 1 to 4, preferably n is 0, 1, 2 or 3;

A^1 is
- optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl or
- a direct bond;

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring;

and

Y^2 is C or N, wherein
- both Y^2 may be C or
- one Y^2 may be N and one Y^2 may be C;

or pharmaceutically acceptable salts thereof.

Therein and throughout the invention, the above-mentioned substituent groups are defined as follows:

Optionally substituted alkyl preferably indudes:
linear or branched alkyl preferably containing 1 to 8, more preferably 1 to 6, particularly preferably 1 to 4, even more preferred 1, 2 or 3 carbon atoms.

Optionally substituted alkyl further includes cycloalkyl containing preferably 3 to 8, more preferably 5 or 6 carbon atoms.

Examples of alkyl residues containing 1 to 8 carbon atoms include: a methyl group, an ethyl group, an n-propyl group, an i-propyl group, an n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an n-pentyl group, an i-pentyl group, a sec-pentyl group, a t-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, an n-octyl group, a 1-methylheptyl group, a 2-methylheptyl group, a 3-methylheptyl group, a 4-methylheptyl group, a 5-methylheptyl group, a 6-methylheptyl group, a 1-ethylhexyl group, a 2-ethylhexyl group, a 3-ethylhexyl group, a 4-ethylhexyl group, a 5-ethylhexyl group, a 1,1-dimethylhexyl group, a 2,2-dimethylhexyl group, a 3,3-dimethylhexyl group, a 4,4-dimethylhexyl group, a 5,5-dimethylhexyl group, a 1-propylpentyl group, a 2-propylpentyl group, etc. Those containing 1 to 6, preferably 1 to 4 carbon atoms, such as in particular methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, and t-butyl are preferred. C_1-C_3 alkyl, in particular, methyl, ethyl and i-propyl are more preferred. Most preferred are C_1 and C_2 alkyl, such as methyl and ethyl.

Cycloalkyl residues containing 3 to 8 carbon atoms preferably include: a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group. A cyclopropyl group, a cyclobutyl group, a cyclopentyl group and a cyclohexyl group are preferred. A cyclopentyl group and a cyclohexyl group are particularly preferred.

Substituents of the above-defined optionally substituted alkyl preferably include 1 to 3 of the same or different substituents, more preferably 1 or 2 of the same or different substituents, selected, for example, from the group consisting of: optionally substituted cycloalkyl, as defined above, hydroxy, an oxo-group (=O), carboxy, halogen, as defined below, cyano, alkoxy, as defined below, optionally substituted acyl, as defined below, optionally substituted acyloxy, as defined below, optionally substituted aryl, as defined below, optionally substituted heteroaryl, as defined below, optionally substituted heterocyclyl, as defined below, optionally substituted amino, as defined below, optionally substituted alkyl, aryl or heterocyclylsulfonyl ($R\text{-}SO_2$-), as defined below as well as an alkylene group such as in particular a methylene-group, forming for example a methylene-substituted ethyl-group (CH_3-($C{=}CH_2$)- or , wherein * indicates the binding site). Preferably the 1 to 3 substituents of alkyl are selected from optionally substituted cycloalkyl, hydroxy, oxo (=O), carboxy, optionally substituted acyloxy, halogen, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted amino, optionally substituted alkyl, aryl or heterocyclylsulfonyl ($R\text{-}SO_2$-) and an alkylene group such as in particular a methylene-group. More preferred are 1 to 3 substituents of alkyl, selected from optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocyclyl and an alkylene group such as in particular a methylene-group. More preferred is one substituent of alkyl. Most preferred is one substituent of alkyl, which is optionally substituted aryl or optionally substituted heteroaryl as defined below.

Within the meaning of the present invention, halogen includes fluorine, chlorine, bromine and iodine, preferably fluorine or chlorine, most preferred is fluorine.

Examples of a linear or branched alkyl residue substituted by halogen and containing 1 to 8 carbon atoms include:

a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a chloromethyl group, a dichloromethyl group, a trichloromethyl group, a bromomethyl group, a dibromomethyl group, a tribromomethyl group, a 1-fluoroethyl group, a 1-chloroethyl group, a 1-bromoethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a 2-bromoethyl group, a difluoroethyl group such as a 1,2-difluoroethyl group,

a 1,2-dichloroethyl group, a 1,2-dibromoethyl group, a 2,2-difluoroethyl group, a 2,2-dichloroethyl group, a 2,2-dibromoethyl group a 2,2,2-trifluoroethyl group, a heptafluoroethyl group, a 1-fluoropropyl group, a 1-chloropropyl group, a 1-bromopropyl group, a 2-fluoropropyl group, a 2-chloropropyl group, a 2-bromopropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 3-bromopropyl group, a 1,2-difluoropropyl group, a 1,2-dichloropropyl group, a 1,2-dibromopropyl group, a 2,3-difluoropropyl group, a 2,3-dichloropropyl group, a 2,3-dibromopropyl group, a 3,3,3-trifluoropropyl group, a 2,2,3,3,3-pentafluoropropyl group, a 2-fluorobutyl group, a 2-chlorobutyl group, a 2-bromobutyl group, a 4-fluorobutyl group, a 4-chlorobutyl group, a 4-bromobutyl group, a 4,4,4-trifluorobutyl group, a 2,2,3,3,4,4,4-heptafluorobutyl group, a perfluorobutyl group, a 2-fluoropentyl group, a 2-chloropentyl group, a 2-bromopentyl group, a 5-fluoropentyl group, a 5-chloropentyl group, a 5-bromopentyl group, a perfluoropentyl group, a 2-fluorohexyl group, a 2-chlorohexyl group, a 2-bromohexyl group, a 6-fluorohexyl group, a 6-chlorohexyl group, a 6-bromohexyl group, a perfluorohexyl group, a 2-fluoroheptyl group, a 2-chloroheptyl group, a 2-bromoheptoyl group, a 7-fluoroheptyl group, a 7-chloroheptyl group, a 7-bromoheptyl group, a perfluoroheptyl group, etc. Fluoroalkyl, difluoroalkyl and trifluoroalkyl are mentioned in particular, and trifluoromethyl and mono- and di-fluoroethyl is preferred. Particularly preferred is trifluoromethyl and 2,2-difluoroethyl.

Examples of a cycloalkyl residue substituted by halogen and containing 3 to 8 carbon atoms include: a 2-fluorocyclopentyl group, a 2-chlorocyclopentyl group, a 2-bromocyclopentyl group, a 3-fluorocyclopentyl group, a 3-chlorocyclopentyl group, a 3-bromocyclopentyl group, a 2-fluorocyclohexyl group, a 2-chlorocyclohexyl group, a 2-bromocyclohexyl group, a 3-fluorocyclohexyl group, a 3-chlorocyclohexyl group, a 3-bromocyclohexyl group, a 4-fluorocyclohexyl group, a 4-chlorocyclohexyl group, a 4-bromocyclohexyl group, a di-fluorocyclopentyl group, a di-chlorocyclopentyl group, a di-bromocyclopentyl group, a di-fluorocyclohexyl group, a di-chlorocyclohexyl group, a di-bromocyclohexyl group, a tri-fluorocyclohexyl group, a tri-chlorocyclohexyl group, a tri-bromocyclohexyl group, etc..

Examples of a hydroxy-substituted alkyl residue include the above-mentioned alkyl residues which contain 1 to 3 hydroxyl residues such as, for example, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, etc. Hydroxymethyl being preferred.

Examples of an oxo-substituted alkyl residue includes the above-mentioned alkyl residues, wherein at least one carbon atom is substituted by an oxo-group forming a carbonyl group [–(C=O)-] in the alkyl chain or an alkanoyl-group [alkyl-(C=O)-)], such as C_1 to C_6 alkanoyl, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.. Preferred is an oxo-substitution of the alkyl residue in the form of a carbonyl-group [–(C=O)-] or an acetyl-group like [–(C=O)-CH_3] or [–(C=O)-CH_2–].

Examples of an alkoxy-substituted alkyl residue include the above-mentioned alkyl residues which contain 1 to 3 alkoxy residues as defined below such as, for example, methoxymethyl, ethoxymethyl, 2-methoxyethylene, etc.

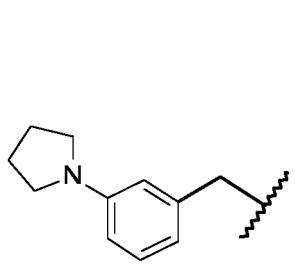
Examples of an acyl-substituted alkyl residue include the above-mentioned alkyl residues which contain 1 to 3 acyl residues as defined below.

Examples of an acyloxy-substituted alkyl residue include the above-mentioned alkyl residues which contain 1 to 3, preferably 1 acyloxy residues [–O-(C=O)-].

Examples of a cycloalkyl-substituted alkyl group include the above-mentioned alkyl residues containing 1 to 3, preferably 1 (optionally substituted) cycloalkyl group such as, for example: cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl 2-cyclohexylethyl, 2- or 3-cyclopropylpropyl, 2- or 3-cyclobutylpropyl, 2- or 3-cyclopentylpropyl, 2- or 3-cyclohexylpropyl, etc. Preferred are cyclopropylmethyl and cyclohexylmethyl.

Examples of an aryl-substituted alkyl group include the above-mentioned alkyl residues containing 1 to 3, preferably 1 (optionally substituted) aryl group, as defined below, such as, for example, phenylmethyl, 1- or 2-phenylethyl, 2- or 3-phenylpropyl, etc., phenylmethyl, 1-phenylethyl, 2-phenylethyl,

and 2-phenylpropyl being preferred. Also particularly preferred are alkyl groups, as defined above, which are substituted by substituted aryl, as defined below, in particular by phenyl being substituted with 1 to 3, preferably 1 or 2 of the same of different substituents, preferably selected from halogen, such as preferably F and Cl, cyano, optionally substituted alkyl, such as preferably methyl, ethyl, halogen-substituted alkyl such as trifluoromethyl, optionally substituted alkoxy, such as methoxy, ethoxy, halogen-substituted alkoxy such as difluoromethoxy, trifluoromethoxy, an optionally substituted amino group such as amino (NH_2-) or mono- or di-alkylamino such as preferably dimethylamino, an optionally substituted heterocyclyl group, such as pyrrolidinyl, alkyl-substituted piperazinyl, or morpholinyl, or an optionally substituted heterocyclyl-sulfonyl group, such as N-morpholinyl-sulfonyl, forming in particular alkyl-groups, which are substituted with substituted aryl according to the formulas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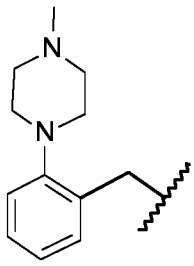
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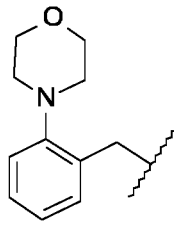
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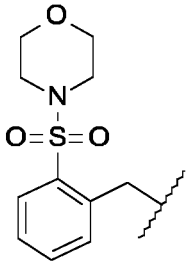
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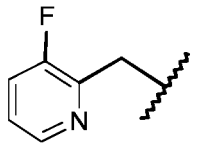
which are particularly preferred for R^1 and/or R^2.

Examples of a heterocyclyl-substituted alkyl group include the above-mentioned alkyl residues containing 1 to 3, preferably 1 (optionally substituted) heterocyclyl group, as defined below, which may be substituted with 1 to 3, preferably with 1 substituent. Preferably the heterocyclyl group as a substituent of alkyl is for example a morpholinyl group, a piperazinyl group, a piperidinyl group etc.. As defined above, the heterocylcyl group may be substituted and a preferred substituent is an optionally substituted alkyl group, preferably a methyl or ethyl group or a trifluoromethyl group. Particularly preferred is a a piperidinyl group and a methyl-substituted morpholinyl group.

Examples of a heteroaryl-substituted alkyl group include the above-mentioned alkyl residues containing 1 to 3, preferably 1 (optionally substituted) heteroaryl group, as defined below, such as, for example a pyridinyl, a pyridazinyl, a pyrimidinyl, a pyrazinyl, a pyrazolyl, an imidazolyl, a benzimidazolyl, a thiophenyl, or an oxazolyl group, such as pyridine-2-yl-methyl, pyridine-3-yl-methyl, pyridine-4-yl-methyl, 2-pyridine-2-yl-ethyl, 2-pyridine-1-yl-ethyl, 2-pyridine-3-yl-ethyl, pyridazine-3-yl-methyl, pyrimidine-2-yl-methyl, pyrimidine-4-yl-methyl, pyrazine-2-yl-methyl, pyrazol-3-yl-methyl, pyrazol-4-yl-methyl, pyrazol-5-yl-methyl, imidazole-2-yl-methyl, imidazole-5-yl-methyl, benzimidazol-2-yl-methyl, thiophen-2-yl-methyl, thiophen-3-yl-methyl, 1,3-oxazole-2-yl-methyl.

Preferred is an alkyl group which is substituted with optionally substituted pyridazinyl, such as in particular pyridazin-3-yl-methyl and pyridazin-3-yl-ethyl, optionally substituted pyridinyl, such as in particular optionally substituted pyridine-2-yl-methyl, pyridine-3-yl-methyl, pyridine-4-yl-methyl, 2-pyridine-2-yl-ethyl, 2-pyridine-1-yl-ethyl, 2-pyridine-3-yl-ethyl, very particularly optionally substituted pyridine-2-yl-methyl and 2-pyridin-2-yl-ethyl, optionally substituted pyrazol-3-yl-methyl, pyrazol-4-yl-methyl, pyrazol-5-yl-methyl, pyrazol-3-yl-ethyl, pyrazol-4-yl-ethyl, pyrazol-5-yl-ethyl. Particularly preferred is substituted pyridinyl-alkyl, such as substituted pyridinyl-methyl or substituted pyridinyl-ethyl, wherein the 1, 2 or 3 substituents are selected from halogen, such as fluorine, C_1-C_3-alkyl, such as methyl, and trifluoromethyl. Particularly preferred is fluorine substituted pyridinyl-alkyl, such as fluorine substituted pyridinyl-methyl or fluorine substituted pyridinyl-ethyl. Most preferred is fluorine substituted pyridinyl-methyl according to formula



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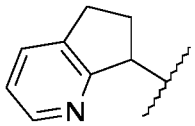
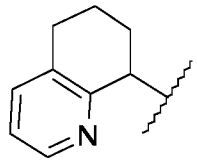
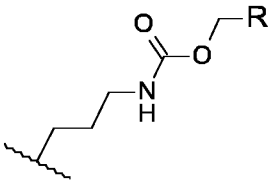
Examples of a heteroaryl-substituted alkyl group includes further in particular a cyclo-alkyl residue as defined above, which is bound to the heteroaryl-substituent by forming a fused ring with the heteroaryl-substituent as defined above, preferably the fused cyclo-alkyl- residue is cyclopentyl or cyclohexyl. Further, preferably the fused heteroaryl-subsituten is pyridinyl, forming for example fused rings such as cyclopenta-pyridinyl and cyclohexa-pyridinyl, according to the formulas

 and , which are particularly preferred for R^2 or a group Cycl-$[CQ]_n$, wherein Q is C_1-C_4-alkyl, which forms a fused 5- or 6-membered ring with Cycl.

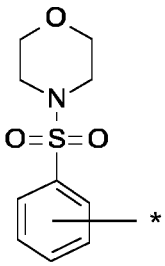
In each case the heterocyclyl-substituent of an alkyl-residue as defined herein may be substituted with 1 to 3, preferably 1 or 2 of the same or different substituents, which are preferably selected from halogen, such as preferably F and Cl, cyano, optionally substituted alkyl, such as preferably methyl, ethyl, halogen-substituted alkyl such as trifluoromethyl and hydroxy-substituted alkyl such as hydroxymethyl, optionally substituted alkoxy, such as preferably methoxy and ethoxy, an oxo-group (=O), a heterocyclyl group as defined below, such as an N-morpholinyl group, an aminocarbonyl group, an optionally substituted amino group, such as preferably amino (NH_2-) or mono- or di-alkylamino such as preferably dimethylamino.

Examples of an amino-substituted alkyl residue include the above-mentioned alkyl residues containing 1 to 3, preferably 1 (optionally substituted) amino group, as defined below, such as, for example, aminoalkyl (NH_2-alkyl) or mono- or dialkylamino-alkyl, such as aminomethyl, 2-aminoethyl, 2- or 3-aminopropyl, methylaminomethyl, methylaminoethyl, methylaminopropyl, 2-ethylaminomethyl, 3-ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminoethyl, etc. or an alkyl group, which may be substituted with an optionally substituted alkyloxycarbonylamino group such as a group according to formula

, wherein R defines a substituent of alkyl as defined above, preferably a phenyl group, such group being particularly preferred for R^3.

Throughout the invention, optionally substituted aryl preferably includes:
aromatic hydrocarbon residues containing 6 to 14 carbon atoms (excluding the carbon atoms of the possible substituents), which may be monocyclic or bicyclic, including, for example: phenyl, naphthyl, phenanthrenyl and anthracenyl, which may optionally be substituted preferably by 1 to 3 of the same or different substituents (e.g. indicated as R^6) selected from hydroxy, halogen, as defined above, cyano, optionally substituted amino, as defined below, optionally substituted alkyl, as defined above, optionally substituted acyl, as defined below, and optionally substituted alkoxy, as defined below, optionally substituted aryloxy, as defined below, optionally substituted heterocyclyloxy, as defined below, optionally substituted aryl, as defined herein, optionally substituted heterocyclylyl, as defined below. Optionally substituted phenyl is preferred, such as unsubstituted phenyl and phenyl which is substituted with 1 to 3, more preferably with 1 or 2 substituents R^6, which may be the same or different. The 1 to 3 phenyl substituents (e.g. indicated as R^6) are in particular selected from the group consisting of heterocyclyl as

defined below, halogen as defined above such as in particular F, optionally substituted amino as defined below such as in particular (-NH_2) or mono- or dialkylamino with dimethylamino being preferred, cyano, optionally substituted alkoxy as defined below such as in particular di-fluoromethoxy and trifluoromethoxy, and an optionally substituted sulfonyl-group which may form in particular a group



with * indicating the binding site of the substituted phenyl substituent. Most preferred is halogen-substituted phenyl, alkoxy-substituted phenyl and hydroxyl-substituted phenyl. The aforementioned substituents of phenyl are particularly preferred for the group "Cycl" in the formulae as defined herein with the meaning of a substituted aryl group being substituted phenyl.

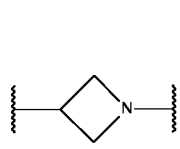
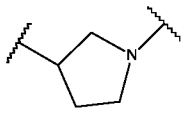
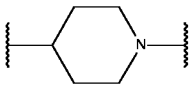
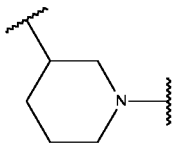
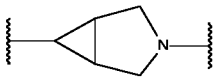
Examples of an alkyl-substituted aryl group preferably include: aryl, as described above which is substituted by straight-chain or branched alkyl containing 1 to 8, preferably 1 to 4 carbon atoms, as described above. Toluoyl is the preferred alkylaryl.

Examples of a hydroxy-substituted aryl group preferably include: aryl, as described above, which is substituted by 1 to 3 hydroxyl residues such as, for example 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,4-di-hydroxyphenyl, 2,5-di-hydroxyphenyl, 2,6-di-hydroxyphenyl, 3,5-di-hydroxyphenyl, 3,6-di-hydroxyphenyl, 2,4,6-tri-hydroxyphenyl, etc..

Examples of a halogen-substituted aryl group preferably include: aryl, as described above, which is substituted by 1 to 3 halogen atoms such as, for example 2-chloro- or fluorophenyl, 3-chloro- or fluorophenyl, 4-chloro- or fluorophenyl, 2,4-di-(chloro- and/or fluoro)phenyl, 2,5-di-(chloro- and/or fluoro)phenyl, 2,6-di-(chloro- and/or fluoro)phenyl, 3,5-di-(chloro- and/or fluoro)phenyl, 3,6-di-(chloro- and/or fluoro)phenyl, 2,4,6-tri-(chloro- and/or fluoro)phenyl, etc..

Examples of an alkoxy-substituted aryl group preferably include: aryl, as described above, which is substituted by 1 to 3 alkoxy residues, as described below, such as preferably 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2,4-di-methoxyphenyl, etc., as well as di-fluoromethoxyphenyl and trifluoromethoxyphenyl.

Throughout the invention, optionally substituted heterocyclyl preferably includes:
Saturated or unsaturated mono- or bicyclic 4- to 8-membered heterocyclic residues containing 1 to 3, preferably 1 to 2 same or different hetero atoms, selected from N, O and S and which may optionally be substituted preferably by 1 to 3 substituents, wherein reference may be made to the definition of possible substituents for optionally substituted heterocyclyl. 4-, 5- and 6-membered saturated or unsaturated, mono- or bicyclic optionally substituted heterocyclic residues are preferred, and examples comprise azetidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholinyl, etc., such as azetidin-1-yl, azetidin-2-yl, azetidin-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydro-thiophen-2-yl, tetrahydro-thiophen-3-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholin-1-yl, morpholin-2-yl, morpholin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, etc., which may optionally be condensed with aromatic rings. Particularly preferred are azetidinyl, pyrrolidinyl, piperidinyl, and morpholinyl residues. Particularly preferred are the following heterocyclic residues, which may be substituted as defined above: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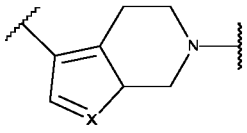
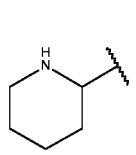
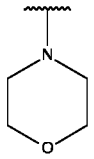


(with X being N, O or S, preferably S), which are particularly preferred for A^1, and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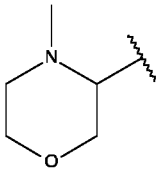
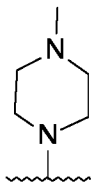
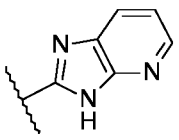
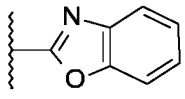

, being particularly preferred for R^1 and/or R^2, and

, which is particularly preferred as a substituent for an aryl group.

Preferred substituents of heterocyclyl-residues comprise an alkyl-group such as preferably methyl and ethyl, a hydroxyl-group, and an oxo-group (=O).

Throughout the invention, optionally substituted heteroaryl includes:

heteroaromatic hydrocarbon residues containing 4 to 9 ring carbon atoms, which additionally preferably contain 1 to 3 of the same or different heteroatoms from the series S, O, N in the ring and therefore preferably form 5- to 12-membered heteroaromatic residues which may preferably be monocyclic but also bicyclic. Preferred aromatic heterocyclic residues include: pyridyl (pyridinyl), pyridyl-N-oxide, pyridazinyl, pyrimidyl, pyrazinyl, thienyl (thiophenyl), furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl or isoxazolyl, indolizinyl, indolyl, benzo[b]thienyl, benzo[b]furyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl, quinoxalinyl. 5- or 6-membered aromatic heterocycles are preferred, such as from the group of 5-membered heteroaryl, for example thiazolyl such as thiazol-2-yl, 2-thiazol-2-yl, 2-thiazol-4-yl, thienyl (thiophenyl) such as thien-3-yl, pyrazolyl such as 1-pyrazol-4-yl, 3-pyrazol-5-yl, imidazolyl such as imidazole-2-yl, 2-imidazol-4-yl, 1-imidazol-4-yl, triazolyl such as 1-triazol-3-yl, 1-triazol-4-yl, such as 1,2,4-triazol-3-yl or 1,2,3-triazol-4-yl, oxazolyl such as 2-oxazol-4-yl, 2-oxazol-5-yl, oxadiazolyl such as 1,2,4-oxadiazol-3-yl and from the group of 6-membered heteroaryl, for example pyridyl (pyridinyl) such as pyrid-1-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2-pyrid-4-yl, 2-pyrid-6-yl, 3-pyrid-5-yl (pyridin-1-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-pyridin-4-yl, 2-pyridin-6-yl, 3-pyridin-5-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, and from the group of bicyclic heteroaromatic residues in particular benzimidazolyl such as benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, as well as benzimidazol-pyridinyl according to formula


; or benzoxazol-2-yl according to formula

, or benzimidazol forming a fused ring with a heterocyclyl residue, as defined above.

The aforementioned heteroaryl-groups may have one or more, preferably 1 to 3, more preferably 1 or 2 same or different substituents, which are in particular selected from halogen, such as preferably F and Cl, cyano, optionally substituted alkyl as defined above, such as preferably methyl, ethyl,n-propyl, i-propyl, halogen-substituted alkyl such as difluoromethyl or trifluoromethyl, hydroxy-substituted alkyl such as hydroxymethyl, aminocarbonyl-substituted alkyl such as aminocarbonylmethyl, carboxyl-substituted alkyl such as carboxylmethyl, an alkenyl group such as propenyl, optionally substituted alkoxy, such as preferably methoxy and ethoxy, a hydroxyl group (-OH), an oxo-group (=O), a carboxyl group [-(C=O)-OH], a heterocyclyl group as defined above, such as a N-morpholinyl group, an aminocarbonyl group, such as

NH_2-(C=O)-, an optionally substituted amino group, such as preferably amino (NH_2-) or mono- or di-alkylamino such as preferably dimethylamino.

In particular, examples of an alkyl-substituted heteroaryl group preferably include: heteroaryl, as described above, which is substituted by linear or branched, optionally substituted alkyl containing 1 to 8, preferably 1 to 4 carbon atoms, as described above, such as in particular methylimidazolyl such as in particular N-methylimidazolyl, methylbenzimidazolyl such as in particular N-methylbenzimidazolyl, 5-methylbenzimidazolyl, 4-trifluoromethylbenzimidazolyl, 5-trifluoromethylbenzimidazolyl, N-aminocarbonylmethylbenzimidazolyl, N-carboxylmethylaminocarbonyl, N-methylpyrazolyl, 1(N),5-dimethylpyrazolyl, methylpyridinyl such as 2-methylpyridin-3-yl, 2-methylpyridin-4-yl, 3-methylpyridin-2-yl, 3-methylpyridin-3-yl, 3-methylpyridin-4-yl, 4-methylpyridin-2-yl, 5-methylpyridin-2-yl, 6-methylpyridin-2-yl etc., dimethylpyridinyl such as 3,5-dimethylpyridin-2-yl, 4,6-dimethylpyridin-3-yl, trifluoromethylpyridinyl, in particular 3- or 4- trifluoromethylpyridin-2-yl, 6-trifluoromethylpyridin-3-yl, 3-hydroxymethylpyridin-2-yl, 5-methylpyrimidin-2-yl, etc..

Examples of a halogen-substituted heteroaryl group preferably include: heteroaryl, as described above, which is substituted by 1 to 3, preferably 1 or 2 halogen atoms such as preferably by F and/or Cl, including in particular fluoropyridinyl such as 3-fluoro-pyridin-2-yl, 4-fluoro-pyridin-2-yl, 5-fluoro-pyridin-2-yl, 6-fluoro-pyridin-2-yl, 3-chloro-pyridin-2-yl, 4-chloro-pyridin-2-yl, 5-chloro-pyridin-2-yl, 6-chloro-pyridin-2-yl, 2-fluoro-pyridin-3-yl, 4-fluoro-pyridin-3-yl, 5-fluoro-pyridin-3-yl, 6-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 4-chloro-pyridin-3-yl, 5-chloro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-fluoro-pyridin-4-yl, 3-fluoro-pyridin-4-yl, 5-fluoro-pyridin-4-yl, 6-fluoro-pyridin-4-yl, 2-chloro-pyridin-4-yl, 3-chloro-pyridin-4-yl, 5-chloro-pyridin-4-yl, 6-chloro-pyridin-4-yl, etc., di-fluoropyridinyl such as 3,5-di-fluoropyridin-2-yl, fluoro-chloro-pyridinyl such as 3-chloro-5-fluoro-pyridin-2-yl, etc..

Examples of a halogen- and alkyl-substituted heteroaryl group preferably include: heteroaryl, as described above, which is substituted by 1 to 3 halogen atoms such as preferably by F and/or Cl, and 1 to 3 linear or branched, optionally substituted alkyl-residues as described above, such as in particular 3-fluoro-6-methylpyridin-2-yl, 3-chloro-5-trifluoromethylpyridin-2-yl.

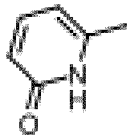
Further preferred examples of substituted heteroaryl-groups include:

methoxypyridinyl such as 3-, 4-, 5- or 6-methoxypyridin-2-yl, 2-, 4-, 5- or 6-methoxypyridin-3-yl, 2-, 3-, 5- or 6-methoxypyridin-4-yl, etc., hydroxypyridinyl such as 3-, 4-, 5- or 6-hydroxypyridin-2-yl, 2-, 4-, 5- or 6-hydroxypyridin-3-yl, 2-, 3-, 5- or 6-hydroxypyridin-4-yl, etc., oxo-pyridinyl such as 6-oxo-1,6-dihydropyridin-2-yl, 2-oxo-1,2-dihydropyridin-3-yl etc., aminopyridinyl such as 6-dimethylaminopyridin-3-yl, aminocarbonylpyridinyl such as 6-aminocarbonylpyridin-3-yl, cyanopyridinyl such as 3-, 4-, 5- or 6-cyanopyridin-2-yl, 2-, 4-, 5- or 6-cyanopyridin-3-yl, 2-, 3-, 5- or 6-cyanopyridin-4-yl, etc., as well as 2-morpholin-4-yl-pyridin-4-yl.

With respect to the meaning of R^4 as 1 to 3, preferably 1 or 2 same or different substituents of a bicyclic heteroaryl group Het-2 according to any of the formulae as defined herein said heteroaryl-substituents are preferably selected from halogen, such as preferably F and Cl, cyano, optionally substituted alkyl as defined above, such as preferably methyl, ethyl, n-propyl, i-propyl, halogen-substituted alkyl such as difluoromethyl or trifluoromethyl, aminocarbonyl-substituted alkyl such as aminocarbonylmethyl, carboxyl-substituted alkyl such as carboxylmethyl, optionally substituted alkoxy, such as preferably methoxy and ethoxy and a carboxyl group [-(C=O)-OH]. It is most preferred, that R^4 indicates 1 or 2 same or different substituents selected from F, Cl, cyano, optionally substituted alkyl such as methyl and trifluoromethyl, aminocarbonyl-substituted alkyl such as aminocarbonylmethyl, carboxyl-substituted alkyl such as carboxylmethyl, optionally substituted alkoxy, such as methoxy and a carboxyl group [-(C=O)-OH].

With respect to the meaning of R^5 as 1 to 4, preferably 1 to 3, more preferably 1 or 2 same or different substituents of a heteroaryl group Cycl according to any of the formulae as defined herein said heteroaryl-substituents are preferably selected from halogen, such as preferably F and Cl, cyano,

optionally substituted alkyl as defined above, such as preferably methyl, ethyl, n-propyl, i-propyl, halogen-substituted alkyl such as difluoromethyl or trifluoromethyl, hydroxy-substituted alkyl such as hydroxymethyl, optionally substituted alkoxy, such as preferably methoxy and ethoxy, an oxo-group (=O), a heterocyclyl group as defined above, such as a N-morpholinyl group, an aminocarbonyl group such as NH_2-(C=O)-, an optionally substituted amino group, such as preferably amino (NH_2-) or mono- or di-alkylamino such as preferably dimethylamino. It is most preferred, that R^5 indicates 1 or 2 same or different substituents selected from F, Cl, cyano, optionally substituted alkyl such as methyl, trifluoromethyl, and hydroxymethyl, optionally substituted alkoxy, such as methoxy, an oxo-group (=O), forming for example an oxo-substituted heteroaryl of the formula

or , a heterocyclyl group such as a N-morpholinyl group, an aminocarbonyl group such as NH_2-(C=O)-, an optionally substituted amino group, such as di-alkylamino such as dimethylamino.

Optionally substituted acyl here and hereinafter includes: formyl (-CH(=O)), optionally substituted aliphatic acyl (alkanoyl = alkyl-CO, wherein reference may be made to the foregoing definition of optionally substituted alkyl with respect to the alkyl group), optionally substituted aromatic acyl (aroyl = aryl-CO-, wherein reference may be made to the foregoing definition of optionally substituted arylwith respect to the aryl group), optionally substituted heteroaromatic acyl (heteroaroyl = heteroaryl-CO-, wherein reference may be made to the foregoing definition of optionally substituted heteroaryl with respect to the heteroaryl group), or heterocyclic acyl (heterocycloyl = heterocyclyl-CO-, wherein reference may be made to the foregoing definition of optionally substituted heterocyclyl with respect to the heterocyclyl group). Aliphatic acyl = alkanoyl = alkyl-CO- is preferred.

Optionally substituted amino according to the invention preferably includes: amino (-NH_2), optionally substituted mono- or dialkylamino (alkyl-NH-, $(alkyl)_2N$-), wherein with respect to "alkyl" reference can be made to the definition of optionally substituted alkyl above. Further included are optionally substituted mono- or diarylamino, mono- or diheteroarylamino and mono- or diheterocyclylamino radicals or mixed optionally substituted alkylarylamino, alkylheteroarylamino and alkylheterocyclylamino radicals, wherein reference can be made to the above definitions of optionally substituted alkyl, aryl, heteroaryl and heterocyclyl. According to the present invention an amino group further includes a group –NH-.

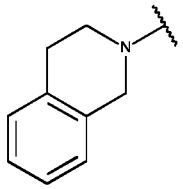
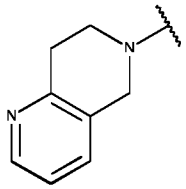
Optionally substituted amino is preferably optionally substituted mono- or dialkylamino (alkyl-NH-, $(alkyl)_2N$-), in particular with 1 to 8, preferably 1 to 6, more preferably 1 to 3 carbon atoms, as previously mentioned. Most preferred optionally substituted amino is mono- or dimethylamino and mono- or diethylamino. Most preferred is an amino group (-NH_2) or (-NH-) and a dimethylamino group.

Throughout the invention, optionally substituted alkanediyl is preferably a divalent straight-chained or branched alkanediyl radical having from 1 to 7, preferably from 1 to 6, more preferably from 1 to 4, carbon atoms, which can optionally carry from 1 to 3, preferably 1 or 2 substituents selected from the group consisting of halogen, hydroxy, an oxo group (forming a carbonyl or acyl group) and an amino group as defined above. The following may be mentioned as preferred examples: methylene, ethane-1,2-diyl, ethane-1,1-diyl, propane-1,3-diyl, propane-1,1-diyl, propane-1,2-diyl, propane-2,2-diyl, butane-1,4-diyl, butane-1,2-diyl, butane-1,3-diyl, butane-2,3-diyl, butane-1,1-diyl, butane-2,2-diyl, butane-3,3-diyl, pentane-1,5-diyl, etc. Particularly preferred is methylene, ethane-1,2-diyl, ethane-1,1-diyl, propane-1,3-diyl, propane-2,2-diyl, and butane-2,2-diyl. Most preferred are methylene and ethane-1,2-diyl.

A preferred substituted alkanediyl radical is a hydroxy-substituted alkanediyl such as a hydroxyl-substituted ethanediyl, an oxo-substituted alkanediyl such as an oxo-substituted methylene or ethanediyl radical, forming a carbonyl or an acyl (acetyl) group, a halogen substituted alkanediyl group such as an

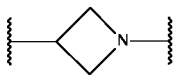
alkanediyl group being substituted with one or two halogen atoms selected from F and Cl, preferably 2,2-di-fluoro-ethanediyl, or an alkanediyl group which is substituted with an oxo and an amino group, forming an aminocarbonyl group such as preferably a group [-(C=O)-NH-].

According to the present invention the substituents R^1 and R^2 or a respective group -$[CQ]_n$-, wherein Q is C_1-C_4-alkyl, may together with the nitrogen atom to which they are bonded form an optionally substituted 3- to 6-membered ring, which may optionally contain further heteroatoms. Therein, R^1 and R^2 (or the group -$[CQ]_n$-, wherein Q is C_1-C_4-alkyl) may preferably together with the nitrogen atom to which they are bonded form a 5- or 6-membered ring, which may contain further heteroatoms, preferably one further heteroatom selected from N and O. Therein it is most preferred that R^1 and R^2 (or the group -$[CQ]_n$-, wherein Q is C_1-C_4-alkyl) together with the nitrogen atom to which they are bonded form a 6-membered ring, which contains no further heteroatom, forming an N-piperidinyl ring or a 6-membered ring, which contains one further heteroatom O, forming an N-morpholinyl ring. In particular such N-piperidinyl ring may be substituted with aryl or heteroaryl as defined above, preferably with phenyl or piperidinyl, forming a biciclyc ring according to the formula

or .

According to the present invention it is further possible that A^1, having the meaning of a linear or branched alkanediyl group as defined above, and R^3, having the meaning of an optionally substituted alkyl group as defined above, together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered aliphatic mono- or bicyclic ring, which may be substituted with 1 to 3 substituents as defined above, such as for example according to the following formulas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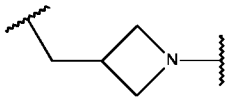
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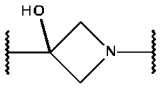
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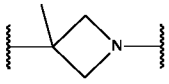
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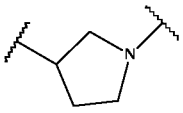
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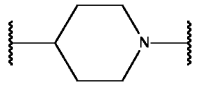
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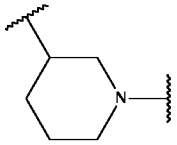
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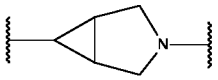
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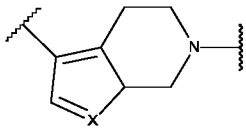
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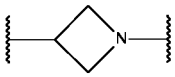
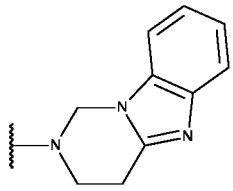
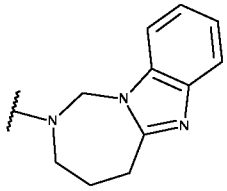
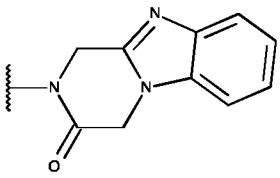
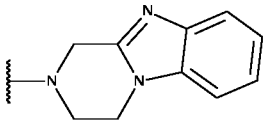

N, O or S, preferably S), wherein is preferred.

In the context of the present invention it is further possible that R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring, wherein optional substituents are preferably selected from heteroaryl as defined above and an oxo group. A heteroaryl substituent may then also form a fused ring with the 4- to 7-membered ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded. Examples include residues according to the following formulas: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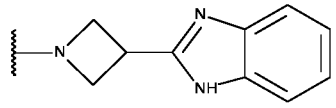
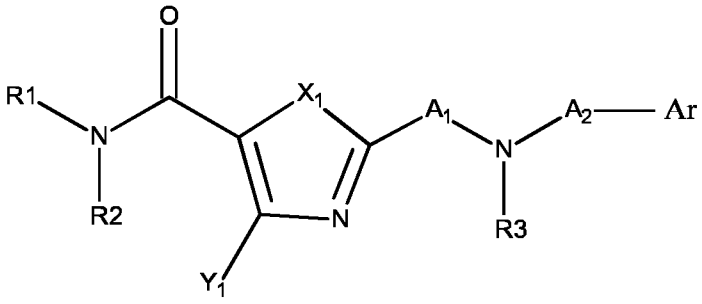


In a further aspect, the invention relates to novel compounds of general formula (I)



(I)

wherein

R^1 and R^2 are the same or different and are independently selected from the group consisting of
- hydrogen,
- optionally substituted alkyl,
- optionally substituted aryl,
- optionally substituted heteroaryl,
- optionally substituted heterocyclyl, or
- R^1 and R^2 together with the nitrogen atom to which they are bonded form an optionally substituted 3- to 6-membered ring, which may optionally contain further heteroatoms;

X^1 is O or S,

Y^1 is hydrogen, optionally substituted alkyl or halogen,
preferably hydrogen or C_1-C_3-alkyl, preferably hydrogen or methyl;

A^1 is optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl,
- a direct bond, or
- a sulfonyl group (-SO_2-);

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring; and

Ar is
- optionally substituted aryl,
- optionally substituted monocyclic heteroaryl, or
- optionally substituted bicyclic heteroaryl, which may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded;

or pharmaceutically acceptable salts thereof.

It is particularly preferred that the subsitutents in the formula (I) above have the meaning as follows:

R^1 and R^2 are the same or different and are independently selected from the group consisting of
- hydrogen,
- optionally substituted alkyl, or
- R^1 and R^2 together with the nitrogen atom to which they are bonded form and optionally substituted 3- to 6-membered ring, which may optionally contain further heteroatoms;

X^1 is O or S;

Y^1 is hydrogen or C_1-C_3-alkyl, such as preferably hydrogen or methyl;

A^1 is optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl, or
- a direct bond;

R^3 is
- hydrogen, or
- C_1-C_3-alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered monocyclic ring; or

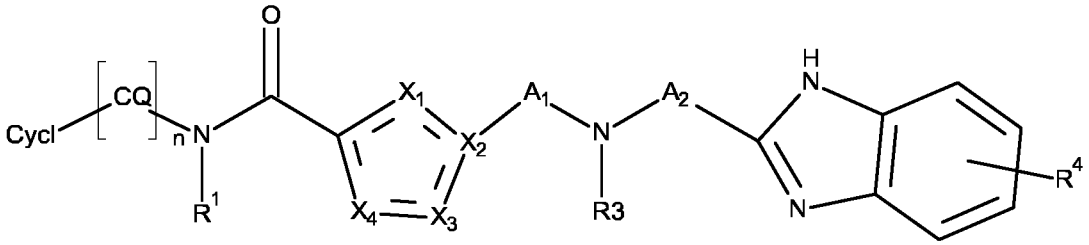
R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring; and

Ar is optionally substituted bicyclic heteroaryl.

Preferred Embodiments:

Embodiment A-2:

A further preferred embodiment of the present invention relates to novel compounds according to formula (A-II)



(A-II)

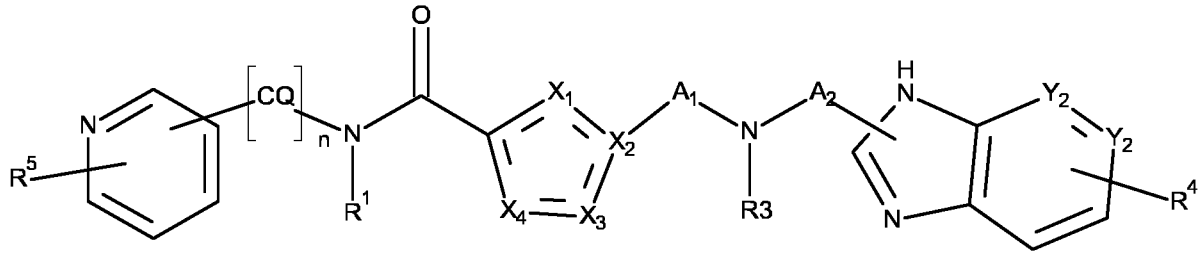
wherein Cycl, Q, R^1, X^1, X^2, X^3, X^4, R^3, A^1, A^2, R^4 and n have the meaning as defined above for formula (A-I); or pharmaceutically acceptable salts thereof.

Embodiment A-3:

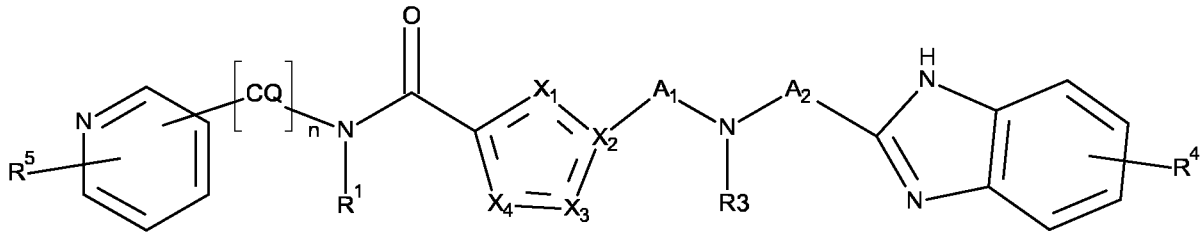
A further preferred embodiment of the present invention relates to novel compounds according to formula (A-I) and (A-II) as defined above, wherein Cycl is substituted or unsubstituted heteroaryl as defined above. Therein, the heteroaryl may be substituted with 1 to 4, preferably 1 to 3, more preferably 1 or 2 substituents R^5 as defined above and as defined below in context with compounds according to any of the formulae (A-IIIa) (A-IIIb), (A-IVa), (A-IVb), (A-IVc) and (A-IVd).

Embodiments A-3a and A-3b:

A further preferred embodiment of the present invention relates to novel compounds according to formula (A-I) and (A-II) as defined above, wherein Cycl is a substituted or unsubstituted heteroaryl, which is selected from a substituted or unsubstituted pyridinyl, forming compounds according to formula (A-IIIa) or (A-IIIb), respectively:



(A-IIIa)



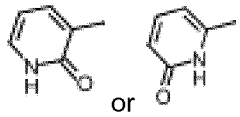
(A-IIIb)

wherein Q, R^1, X^1, X^2, X^3, X^4, R^3, A^1, A^2, Y^2, R^4 and n have the meaning as defined above for formula (A-I) or (A-II), and wherein

R^5 indicates 1 to 4, preferably 1 to 3, more preferably 1 or 2 optional substituents, which may independently be selected from the group consisting of

- halogen, preferably F and Cl,
- optionally substituted alkyl, preferably methyl, trifluoromethyl, hydroxymethyl,

- hydroxy,
- alkoxy, preferably methoxy,
- an oxo group (=O), forming a substituted pyridinyl-group of the formula

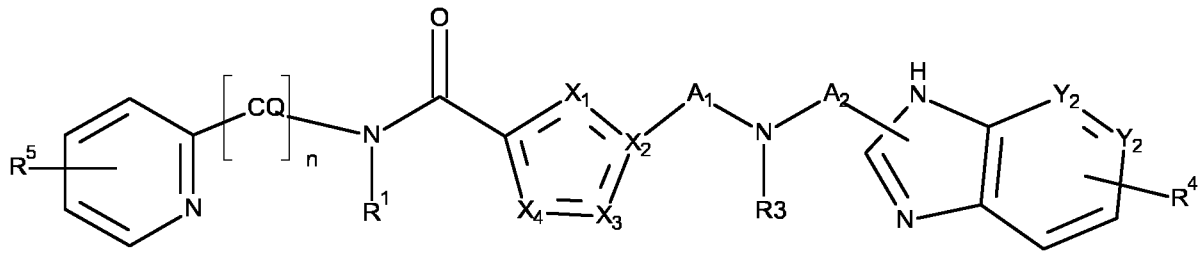


- an amino group, such as $-NH_2$, mono- or dialkylamino, preferably dialkylamino
- an aminocarbonyl group, preferably NH_2-(C=O)-,
- cyano, and
- a heterocyclyl group, preferably a morpholinyl-group,

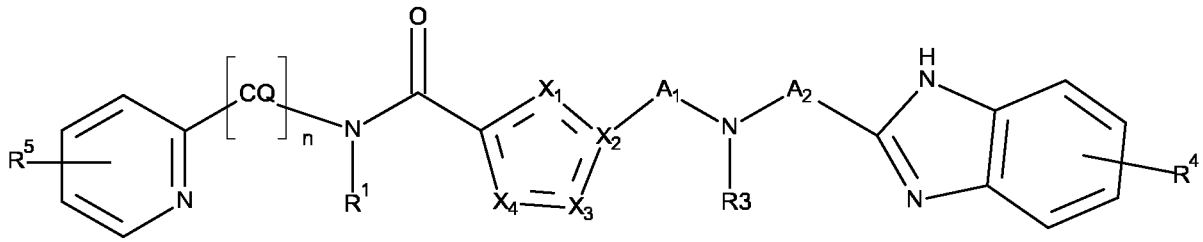
or pharmaceutically acceptable salts thereof.

Embodiments A-4a and A-4b:

A further preferred embodiment of the present invention relates to novel compounds according to formula (A-IVa) and (A-IVb):



(A-IVa)



(A-IVb)

wherein Q, R^1, X^1, X^2, X^3, X^4, R^3, A^1, A^2, Y^2, R^4 and n have the meaning as defined above for formula (A-I), (A-II) or (A-IIIa) and (A-IIIb) and wherein

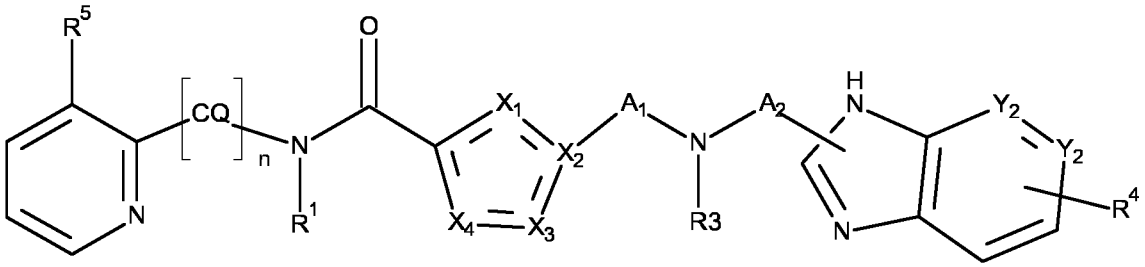
R^5 has the meaning as defined above for formula (A-IIIa) and (A-IIIb), respectively;

or pharmaceutically acceptable salts thereof.

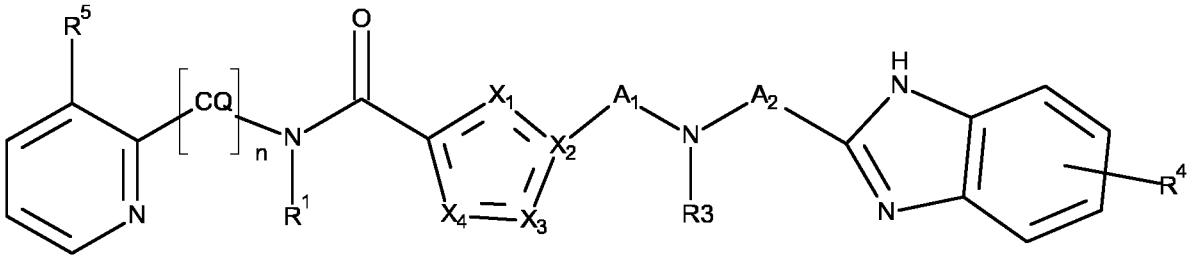
It is particularly preferred that in any of the formulae (A-IIIa), (A-IIIb), (A-IVa) or (A-IVb) R^5 indicates 1 to 3, more preferably 1 or 2 substituents, even more preferred 1 substituent, which may independently have the meaning as defined above.

Embodiments A-4c and A-4d:

A further preferred embodiment of the present invention relates to novel compounds according to the formulae (A-IIIa), (A-IIIb), (A-IVa) or (A-IVb), wherein R^5 indicates 1 substituent, forming compounds according to the formula (A-IVc) and (A-IVd), respectively:



(A-IVc)



(A-IVd)

wherein Q, R^1, X^1, X^2, X^3, X^4, R^3, A^1, A^2, Y^2, R^4 and n have the meaning as defined above for formula (A-I), (A-II), (A-IIIa), (A-IIIb), (A-IVa) and (A-IVb) and wherein
R^5 has the meaning as defined above for formula (A-IIIa), (A-IIIb), (A-IVa) and (A-IVb), respectively;
or pharmaceutically acceptable salts thereof.

Preferably in any of the aforementioned embodiments the one or more substituents R^5 are independently selected from the group consisting of

- halogen, preferably F and Cl,
- optionally substituted alkyl, preferably methyl, trifluoromethyl, hydroxymethyl,
- hydroxy, and
- alkoxy, preferably methoxy.

More preferably in any of the aforementioned embodiments the one or more substituents R^5 are independently selected from the group consisting of

- halogen, preferably F and Cl, and
- optionally substituted alkyl, preferably methyl, trifluoromethyl, hydroxymethyl.

Even more preferably in any of the aforementioned embodiments the one or more substituents R^5 are independently selected from the group consisting of

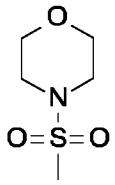
- halogen, preferably F and Cl, most preferred being F.

Embodiment A-5:

A further preferred embodiment of the present invention relates to novel compounds according to formula (A-I) and (A-II) as defined above, wherein Cycl is a substituted aryl as defined above, which is substituted with 1 to 3, preferably 1 or 2 substituents selected from the group consisting of

- hydroxy,
- halogen, preferably F and Cl, preferably F,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino, such as (-NH_2) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted acyl,

- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl, and
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl,
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula

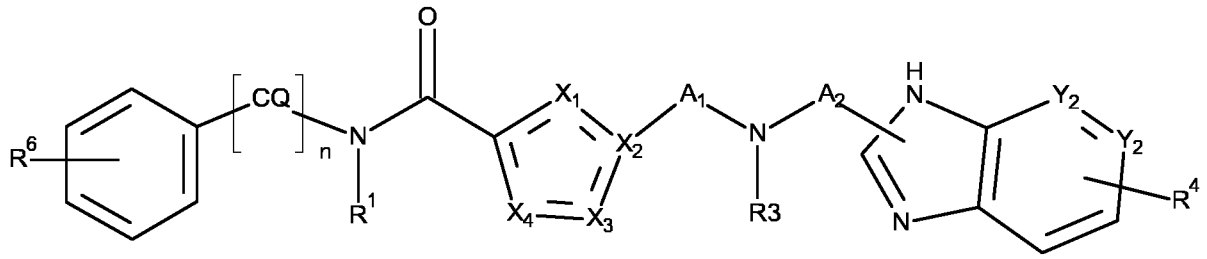


;

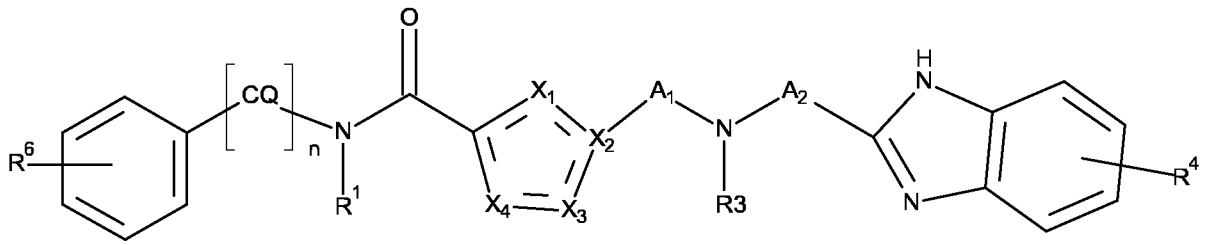
such as preferably with 1 to 3, preferably 1 or 2 substituents R^6 as defined above and as defined below in context with compounds according to any of the formulae (A-Va) and (A-Vb);
or pharmaceutically acceptable salts thereof.

Embodiments A-5a and A-5b:

A further preferred embodiment of the present invention relates to novel compounds according to formula (A-I) and (A-II) as defined above, wherein Cycl is a substituted aryl, which is selected from a substituted phenyl, forming compounds according to formula (A-Va) or (A-Vb), respectively:



(A-Va)

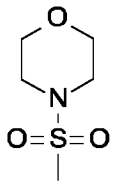


(A-Vb)

wherein Q, R^1, X^1, X^2, X^3, X^4, R^3, A^1, A^2, Y^2, R^4 and n have the meaning as defined above for formula (A-I) and (A-II) and wherein
R^6 has the meaning as defined above and in particular indicates 1 to 3, preferably 1 or 2 substituents, more preferably 1 substituent, selected from the group consisting of

- hydroxy,
- halogen, preferably F and Cl, preferably F,
- cyano,

- optionally substituted alkyl,
- optionally substituted amino, such as (-NH_2) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted acyl,
- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl, and
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl,
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula

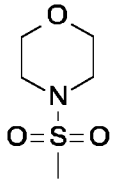


;

or pharmaceutically acceptable salts thereof.

More preferably R^6 has the meaning of 1 or 2 substituents, preferably R^6 indicates 1 substituent, selected from the group consisting of

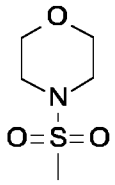
- hydroxy,
- halogen, preferably F and Cl, preferably F,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino, such as (-NH_2) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl, and
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula



;

Even more preferably R^6 indicates 1 substituent selected from the group consisting of

- halogen, preferably F and Cl, preferably F,
- cyano,
- optionally substituted amino, such as (-NH_2) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl, and
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula



Further Embodiments A-6:

Further preferred embodiments of the present invention relate to novel compounds according to any one of the aforesaid embodiments or according to any of the formulae (A-I), (A-II), (A-IIIa), (A-IIIb), (A-IVa), (A-IVb), (A-IVc), (A-IVd), (A-Va) and (A-Vb) as defined above, or pharmaceutically acceptable salts thereof, wherein

Embodiment (A-6a):

X^1 is N

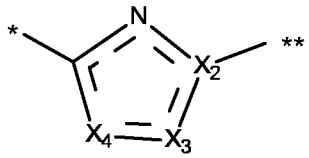
and wherein one or two further heteroatoms X (X^2, X^3, X^4) are present, and wherein

X^2 is C or N;

X^3 is C, N, S or O; and

X^4 is C or N,

forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;

with the proviso that in case of two further heteroatoms both are selected to be N or one is N and one (except X^2) is O;

and wherein X^3 and X^4, when having the meaning of C or N, may carry a further substituent, such as preferably hydrogen (with X^4 = C) or a substituent as defined above for substituted heteroaryl.

Embodiment (A-6b):

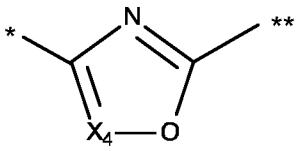
X^1 is N,

X^2 is C and

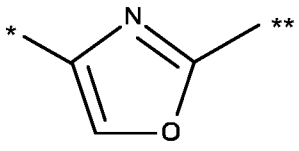
X^3 is O; and

X_4 is C or N,

forming a group

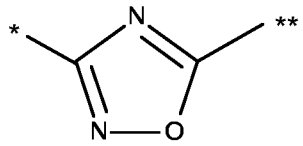


such as preferably a group



(Embodiment (A-6b-1)

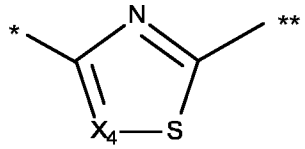
or a group



(Embodiment (A-6b-2)

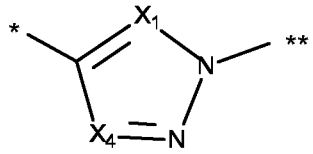
wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group; and wherein
X^4 (being C or N) may carry a further substituent, such as preferably hydrogen (with X^4 = C) or a substituent as defined above for substituted heteroaryl.

Embodiment (A-6c):
X^1 is N,
X^2 is C and
X^3 is S; and
X_4 is C or N, preferably C,
forming a group



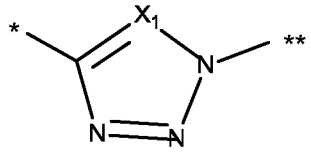
wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^4 may carry a further substituent, such as preferably hydrogen (with X^4 = C) or a substituent as defined above for substituted heteroaryl.

Embodiment (A-6d):
X^2 and X^3 are both N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group; and wherein
X^1 and X^4 are C;
and wherein X^1 and/or X^4 independently may carry hydrogen or a further substituent, such as preferably a substituent as defined above for substituted heteroaryl.

Embodiment (A-6e):
X^1 is C, and
X^2, X^3 and X^4 are N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group; and wherein

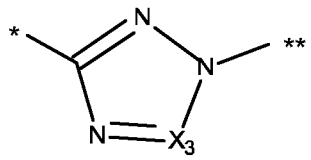
X^1 may carry hydrogen or a further substituent such as preferably a substituent as defined above for substituted heteroaryl.

Embodiment (A-6f):

X^1, X^2 and X^4 are N, and

X^3 is C,

forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group; and wherein

X^3 may carry hydrogen or a further substituent, such as a substituent as defined above for substituted heteroaryl.

Embodiment (A-6g):

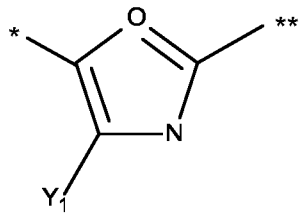
X^1 is O,

X^2 is C,

X^3 is N, and

X^4 is C,

forming a group



wherein

Y^1 indicates

- hydrogen or
- an optional subsitutent to X^4; and

* indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;

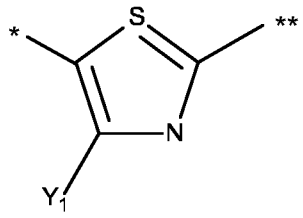
Embodiment (A-6h):

X^1 is S,

X^2 is C,

X^3 is N, and

X^4 is C,
forming a group



wherein
Y^1 indicates

- hydrogen or
- an optional subsitutent to X^4; and

* indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;

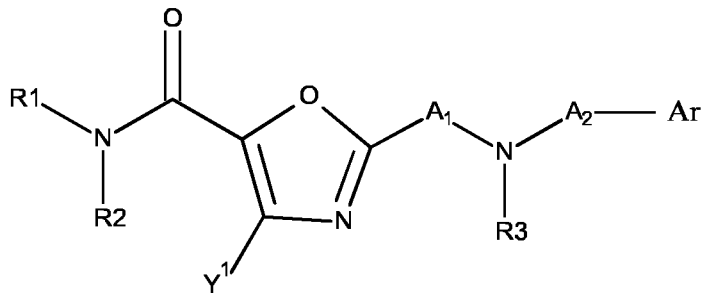
It is particularly preferred that in any of the embodiments described herein the optional further substituents of X^1, X^3 and X^4 are also indicated as Y^1 or correspond to the substituent Y^1 as used herein and are selected from the group consisting of

- halogen, preferably Cl and F, more preferably Cl, and
- optionally substituted alkyl, such as linear or branched C_1-C_3-alkyl, which may be substituted with 1 to 3 halogens or with a methylene-group; such as preferably a methyl-group, an iso-propyl-group, a CF_3-group or a methylene-substituted ethyl-group


, wherein * indicates the binding site.

Further preferred embodiments on the basis of the aforesaid embodiments A-6g and A-6h:
Further preferred embodiment 2a:

A further preferred embodiment of the present invention relates to novel compounds according to the aforesaid embodiment A-6g and the formula (I) as defined above, wherein X is O, forming compounds according to formula (IIa):

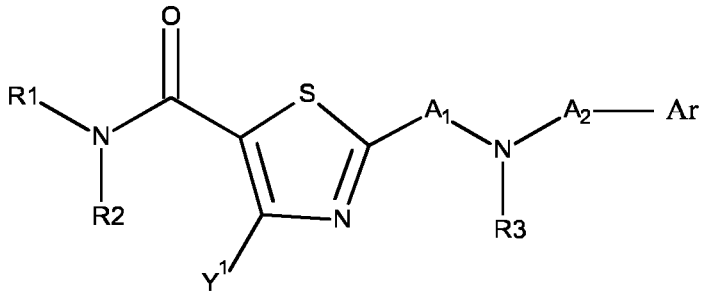


(IIa)

wherein R^1, R^2, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined above; or pharmaceutically acceptable salts thereof.

Further embodiment 2b:

A further preferred embodiment of the present invention relates to novel compounds according to the aforesaid embodiment A-6h and the formula (I) as defined above, wherein X is S , forming compounds according to formula (IIb):

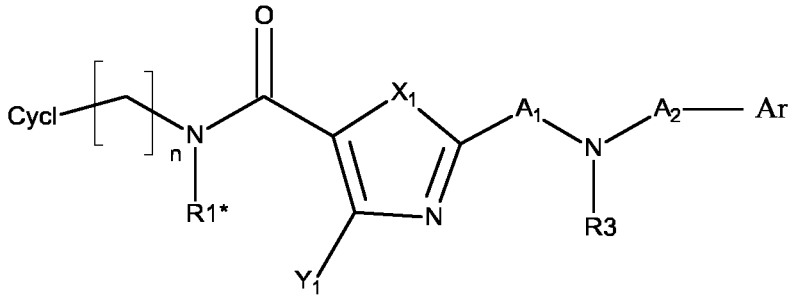


(IIb)

wherein R^1, R^2, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined above for formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Further embodiment 3:

A further preferred embodiment of the present invention relates to any one of the compounds as defined above as embodiment A-6g and A-6h, embodiment 2a and embodiment 2b, wherein at least one of R^1 and R^2 is a linear alkyl group, as defined above, which is substituted with a cyclic group "Cycl", designated as R^{2*}; forming compounds according to formula (III):



(III)

,

wherein "Cycl" is selected from

- optionally substituted aryl, as defined above,
- optionally substituted heteroaryl, as defined above, and
- optionally substituted heterocyclyl, as defined above,

preferably optionally substituted aryl or heteroaryl, as defined above;

n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and

the remaining of R^1 or R^2 (designated as R^{1*}) is selected from

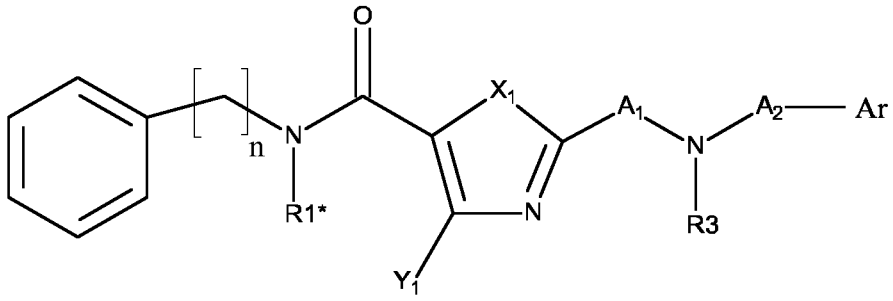
- hydrogen,
- optionally substituted alkyl, as defined above,

preferably hydrogen and optionally substituted alkyl, as defined above; and

X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3a:

Another particularly preferred embodiment (3a) of the present invention relates to compounds as defined herein as embodiment A-6g and A-6h, embodiment 2a, embodiment 2b and embodiment 3 and in particular to compounds according to formula (III) above, wherein at least one of R^1 and R^2 is a linear alkyl group, as defined above, which is substituted with a cyclic group "Cycl", designated as R^{2*}; which is selected from optionally substituted aryl, as defined above, such as in particular an optionally substituted phenyl group forming compounds according to formula (IIIa)



(IIIa)

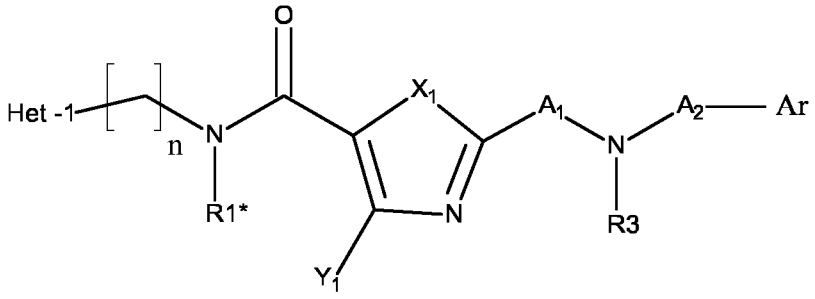
,

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the phenyl-ring may optionally be substituted with 1 to 3, preferably 1 or 2, preferably 1 substituents as defined above, preferably the substituents of the phenyl ring are selected from halogen and hydroxy; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined for formula (I) and as defined in context with embodiment 3 above; and

X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b:

Another preferred embodiment (3b) of the present invention relates to compounds as defined herein as embodiment A-6g and A-6h, embodiment 2a, embodiment 2b, embodiment 3 and embodiment 3a and in particular to compounds according to formula (III) above, wherein at least one of R^1 and R^2 is a linear alkyl group, as defined above, which is substituted with a cyclic group "Cycl" being an optionally substituted heterocyclic group as defined above, "Het-1", forming compounds according to formula (IIIb)



(IIIb)

,

with Het-1 being selected from

- an optionally substituted, optionally fused 5- to 6-membered heteroaryl, as defined above, or
- an optionally substituted 5- or 6-membered aliphatic heterocyclyl, preferably a 6-membered aliphatic heterocyclyl, each as defined above,

wherein the Het-1 group contains 1 or 2 identical or different heteroatoms selected from N, O and S, preferably selected from N and O, more preferably N; and

the Het-1 group may carry 1 to 3, preferably 1 or 2, preferably 1 substituents as defined above, preferably selected from halogen, cyano, optionally substituted alkyl as defined above, optionally substituted alkoxy, a hydroxyl group (-OH), an oxo-group (=O), a carboxyl group [-(C=O)-OH], a heterocyclyl group as defined above, an aminocarbonyl group, an optionally substituted amino group;

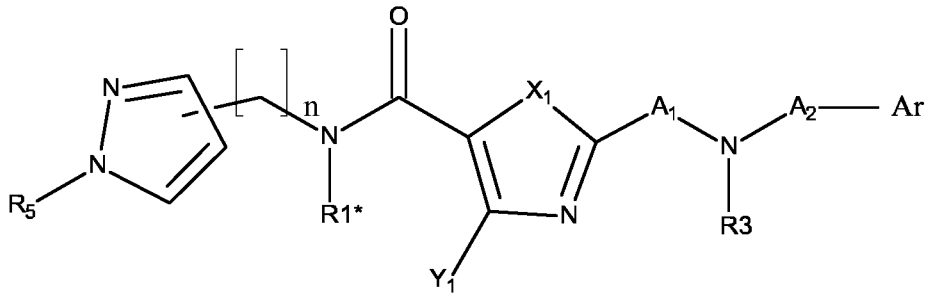
n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and

the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 above and

X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-a:

Another preferred embodiment (3b-a) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from an optionally substituted 5- membered heteroaryl, as defined above, preferably an optionally substituted pyrazolyl, forming for example compounds according to formula (IIIb-a)



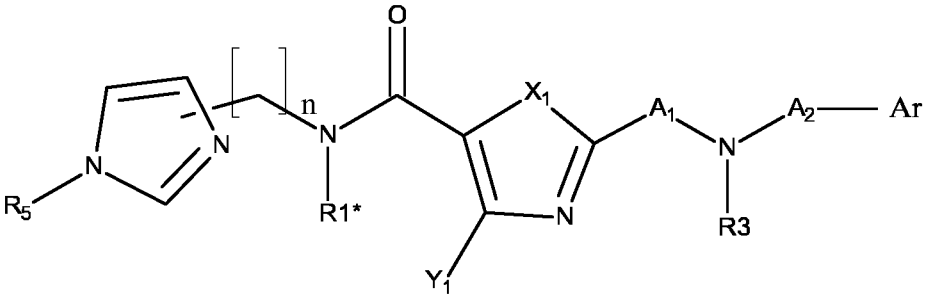
(IIIb-a)

,

wherein R^5 is hydrogen or alkyl as defined above, preferably C_1-C_3-alkyl,
n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and
the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and wherein the pyrazolyl ring may carry 1 or 2 further substituents as defined above; and
X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-b:

Another preferred embodiment (3b-b) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from an optionally substituted 5- membered heteroaryl, as defined above, preferably an optionally substituted imidazolyl, forming for example compounds according to formula (IIIb-b)



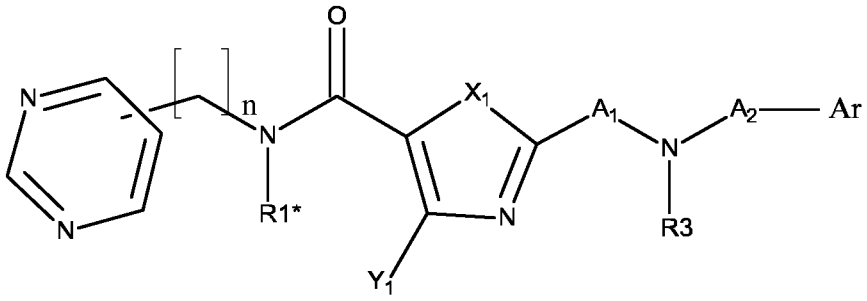
(IIIb-b)

,

wherein R^4 is hydrogen or alkyl as defined above, preferably C_1-C_3-alkyl,
n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and
the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and wherein the imidazolyl ring may carry 1 or 2 further substituents as defined above; and
X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-c:

Another preferred embodiment (3b-c) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from an optionally substituted 6- membered heteroaryl, as defined above, preferably an optionally substituted pyrimidinyl, forming for example compounds according to formula (IIIb-c)

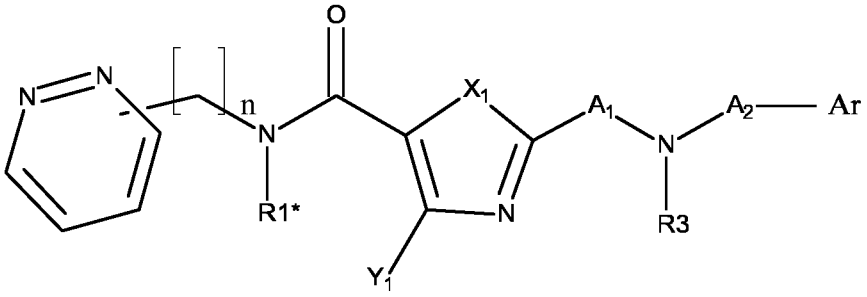


(IIIb-c)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and wherein the pyrimidinyl ring may carry 1 to 3, preferably 1 or 2 further substituents as defined above; and X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-d:

Another preferred embodiment (3b-d) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from an optionally substituted 6- membered heteroaryl, as defined above, preferably an optionally substituted pyridazinyl, forming for example compounds according to formula (IIIb-d)

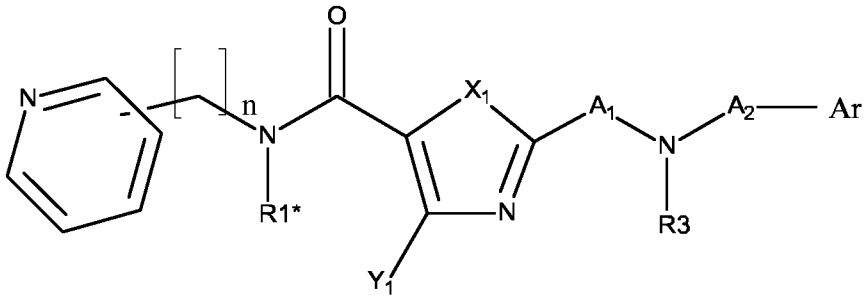


(IIIb-d)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and wherein the pyridazinyl ring may carry 1 to 3, preferably 1 or 2 further substituents as defined above; and X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-e:

Another particularly preferred embodiment (3b-e) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from an optionally substituted 6- membered heteroaryl, as defined above, preferably an optionally substituted pyridinyl, forming for example compounds according to formula (IIIb-e)

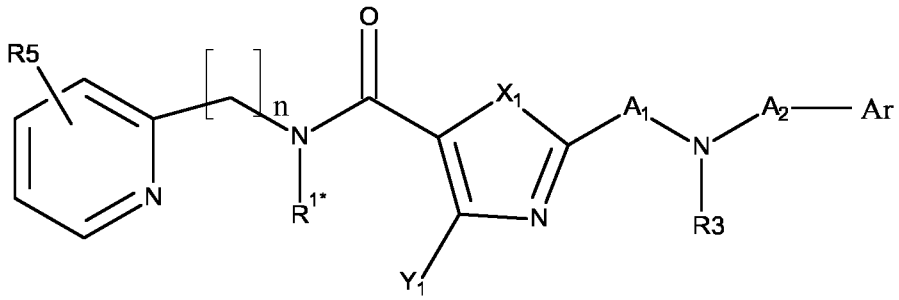


(IIIb-e)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and wherein the pyridinyl ring may carry 1 to 3, preferably 1 or 2 further substituents as defined above; and
X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-f:

Another particularly preferred embodiment (3b-f) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb) above, wherein Het-1 is selected from a substituted pyridinyl, forming compounds according to formula (IIIb-f)



(IIIb-f)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined above, particularly as defined in formula (I) and as defined in context with embodiment 3 and 3b above, and
wherein R^5 indicates 1 to 4, preferably 1 to 3, preferably 1 or 2, more preferably 1 optional substituents, which may idenpendently be selected from

- hydrogen
- halogen, preferably Cl or F, more preferably F,
- optionally substituted alkyl, preferably C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl
- hydroxy, and
- alkoxy, preferably methoxy;

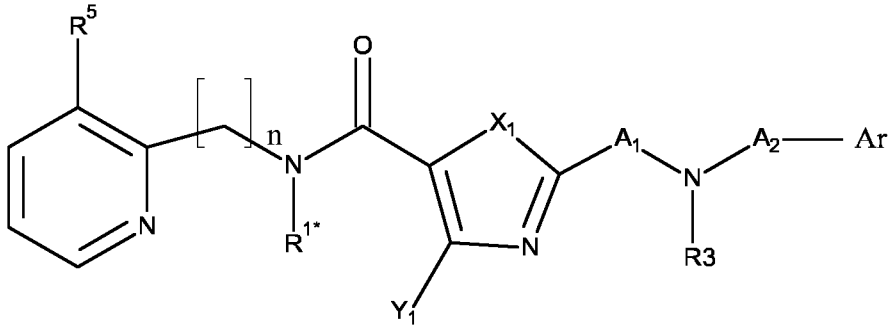
more preferably R^5 indicates 1 to 3, preferably 1 or 2, more preferably 1 substituent, which may idenpendently be selected from

- hydrogen,
- halogen, preferably Cl or F, more preferably F, and
- optionally substituted alkyl, preferably C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl; and

X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein; or pharmaceutically acceptable salts thereof.

Embodiment 3b-g:

Another particularly preferred embodiment (3b-g) of the present invention relates to compounds according to embodiment 3b and according to formula (IIIb), in particular according to embodiment 3b-f and formula (IIIb-f), forming compounds according to formula (IIIb-g)



(IIIb-g)

,

wherein n, the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined for embodiment 3b-f, and wherein R^5 is selected from

- halogen, preferably Cl or F, more preferably F,
- optionally substituted alkyl, preferably C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl
- hydroxy,
- alkoxy, preferably methoxy;

more preferably R^5 is selected from

- halogen, preferably Cl or F, more preferably F, and
- C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl; and

X^1, Y^1, R^3, A^1, A^2 and Ar have the meaning as defined in formula (I) and in any one of the embodiments as described herein, particularly as described in context with embodiment (IIIb-f) above;
or pharmaceutically acceptable salts thereof.

It is further very particularly preferred that in the compounds as defined informula (A-I) and (I) as well as in embodiments A-2, A-3, A-3a, A-3b, A-4a, A-4b, A-4c, A-4d, A-5, A-5a, A-5b, A-6 and A-6a to A-6h and embodiments 3, 3a, 3b, 3b-a, 3b-b, 3b-c, 3b-d, 3b-e, 3b-f and 3b-g the at least one of R^1 and R^2 being a linear, branched or cyclic alkyl group substituted with a cyclic group "Cycl". Such linear, branched or cyclic alkyl group means a linear or branched alkyl group $-[CQ]_n-$ with Q = H or C_1-C_4-alkyl, which is substituted with said cyclic group "Cycl". In particular when one of R^1 and R^2 is a branched alkyl group $-[CQ]_n-$ with Q = C_1-C_4-alkyl, it is possible and preferred that the alkyl-group of Q forms a cyclic alkyl residue in the form of a fused ring with the cyclic group "Cycl". Accordingly said "linear, branched or cyclic alkyl residue (which is substituted with a cyclic group "Cycl") is selected from

- an optionally substituted linear or branched alkanediyl group, as defined above, which is preferably selected from
  - methylene,
  - ethane-1,2-diyl,
  - ethane-1,1-diyl,
  - propane-1,3-diyl,
  - propane-1,1-diyl,
  - propane-1,2-diyl, and
  - propane-2,2-diyl; or
- (in particular with Q being a C_1-C_4-alkyl forming) an optionally substituted cycloalkyl group, as defined above, which is preferably selected from

- cyclopropane and
- cyclohexane;

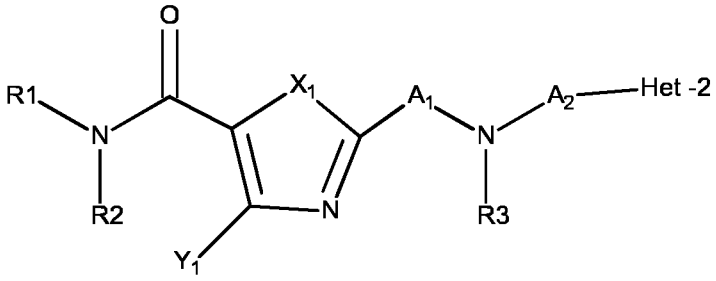
which in a further preferred embodiment may preferably form a fused bicyclic ring with Cycl being a Het-1 group selected from a 6-membered heteroaryl as defined above.

More preferred is an optionally substituted linear or branched alkanediyl residue, as defined above. Even more preferably such optionally substituted alkanediyl residue is selected from the group consisting of methylene, ethane-1,2-diyl, ethane-1,1-diyl and propane-2,2-diyl; more preferably methylene or ethane-1,2-diyl; most preferred is methylene.

In each of the above mentioned embodiments A-2, A-3, A-3a, A-3b, A-4a, A-4b, A-4c, A-4d, A-5, A-5a, A-5b, A-6 and A-6a to A-6h and embodiments 3, 3a, 3b, 3b-a, 3b-b, 3b-c, 3b-d, 3b-e, 3b-f and 3b-g the remaining of R^1 or R^2, designated as R^{1*}, X^1, Y^1, R^3, A^1, A^2 and Ar may have the meaning as defined in in formula (A-I) or (I) and as defined context with any one of the embodiments described herein, in particular as defined in context with embodiment 2 above, and 4, 4a, 4b, 4c and 4d below.

Further embodiment 4:

A further embodiment of the present invention relates to any one of the compounds as defined above, such as in particular compounds of embodiment A-6g and A-6h and further embodiments on the basis thereof as defined above, wherein Ar is an optionally substituted mono- or bicyclic heteroaryl, as defined above, "Het-2", forming compounds according to formula (IV)



(IV)

,

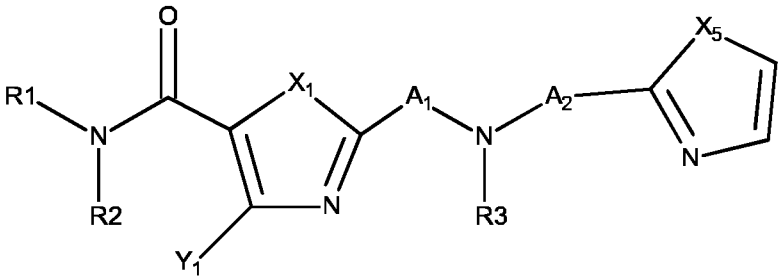
with Het-2 being selected from

- an optionally substituted 5- or 6-membered monocyclic heteroaryl, as defined above, and
- an optionally substituted bicyclic heteroaryl, as defined above, which may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded;

or pharmaceutically acceptable salts thereof.

Embodiment 4a:

Another embodiment (4a) relates to compounds as defined herein, such as in particular compounds of embodiment A-6g and A-6h and further embodiments on the basis thereof as defined above and in particular to compounds according to formula (IV) above, wherein Ar being an optionally substituted mono- or bicyclic heteroaryl "Het-2" is selected from an optionally substituted 5-membered monocyclic heteroaryl, as defined above, forming for example compounds according to formula (IVa)



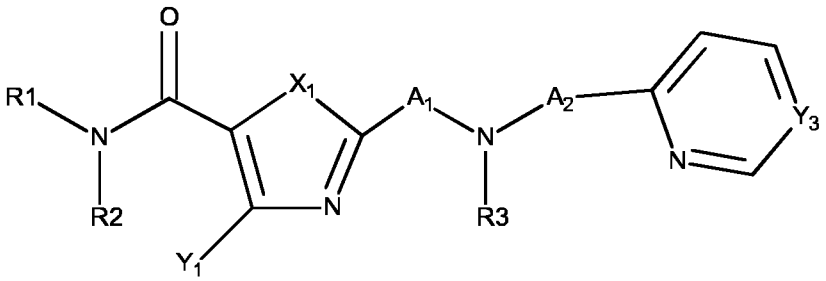
(IVa)

,

wherein X^5 is S or N-R^7 with R^7 having the meaning as defined above for R^5, in particular as R^5 in embodiments 3b-a and 3b-b, and wherein the 5-membered heteroaryl ring of Het-2 may carry 1 to 3 further substituents, preferably 1 or 2 further substituents, more preferably 1 further substituent, as defined above; or pharmaceutically acceptable salts thereof.

Embodiment 4b:

Another embodiment (4b) relates to compounds as defined herein, such as in particular compounds of embodiment A-6g and A-6h and further embodiments on the basis thereof as defined above and in particular to compounds according to formula (IV) above, wherein Ar being an optionally substituted mono- or bicyclic heteroaryl "Het-2" is selected from an optionally substituted 6-membered monocyclic heteroaryl, as defined above, forming for example compounds according to formula(IVb)

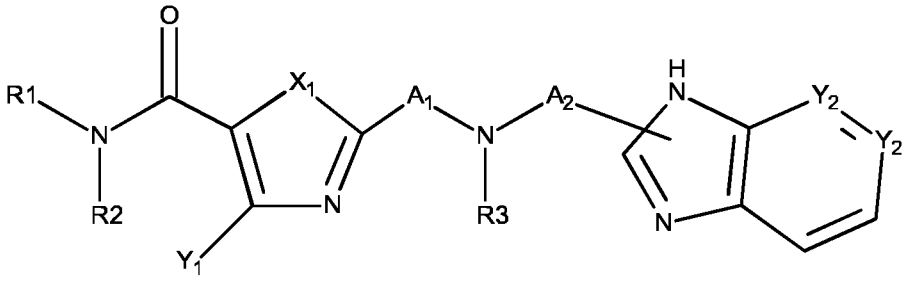


(IVb)

wherein Y^3 is C or N, and wherein the 6-membered heteroaryl ring of Het-2 may carry 1 to 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, as defined above; or pharmaceutically acceptable salts thereof.

Embodiment 4c:

Another embodiment (4c) relates to compounds as defined herein, such as in particular compounds of embodiment A-6g and A-6h and further embodiments on the basis thereof as defined above and in particular to compounds according to formula (IV) above, wherein Ar being an optionally substituted mono- or bicyclic heteroaryl "Het-2" is selected from an optionally substituted bicyclic heteroaryl, as defined above, forming for example compounds according to formula (IVc)



(IVc)

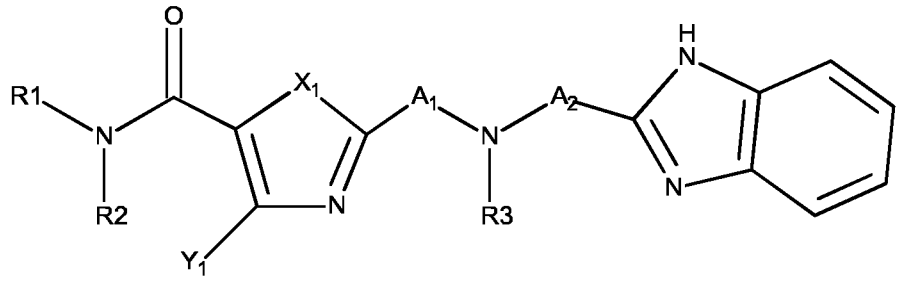
with

- both Y^2 being C or
- one Y^2 being N and one Y^2 being C, and

wherein the bicyclic heteroaryl ring of Het-2 may carry 1 to 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, as defined above, and wherein the optionally substituted bicyclic heteroaryl ring of Het-2 may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded; or pharmaceutically acceptable salts thereof.

Embodiment 4d:

Another embodiment (4d) relates to compounds as defined herein, such as in particular compounds of embodiment A-6g and A-6h and further embodiments on the basis thereof as defined above and in particular to compounds according to formula (IV) and (IVc) above, wherein Ar being an optionally substituted mono- or bicyclic heteroaryl "Het-2" is selected from an optionally substituted bicyclic heteroaryl, which is selected from benzimidazolyl, as defined above, forming compounds according to formula (IVd)



(IVd)

,

wherein the benzimidazolyl ring of Het-2 may carry 1 to 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, as defined above, and

wherein the benzimidazolyl ring of Het-2 may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded;

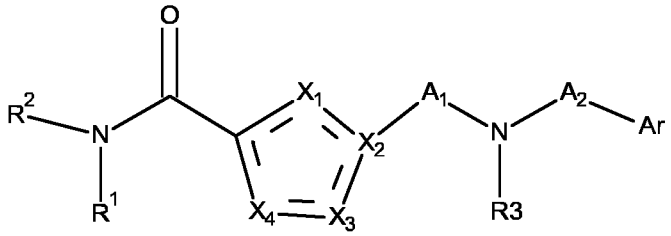
or pharmaceutically acceptable salts thereof.

In each of the above mentioned embodiments 4, 4a, 4b, 4c and 4d the remaining substituents R^1, R^2, X^1, Y^1, R^3, A^1 and A^2 may have the meaning as defined in formula (I) and as defined in context with any one of the embodiments described herein, in particular as defined inin formula (I) and in context with embodiment 2 above, and embodiments 3, 3a, 3b, 3b-a, 3b-b, 3b-c, 3b-d, 3b-e, 3b-f and 3b-g above.

Further Embodiments:

Further embodiment B-2a:

A particularly preferred embodiment (B-2a) relates to compounds of the formula (B-IIa)



(B-IIa)

wherein 1 to 3 heteroatoms X (X^1, X^2, X^3 and/or X^4) are present, wherein X^1 to X^4 may be the same or different and are independently selected from the group consisting of C, N,S and O. Preferably in formula (B-IIa) 1 to 3 heteroatoms X are present, wherein

X^1 is C, N, S or O;

X^2 is C or N;

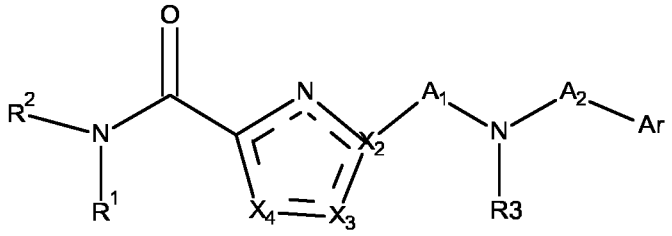
X^3 is C, N, S or O; and

X^4 is C, N, S or O, preferably X^4 is C, N or S,

and wherein X^1, X^3 and X^4 with the meaning of C or N may carry a further substituent.

Embodiment B-2a-a:

Another particularly preferred embodiment (B-2a-a) relates to compounds according to formula (B-IIa) above, wherein X^1 is N, forming a compound of the formula (B-IIa-a)



(B-IIa-a)

wherein one or two further heteroatoms X (X^2, X^3, X^4) are present, and wherein

X^2 is C or N;

X^3 is C, N, S or O; and

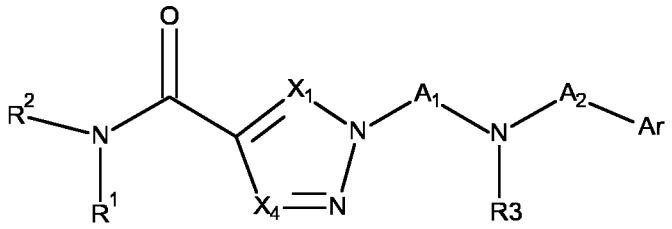
X^4 is C or N;

with the proviso that in case of two further heteroatoms both are selected to be N or one is N and one (except X^2) is O; and

wherein X^3 and X^4 with the meaning of C or N may carry a further substituent, such as preferably hydrogen or a substituent as defined above for substituted heteroaryl.

Embodiment B-2a-b:

Another particularly preferred embodiment (B-2a-b) relates to compounds according to formula (B-IIa) above, wherein X^2 and X^3 are both N, forming a compound of the formula (B-IIa-b)

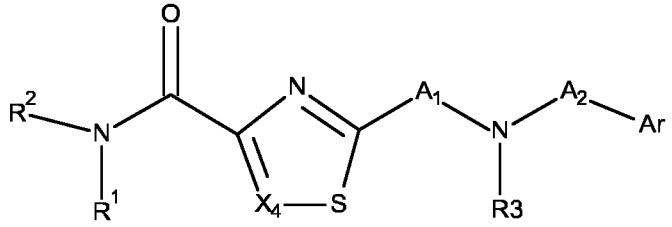


(B-IIa-b)

with X^1 and X^4 being C; and wherein X^1 and/or X^4 may carry hydrogen or a further substituent, such as preferably a substituent as defined above for substituted heteroaryl.

Embodiment B-2a-c:

Another particularly preferred embodiment (B-2a-c) relates to compounds according to formula (B-IIa) or (B-IIa-a) above, wherein X^1 is N, X^2 is C and X^3 is S, forming a compound of the formula (B-IIa-c)

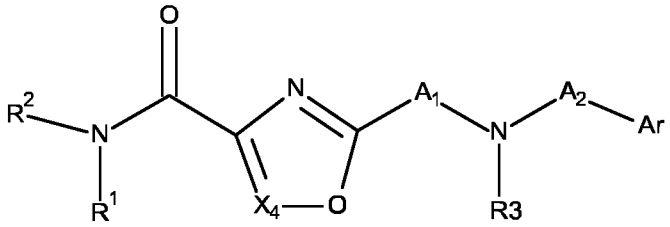


(B-IIa-c)

wherein X^4 is C or N, preferably C, which may carry a further substituent, such as preferably hydrogen or a substituent as defined above for substituted heteroaryl.

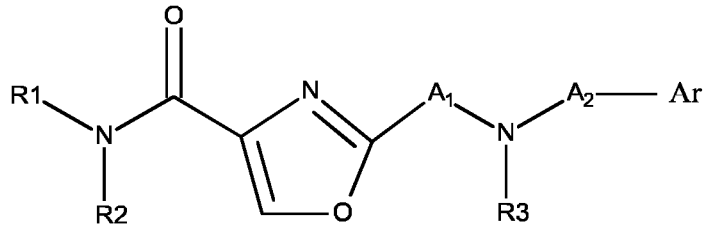
Embodiment B-2a-d:

Another particularly preferred embodiment (B-2a-d) relates to compounds according to formula (B-IIa) or (B-IIa-a) above, wherein X^1 is N, X^2 is C and X^3 is O, forming a compound of the formula (IIa-d)



(B-IIa-d)

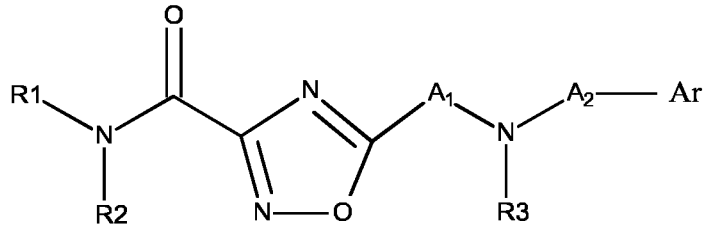
wherein X^4 is C or N, and which may carry a further substituent, such as preferably hydrogen or a substituent as defined above for substituted heteroaryl; forming compounds according to formula (B-IIa-d-1)



(B-IIa-d-1)

wherein X^4 being C may carry hydrogen or a further substituent, and which is preferred; or

forming compounds according to formula (B-IIa-d-2)

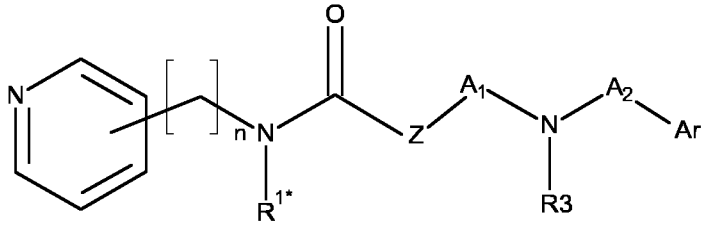


(B-IIa-d-2)

wherein X^4 being N may carry a further substituent.

Embodiment B-3b-e:

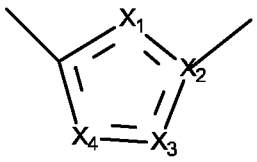
Another particularly preferred embodiment (B-3b-e) of the present invention relates to compounds according to formula (B-IIIb-e)



(B-IIIb-e)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined in the embodiments above, particularly as defined for formula (I), and wherein the pyridinyl ring may carry 1 to 3, preferably 1 or 2 further substituents as defined above, and

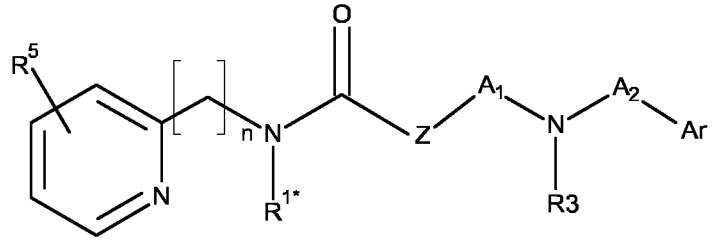
R^3, A^1, A^2 and Ar have the meaning as defined in context with any one of the embodiments described herein, and wherein Z has the meaning of a heterocyclic 5-membered ring as defined in formula (A-I)



and as defined in any one of the embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h, preferably as defined in formula (A-I) and in embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d.

Embodiment B-3b-f:

Another particularly preferred embodiment (B-3b-f) of the present invention relates to compounds according to formula (B-IIIb-f)



(B-IIIb-f)

wherein n is an integer of 1 to 8, preferably 1 to 4, preferably 1 to 3 such as 1, 2 or 3, more preferred 1; and the remaining R^1 or R^2 (designated as R^{1*}) has the meaning as defined in the embodiments above, particularly as defined for formula (I), and

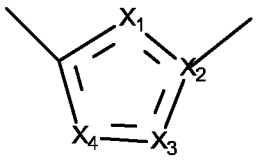
wherein R^5 indicates 1 to 4, preferably 1 to 3, preferably 1 or 2, more preferably 1 optional substituents, which may idenpendently be selected from

- halogen, preferably Cl or F, more preferably F,
- optionally substituted alkyl, preferably C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl
- hydroxy,
- alkoxy, preferably methoxy;

preferably R^5 is selected from

- halogen, preferably Cl or F, more preferably F, and
- C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl; and

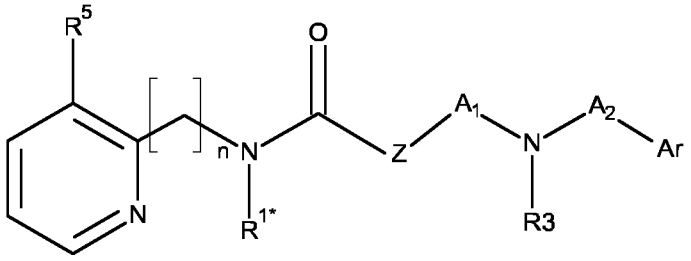
R^3, A^1, A^2 and Ar have the meaning as defined in context with any one of the embodiments described herein, and wherein Z has the meaning of a heterocyclic 5-membered ring as defined in formula (A-I)



and as defined in any one of the embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h, preferably as defined in formula (A-I) and in embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d.

Embodiment B-3b-g:

Another very particularly preferred embodiment (B-3b-g) of the present invention relates to compounds according to formula (B-IIIb-g)



(B-IIIb-g)

,

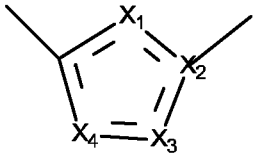
wherein n and the remaining of R^1 or R^2 (designated as R^{1*}) has the meaning as defined for embodiment B-3b-f, and wherein R^5 is selected from

- halogen, preferably Cl or F, more preferably F,
- optionally substituted alkyl, preferably C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl
- hydroxy,
- alkoxy, preferably methoxy;

more preferably R^5 is selected from

- halogen, preferably Cl or F, more preferably F, and
- C_1-C_3-alkyl, such as preferably methyl, or trifluoromethyl; and

R^3, A^1, A^2 and Ar have the meaning as defined in context with any one of the embodiments described herein, and wherein Z has the meaning of a heterocyclic 5-membered ring as defined in formula (A-I)



and as defined in any one of the embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h, preferably as defined in formula (A-I) and in embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d.

It is further very particularly preferred that in the compounds according to formula (A-I) and as defined in embodiments A-2, A-3, A-3a, A-3b, A-4a, A-4b, A-4c, A-4d, A-5, A-5a, A-5b, A-6 and A-6a to A-6h and in embodiments B-3b-e, B-3b-f and B-3b-g the at least one of R^1 and R^2 being a linear, branched or cyclic alkyl group substituted with a cyclic group "Cycl", including the group $-[CQ]_n-$ with Q = H or C_1-C_4-alkyl, the resulting alkyl-residue is

- an optionally substituted linear or branched alkanediyl group, as defined above, which is preferably selected from
  - methylene,
  - ethane-1,2-diyl,
  - ethane-1,1-diyl,
  - propane-1,3-diyl,
  - propane-1,1-diyl,
  - propane-1,2-diyl, and
  - propane-2,2-diyl; or
- (in particular with Q being a C_1-C_4-alkyl forming) an optionally substituted cycloalkyl group, as defined above, which is preferably selected from
  - cyclopropane and
  - cyclohexane;

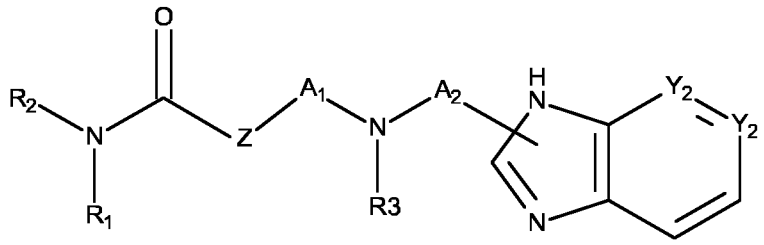
which in a further preferred embodiment may preferably form a fused bicyclic ring withCycl being a 6-membered heteroaryl as defined above.

More preferred is an optionally substituted alkanediyl residue, as defined above. Even more preferably such optionally substituted alkanediyl residue is selected from the group consisting of methylene, ethane-1,2-diyl, ethane-1,1-diyl and propane-2,2-diyl; more preferably methylene or ethane-1,2-diyl; most preferred is methylene.

In each of the above mentioned embodiments B-3b-e, B-3b-f and B-3b-g the remaining of R^1 or R^2, designated as R^{1*}, Z, R^3, A^1, A^2 and Ar may have the meaning as defined in context with any one of the embodiments described herein.

Embodiment B-4c:

Another particularly preferred embodiment (B-4c) relates to compounds as defined herein and in particular to compounds according to formula (B-IVc)



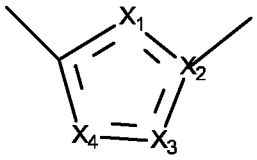
(B-IVc)

with

- both Y^2 being C or
- one Y^2 being N and one Y^2 being C, and

wherein the bicyclic heteroaryl ring may carry 1 to 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, as defined above (e.g. as defined for R^4 above), and wherein the optionally substituted bicyclic heteroaryl ring may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded.

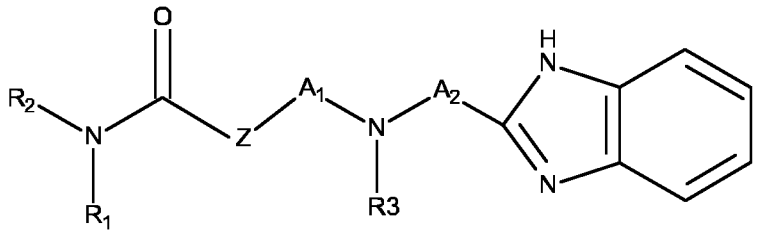
Z has the meaning of a heterocyclic 5-membered ring as defined in formula (A-I)



and as defined in any one of the embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h, preferably as defined in formula (A-I) and in embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d.

Embodiment B-4d:

Another very particularly preferred embodiment (B-4d) relates to compounds as defined herein and in particular to compounds according (B-IVc) above, with the optionally substituted bicyclic heteroaryl being a benzimidazolyl, as defined above, forming compounds according to formula (B-IVd)



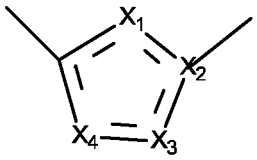
(B-IVd)

,

wherein the benzimidazolyl ring may carry 1 to 3 substituents, preferably 1 or 2 substituents, more preferably 1 substituent, as defined above (e.g. as defined for R^4 above), and

wherein the benzimidazolyl ring may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded, and

Z has the meaning of a heterocyclic 5-membered ring as defined in formula (A-I)



and as defined in any one of the embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h, preferably as defined in formula (A-I) and in embodiments A-6a, A-6b, A-6b-1, A-6b-2, A-6c, A-6d.

In each of the above mentioned embodiments B-4c and B-4d the remaining substituents R^1, R^2, Z, R^3, A^1 and A^2 may have the meaning as defined in context with any one of the embodiments described herein, in particular as defined in context with embodiments B-2a, B-2a-a, B-2a-b, B-2a-c and B-2a-d, as well as B-3b-e, B-3b-f and B-3b-g above.

It is further very particularly preferred that in the compounds according to the present invention, such as in particular in the compounds as defined in formula (A-I) and (I) and in embodiments A-2, A-3, A-3a, A-3b, A-4a, A-4b, A-4c, A-4d, A-5, A-5a, A-5b, A-6 and A-6a to A-6h and embodiments 2, 3, 3a, 3b, 3b-a, 3b-b, 3b-c, 3b-d, 3b-e, 3b-f, 3b-g and 4, 4a, 4b, 4c and 4d as well as B-2a, B-2a-a, B-2a-b, B-2a-c, B-2a-d, B-3b-e, B-3b-f, B-3b-g, B-4c and B-4d above, A^1 and A^2 each are optionally substituted alkanediyl, as defined above, and are the same or different and are independently selected from optionally substituted

- methylene and
- ethane-1,2-diyl, or
- A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring, preferably a 4- or 6-membered mono- or bicyclic ring, more preferably a 4-membered ring, as defined above. Therein, more preferably
- A^1 and A^2 are identical and are methylene,
- A^1 and A^2 are identical and are ethane-1,2-diyl,
- A^1 is methylene and A^2 is ethane-1,2-diyl,
- A^1 is ethane-1,2-diyl and A^2 is methylene,
- A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered aliphatic mono- or bicyclic ring, preferably a 4-membered ring, and A^2 is methylene, or
- A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered aliphatic mono- or bicyclic ring, preferably a 4-membered ring, and A^2 is ethane-1,2-diyl; more preferably
- A^1 and A^2 are identical and are ethane-1,2-diyl,

- A^1 is ethane-1,2-diyl and A^2 is methylene or
- A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered monocyclic ring, and A^2 is ethane-1,2-diyl; even more preferably
- A^1 and A^2 are identical and are ethane-1,2-diyl, or
- A^1 is ethane-1,2-diyl and A^2 is methylene.

In further preferred embodiments of compounds according to the present invention, the individual substituents have the following definitions in each case:

1. a) X^1 has the meaning of O, X^3 has the meaning of N and X^2 and X^4 have the meaning of C and/or
   b) X^1 has the meaning of N, X^3 has the meaning of O and X^2 and X^4 have the meaning of C and/or
   c) X^1 has the meaning of N, X^3 has the meaning of S and X^2 and X^4 have the meaning of C and/or
   d) X^2 and X^4 have the meaning of N and one of X^1 and X^3 has the meaning of N and the remaining has the meaning of C and/or
   e) X^1 and X^4 have the meaning of N, X^2 has the meaning of C and X^3 has the meaning of O;
   particularly preferred is a heterocyclic 5-membered ring selected from oxazolyl, thiazolyl, pyrazolyl, triazoly, oxadiazolyl as well as isooxazolyl and isothiazolyl as defined in embodiments A-6b, A-6b-1, A-6b-2, A-6c, A-6d, A-6e, A-6f, A-6g and A-6h.
2. Y^1 has the meaning of hydrogen, optionally substituted alkyl, as defined above, preferably C_1, C_2 or C_3-alkyl, as defined above, more preferably methyl.
3. n is 1
4. Q is H
5. Cycl is a group of the formula



, wherein * indicates the binding site.

6. One of R^1 and R^2 is designated as R^{1*} and is hydrogen and one of R^1 or R^2 is designated as R^{2*} and is selected from hydrogen, and optionally substituted alkyl, as defined above, preferably aryl-substituted alkyl and heteroaryl-substituted alkyl, wherein the aryl and heteroaryl substituent each may carry 1 to 3 substituents, as defined above. Particularly preferred is that the at least one of R^1 or R^2 which is designated as R^{2*} is optionally substituted aryl-methyl or optionally substituted heteroaryl-methyl, most preferred is optionally substituted heteroaryl-methyl and substituted phenyl.
7. A^1 and A^2 are optionally substituted alkanediyl and are the same or different and are independently selected from
   - A^1 and A^2 are identical and are methylene,
   - A^1 and A^2 are identical and are ethane-1,2-diyl,
   - A^1 is methylene and A^2 is ethane-1,2-diyl,
   - A^1 is ethane-1,2-diyl and A^2 is methylene,
   - A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered monocyclic ring, and A^2 is methylene, or
   - A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4-membered monocyclic ring, and A^2 is ethane-1,2-diyl.

   Particularly preferred is that A^1 is methylene or ethane-1,2-diyl and A^2 is ethane-1,2-diyl, or that A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4-membered monocyclic ring and A^2 is ethane-1,2-diyl.

8. R^3 is hydrogen or optionally substituted alkyl, as defined above, or A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered monocyclic ring, preferably hydrogen.
9. Ar may be Het-1 as defined above, and is preferably optionally substituted mono- or bicyclic heteroaryl, as defined above, preferably optionally substituted benzimidazolyl as defined above.

In a further preferred embodiment R^1 and R^2 are different, with one being hydrogen and the other one being an optionally substituted alkyl. More preferably, one of R^1 and R^2 is hydrogen and the other one is an alkyl residue, which is substituted with

- an optionally substituted aryl group as defined above, preferably with an optionally substituted phenyl group as defined above, or
- with an optionally substituted heteroaryl group as defined above, preferably with
  - an optionally substituted pyridinyl group,
  - an optionally substituted pyridazinyl group,
  - an optionally substituted pyrimidinyl group,
  - an optionally substituted pyrazolyl group,
  - an optionally substituted imidazolyl group.

Even more preferably, one of R^1 and R^2 is hydrogen and the other one is an alkyl residue, which is substituted with

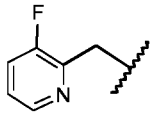
- an optionally substituted phenyl group,
- an optionally substituted pyridinyl group,
- an optionally substituted pyridazinyl group,
- an optionally substituted pyrimidinyl group,

Still more preferably, one of R^1 and R^2 is hydrogen and the other one is an alkyl residue, which is substituted with

- an optionally substituted phenyl group, preferably a substituted phenyl group as defined above, or
- an optionally substituted pyridinyl group,

wherein the optionally substituted pyridinyl group as a substituent of an alkyl residue for one of R^1 and R^2 is most preferred.

More preferably a halogen substituted pyridinyl group such as in particular a pyridinyl group substituted with one fluorine substituent is selected, such as in particular a group according to formula



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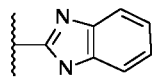
It is further preferred that in the embodiments as defined above Ar has the meaning of a bicyclic heteroaryl, such as in particular benzimidazol, particularly benzimidazol-2-yl according to formula



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It is further preferred that herein A^1 and A^2 each are optionally substituted alkanediyl, as defined above, such as very preferably with A^1 and A^2 being identical and methylene, or A^1 and A^2 being identical and ethane-1,2-diyl, or A^1 being methylene and A^2 being ethane-1,2-diyl, or A^1 being ethane-1,2-diyl and A^2 being methylene, more preferably with A^1 and A^2 being identical and ethane-1,2-diyl, or with A^1 being ethane-1,2-diyl and A^2 being methylene, or wherein A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered monocyclic ring, and A^2 is ethane-1,2-diyl.

Particularly preferably the compounds according to the present inventionare selected from the compounds:

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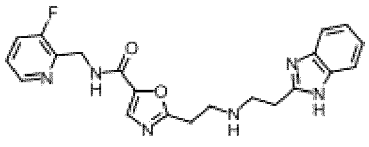
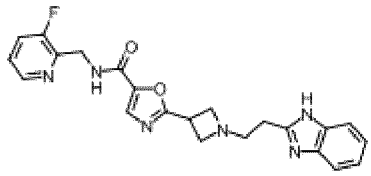
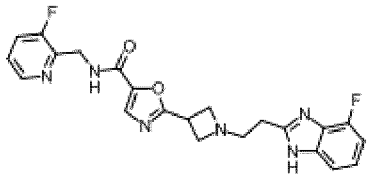
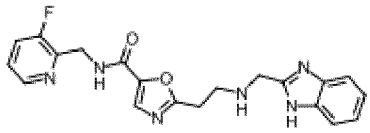
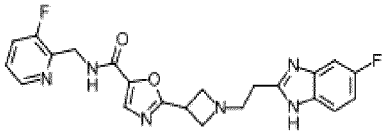
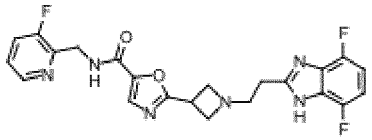
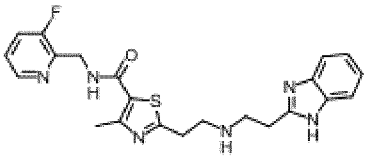
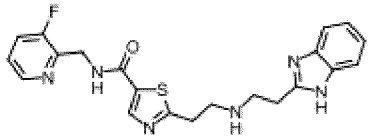
1		2	
3		4	
5		6	
7		8	

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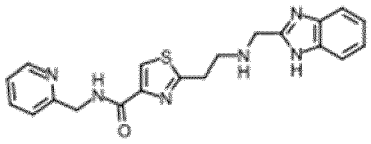
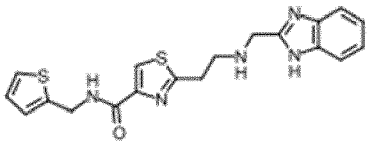
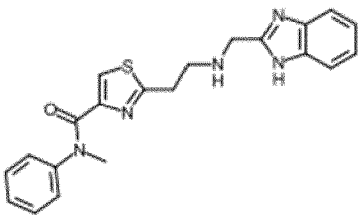
12	
16	
19	

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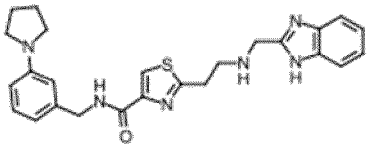
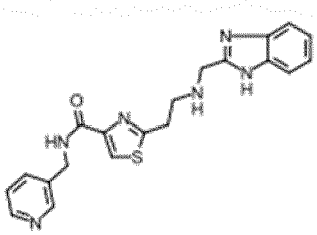
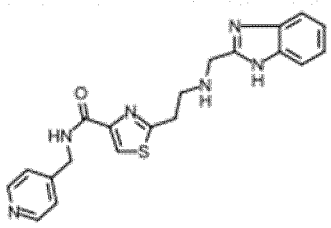
21	
35	
36	

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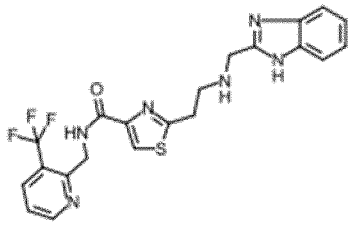
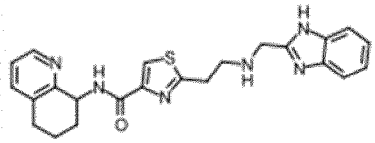
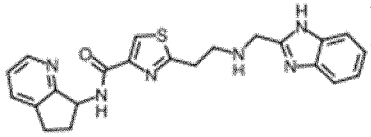
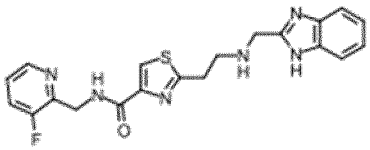
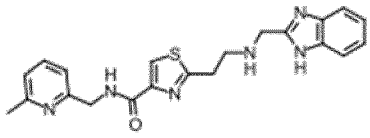
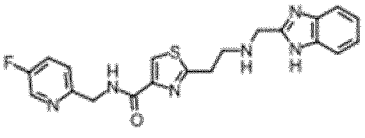
37	
38	
39	
40	
42	
43	

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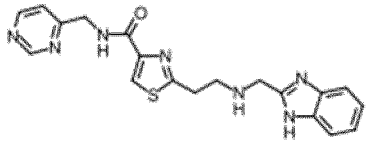
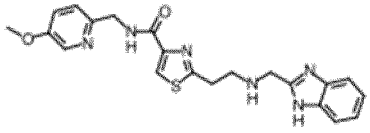
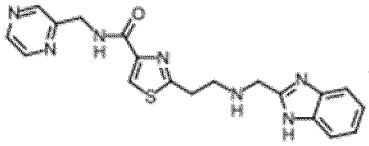
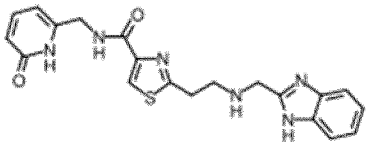
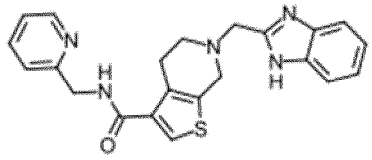
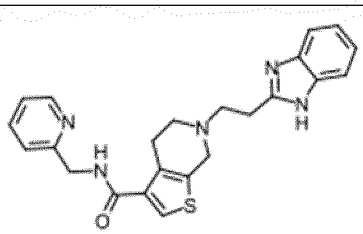
44	
45	
46	
47	
48	
49	

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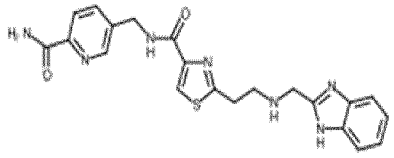
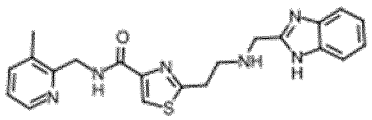
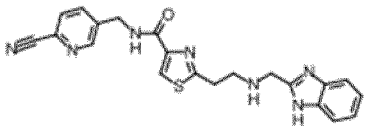
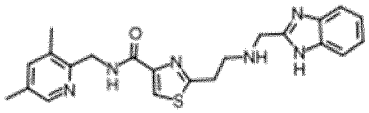
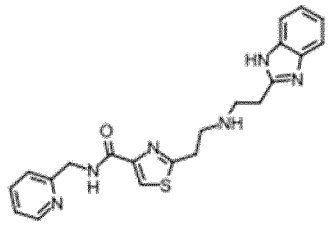
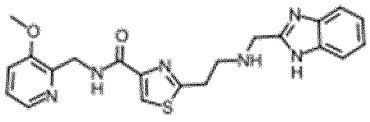
54	
55	
56	
57	
58	
59	

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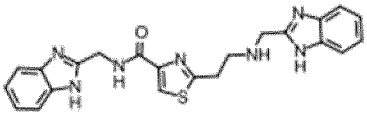
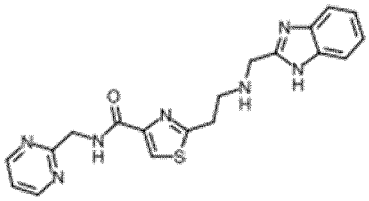
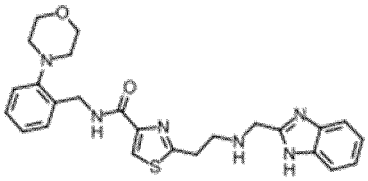
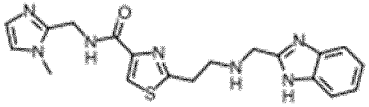
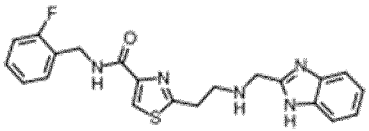
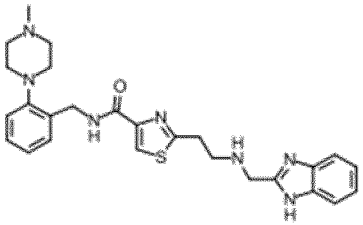
60	
61	
63	
64	
65	
68	

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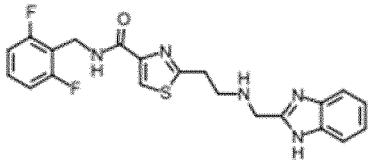
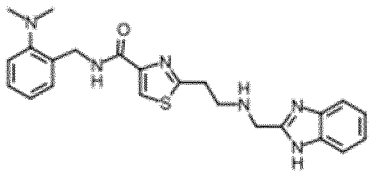
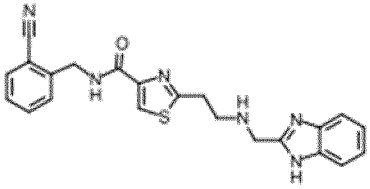
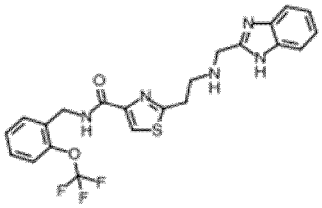
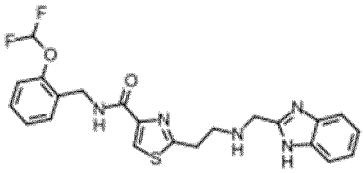
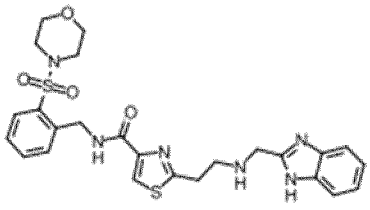
69	
70	
71	
72	
74	
75	

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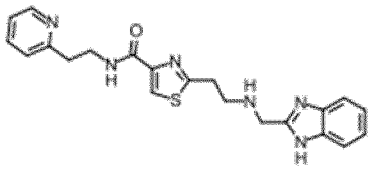
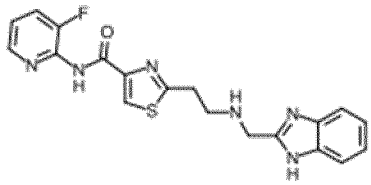
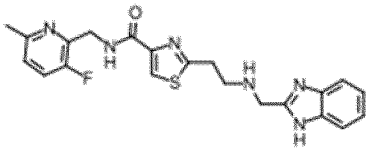
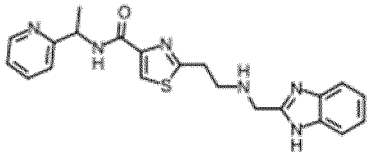
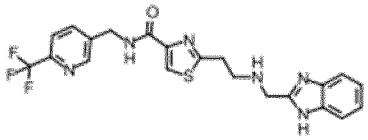
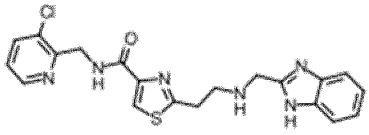
76	
77	
79	
80	
81	
82	

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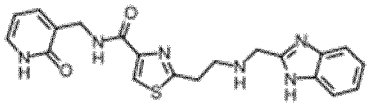
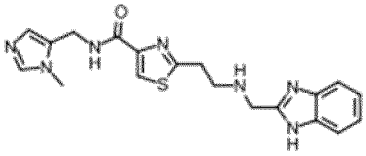
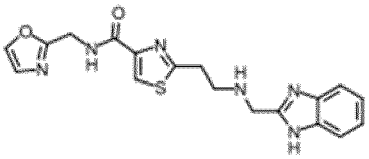
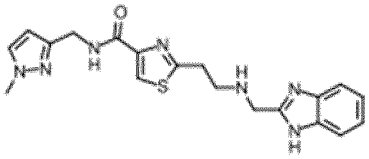
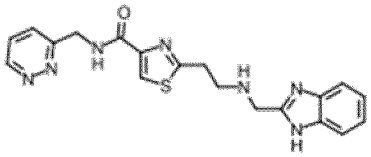
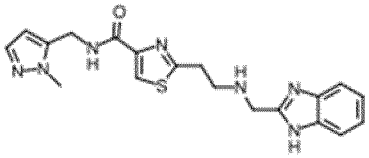
83	
84	
85	
86	
87	
88	

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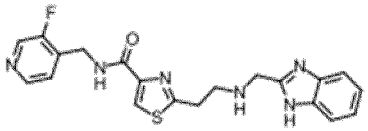
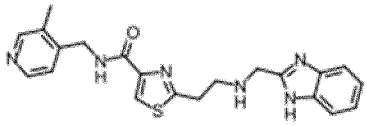
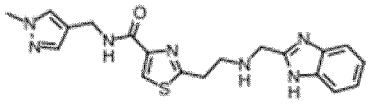
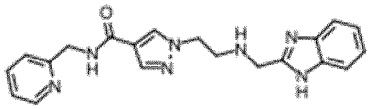
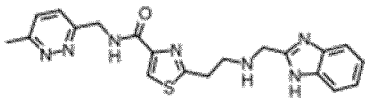
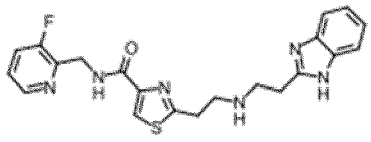
89	
90	
91	
92	
93	
94	

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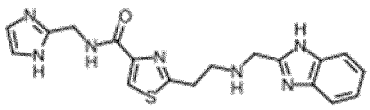
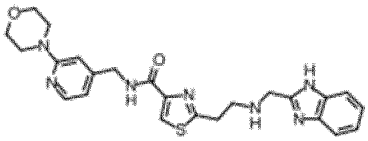
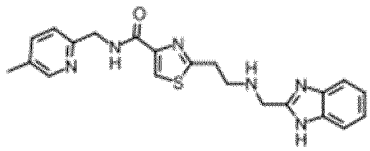
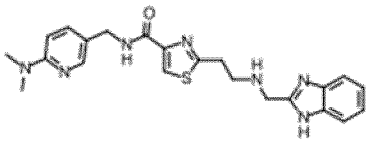
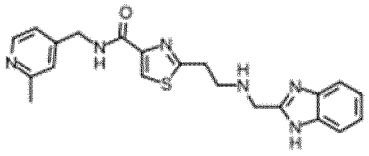
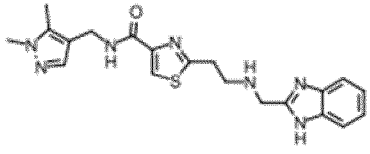
95	
96	
97	
98	
99	
100	

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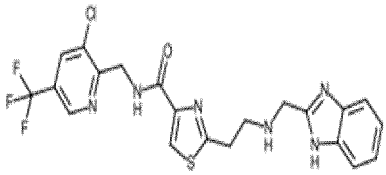
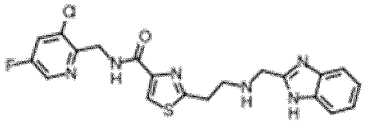
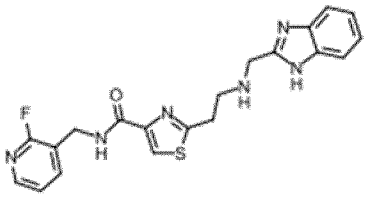
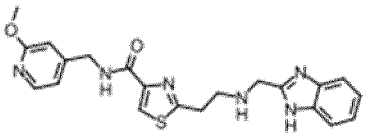
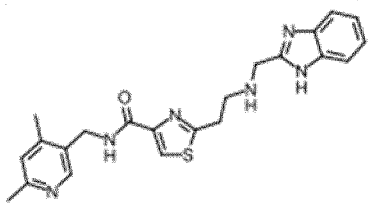
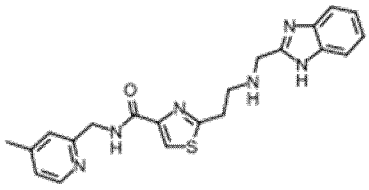
101	
102	
103	
104	
105	
106	

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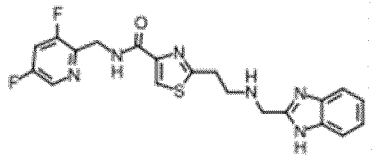
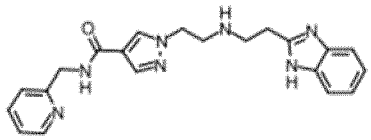
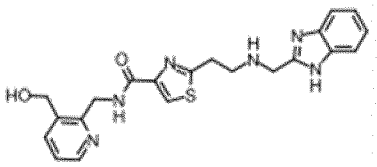
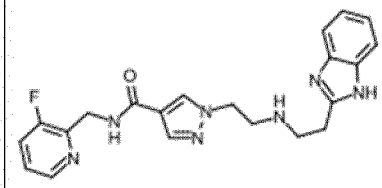
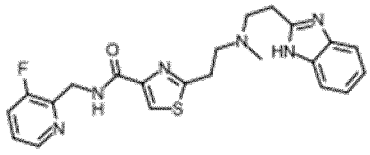
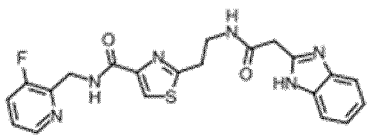
108	
109	
110	
111	
112	
113	

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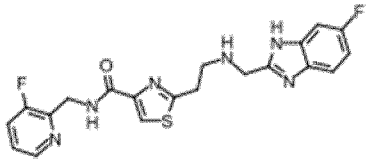
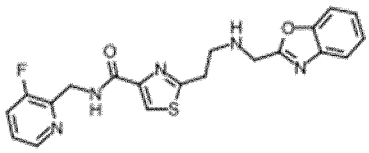
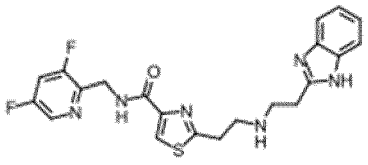
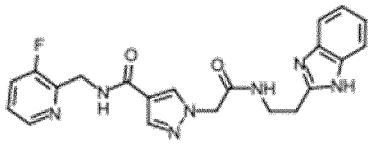
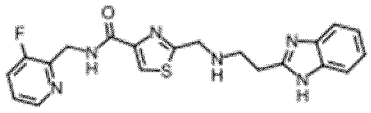
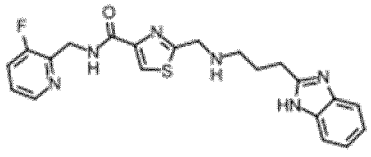
114	
115	
116	
117	
118	
119	

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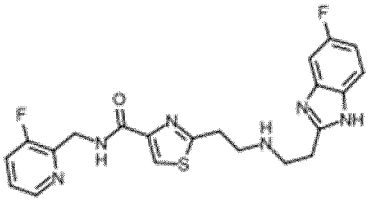
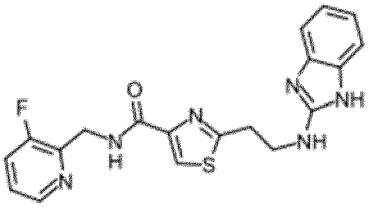
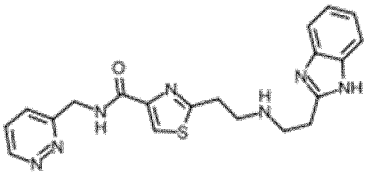
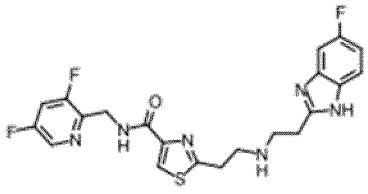
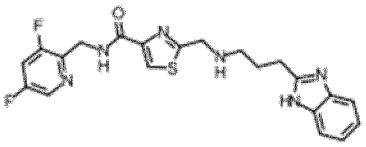
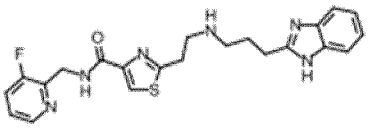
120	
121	
122	
123	
124	
125	

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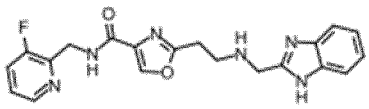
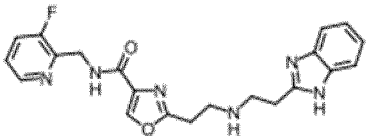
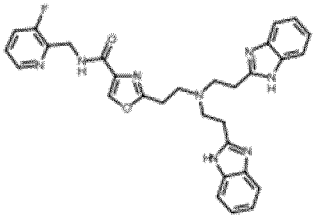
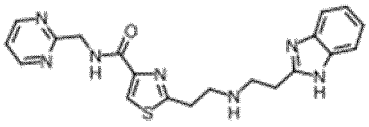
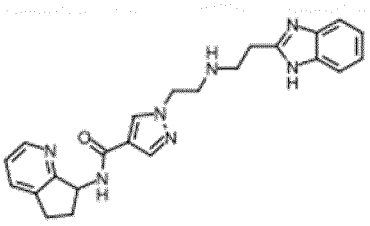
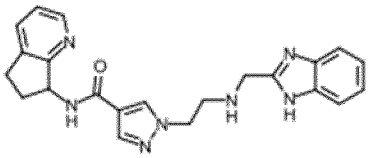
126	
127	
128	
129	
131	
132	

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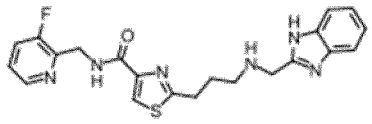
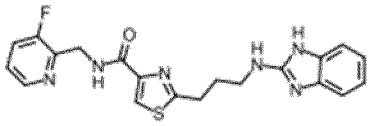
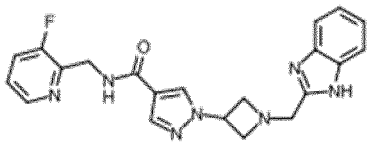
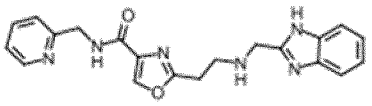
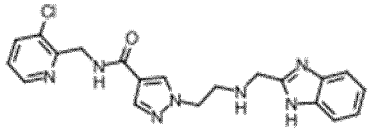
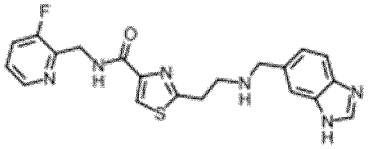
134	
135	
136	
137	
138	
139	

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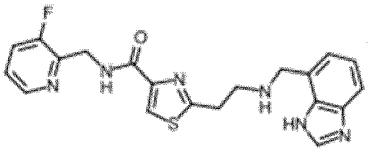
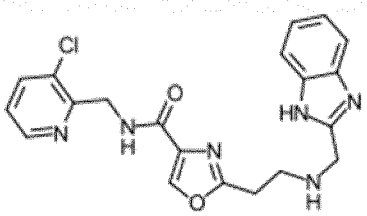
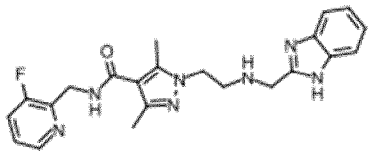
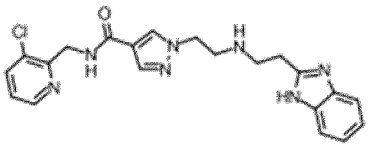
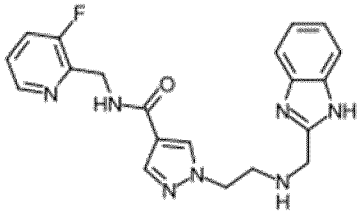
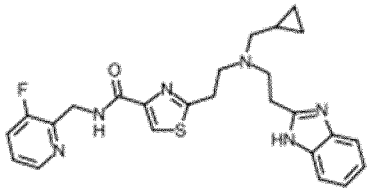
140	
141	
142	
144	
145	
148	

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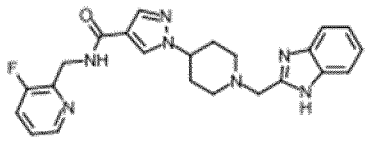
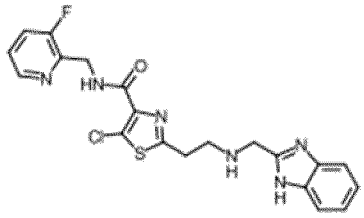
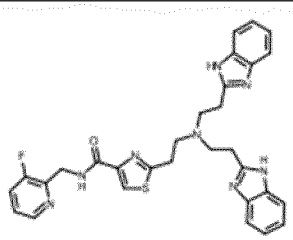
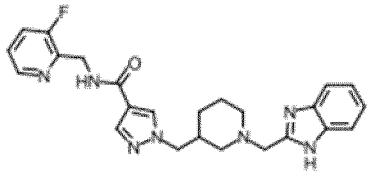
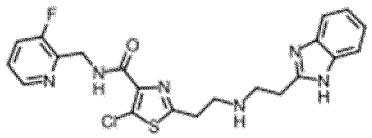
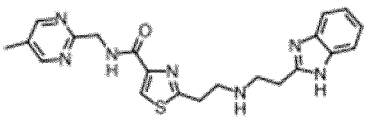
150	
151	
152	
153	
154	
155	

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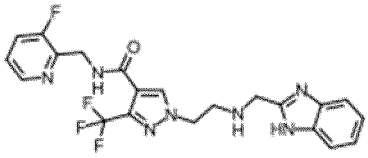
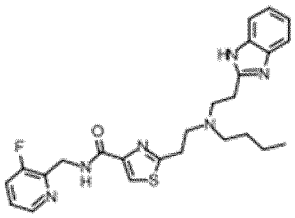
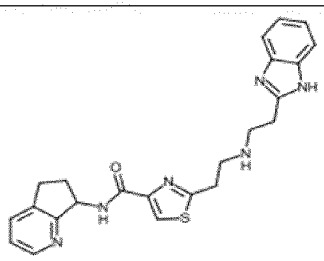
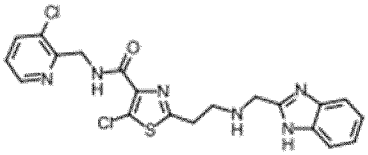
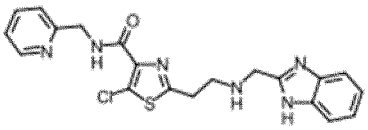
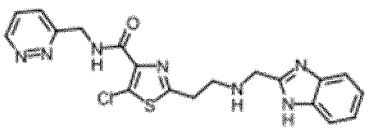
156	
157	
158	
159	
160	
161	

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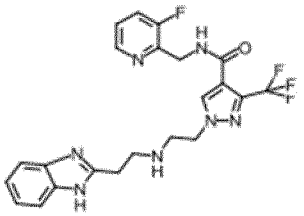
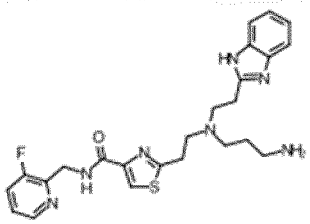
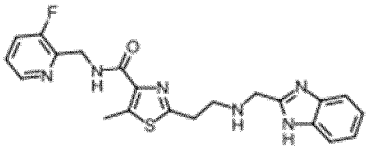
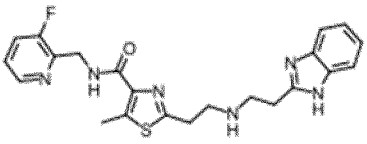
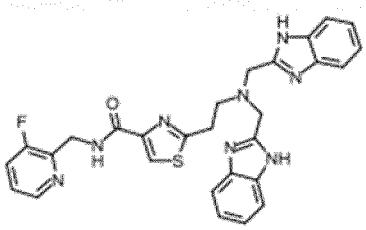
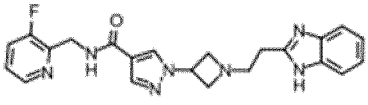
162	
163	
164	
165	
166	
167	

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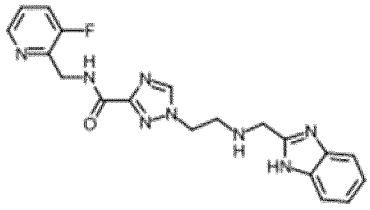
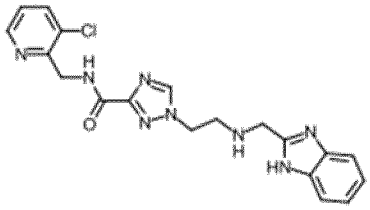
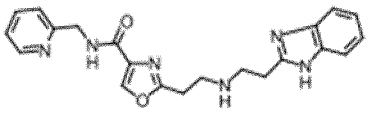
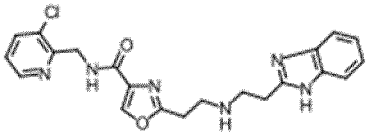
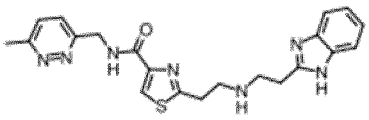
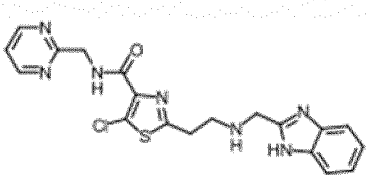
169	
170	
171	
173	
174	
175	

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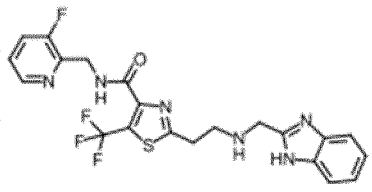
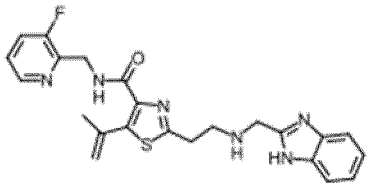
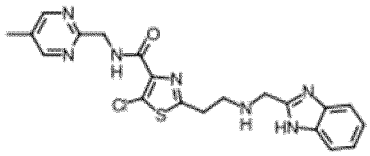
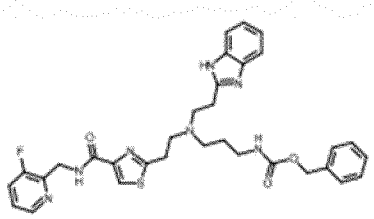
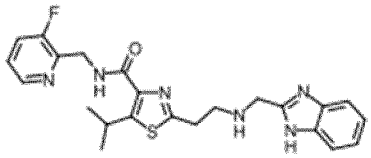
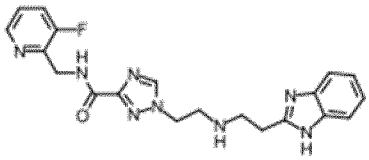
176	
177	
178	
179	
180	
181	

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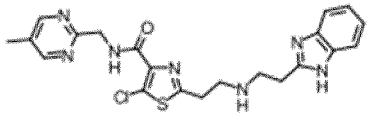
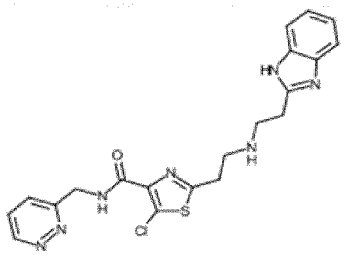
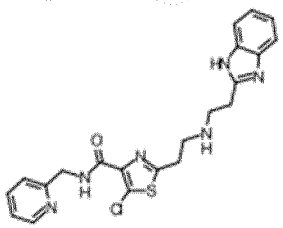
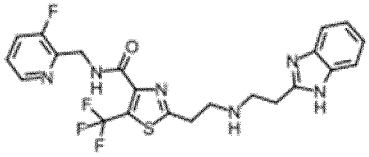
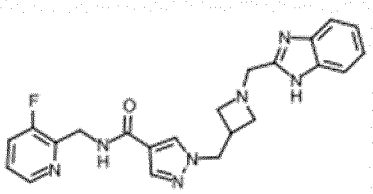
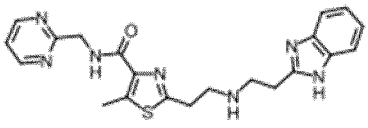
182	
183	
184	
186	
187	
188	

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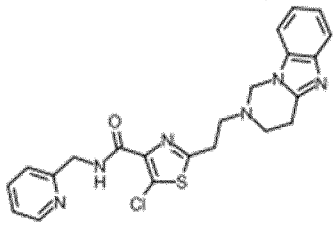
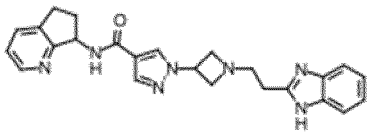
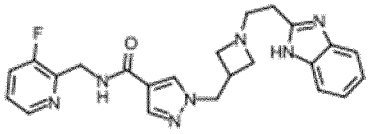
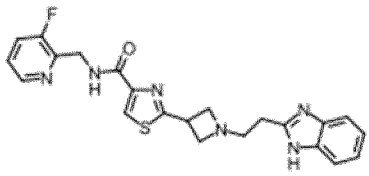
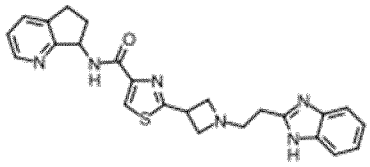
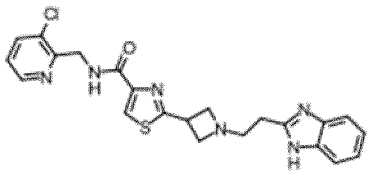
189	
191	
192	
193	
194	
195	

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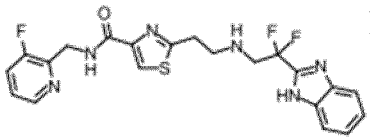
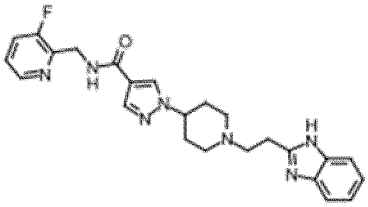
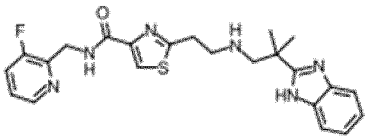
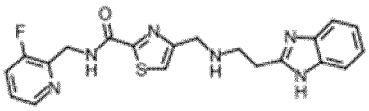
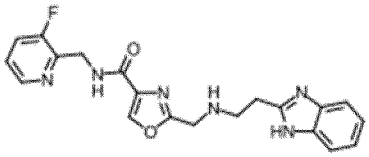
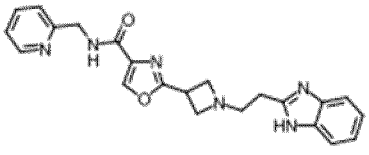
196	
198	
199	
205	
206	
207	

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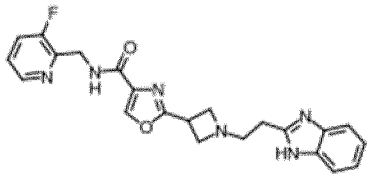
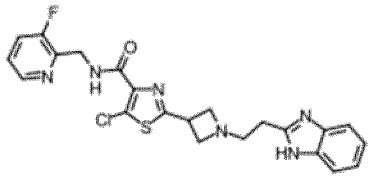
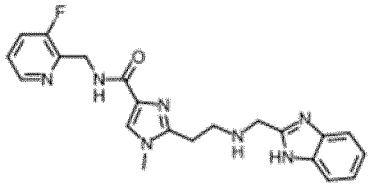
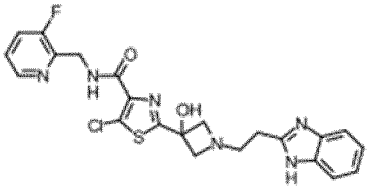
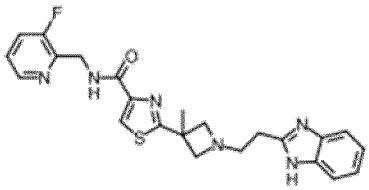
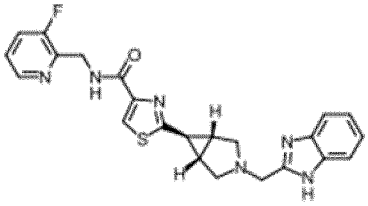
208	
209	
210	
211	
212	
213	

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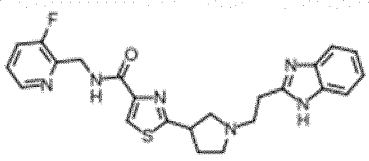
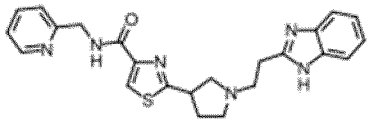
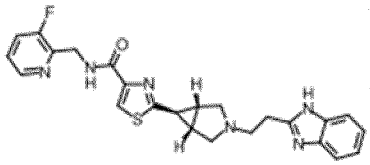
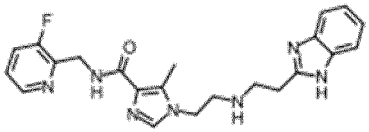
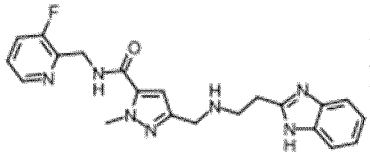
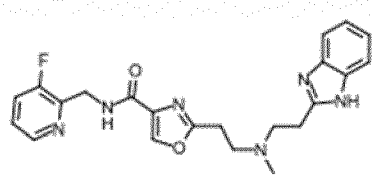
214	
215	
218	
219	
220	
223	

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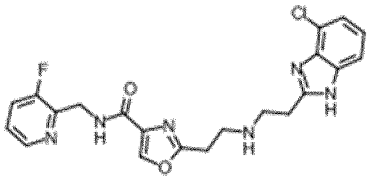
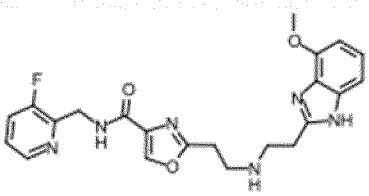
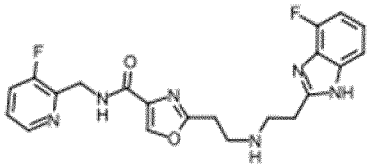
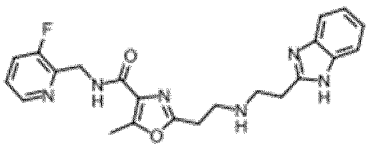
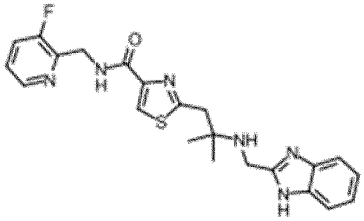
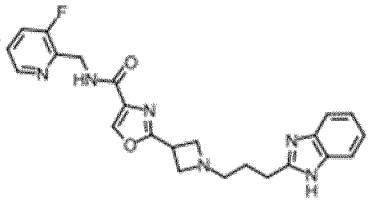
226	
227	
228	
230	
231	
233	

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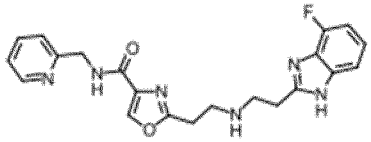
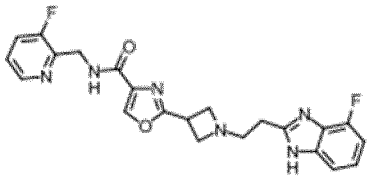
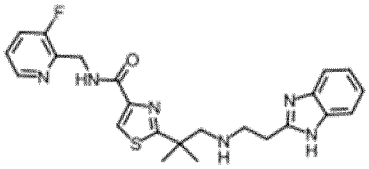
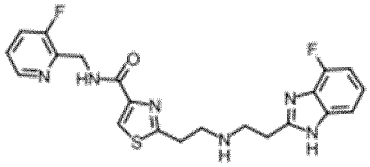
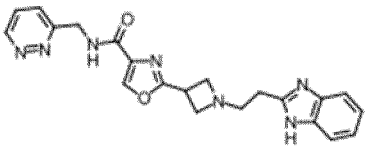
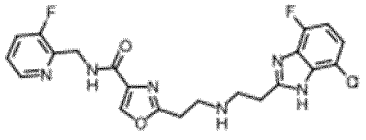
236	
239	
242	
243	
244	
247	

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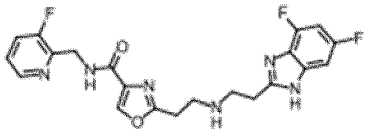
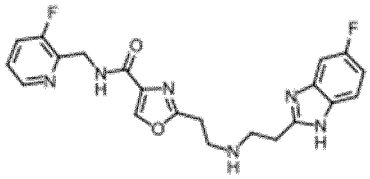
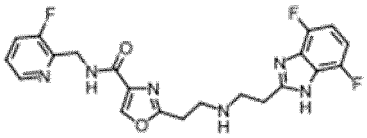
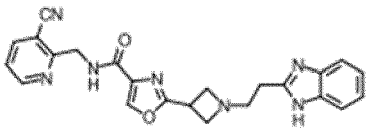
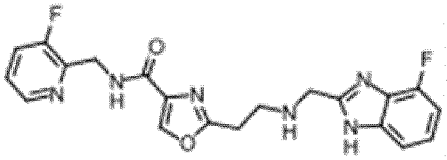
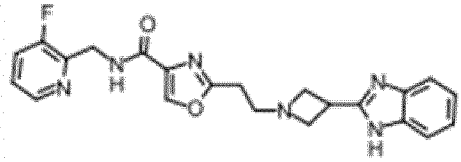
249	
250	
251	
252	
253	
255	

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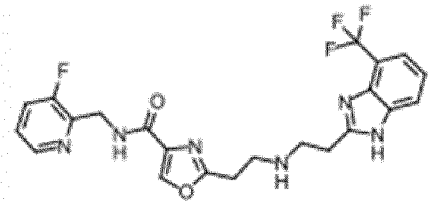
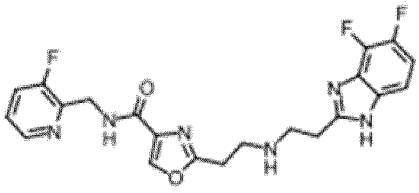
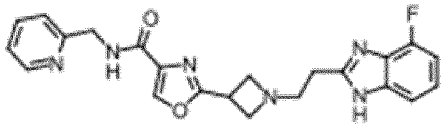
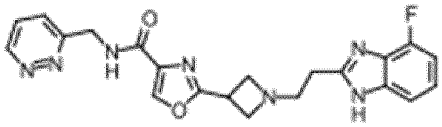
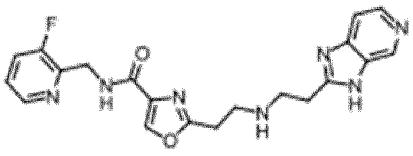
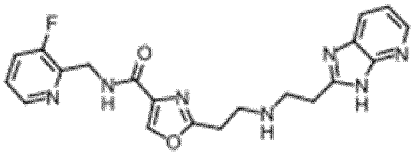
256	
257	
258	
261	
262	
263	

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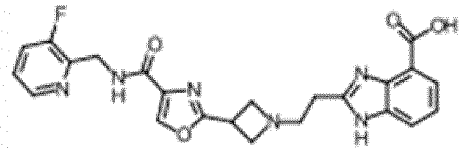
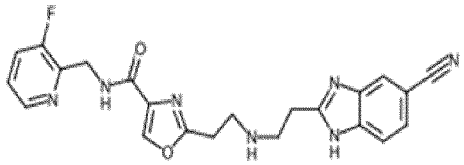
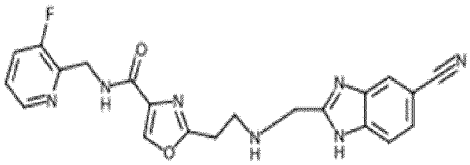
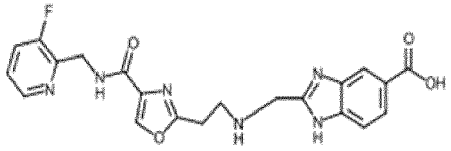
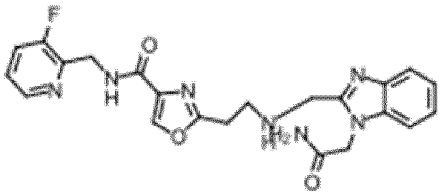
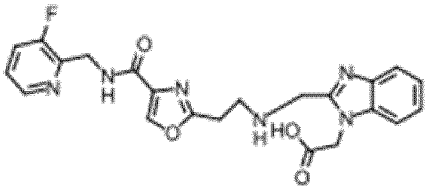
264	
265	
266	
267	
268	
269	

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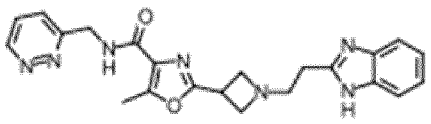
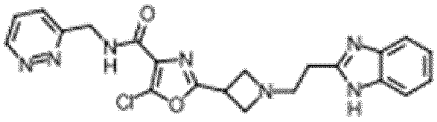
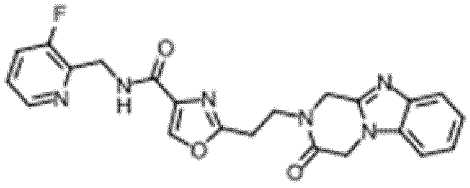
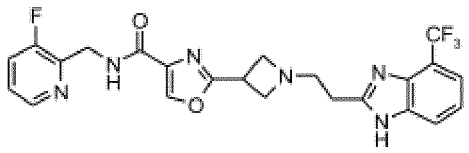
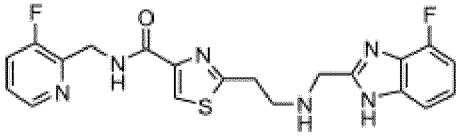
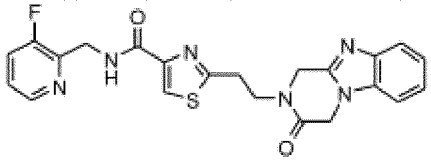
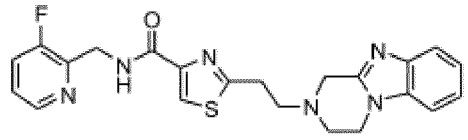
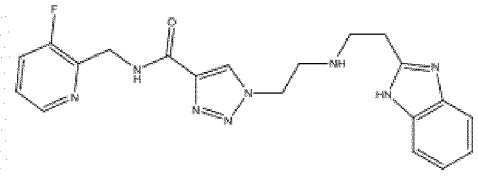
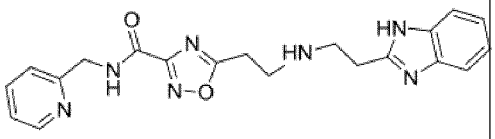
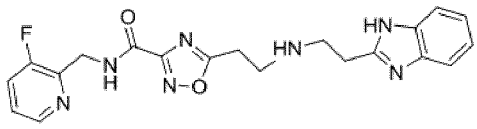
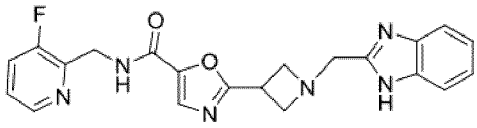
270	
271	
272	
273	
274	
275	

Exp. No.	Structure
276	
277	
278	
279	
280	

or pharmaceutically acceptable salts thereof.

More preferred are the compounds according to formula (A-II), wherein Cycl is an optionally substituted, optionally fused heteroaryl, such as Examples Nos.:
1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 46, 47, 48, 49, 54,55, 56, 57, 58, 59, 60, 61, 64, 76, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 134, 135, 136, 137, 138, 141, 142, 144, 145, 148, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 169, 170, 171, 173,174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 186, 187, 188, 189, 191, 192, 193, 194, 195, 196, 198, 199, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 218, 219, 220, 223, 226, 227, 228, 230, 231, 233, 236, 239, 242, 243, 244, 247, 249, 250, 251, 252, 253, 255, 256, 257, 258, 261, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279 and 280.

More preferred are the compounds according to formula (A-II), wherein Cycl is an optionally substituted, optionally fused 6-membered heteroaryl, such as Examples Nos.:
1, 2, 3, 4, 5, 6, 7, 8, 12, 35, 36, 37, 38, 39, 40, 42, 43, 44, 45, 46, 47, 48, 49, 54, 55, 56, 57, 58, 59, 61, 76, 79, 80, 81, 82, 83, 87, 89, 90, 92, 93, 94, 96, 97, 98, 99, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 134, 135, 136, 137, 138, 141, 142, 144, 145, 148, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 169, 170, 171, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 186,187, 188, 189, 191, 192, 193, 194, 195, 196, 198, 199, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 218, 219, 220, 223, 226, 227, 228, 230, 231, 233, 236, 239, 242, 243, 244, 247, 249, 250, 251, 252, 253, 255, 256, 257, 258, 261, 264, 265, 266, 267, 268,269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279 and 280.

More preferred are the compounds according to formula (A-II), wherein Cycl is an optionally substituted, optionally fused pyridinyl-group, such as Examples Nos.:
1, 2, 3, 4, 5, 6, 7, 8, 12, 35, 36, 37, 38, 39, 40, 42, 43, 45, 47, 48, 49, 54, 55, 56, 57, 58, 59, 76, 79, 80, 81, 82, 83, 89, 90, 92, 94, 96, 97, 98, 99, 101, 102, 103, 104, 105, 106, 108, 109, 110, 111, 112, 113, 114, 116, 117, 118, 119, 120, 121, 123, 124, 125, 126, 127, 128, 131,132, 134, 135, 136, 137, 138, 141, 142, 144, 145, 148, 150, 151, 152, 153, 154, 156, 157, 158, 159, 160, 162, 163, 164, 165, 166, 167, 169, 170, 171, 173, 176, 177, 179, 180, 181, 184, 186, 187, 189, 191, 192, 193, 194, 195, 196, 198, 199, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 218, 219, 220, 223, 226, 227, 228, 230, 231, 233, 236, 239, 242, 243, 247, 249, 250, 251, 252, 253, 255, 256, 257, 258, 264, 265, 266, 267, 268, 269, 272, 273, 274, 275, 276, 277, 278, 279 and 280.

More preferred are the compounds according to formula (A-II), wherein Cycl is an optionally substituted, optionally fused pyridinyl-group and having a 5-membered heterocyclic ring accoding to (A-6-b) forming an oxazolyl-ring, such as Examples Nos.:
126, 127, 128, 137, 141, 171, 173, 206, 207, 208, 223, 226, 227, 228, 230, 233, 236, 239, 247, 249, 250, 251, 252, 253, 255, 256, 257, 258, 264, 265, 266, 267, 268, 269, 272, 273;

and/or having a 5-membered heterocyclic ring accoding to (A-6-c) forming a thiazolyl-ring such as Examples Nos.:
12, 35, 36, 37, 38, 39, 40, 42, 43, 45, 47, 54, 55, 56, 57, 58, 59, 76, 79, 80, 81, 82, 83, 89, 90, 94, 96, 97, 98, 99, 101, 102, 103, 104, 105, 106, 108, 110, 112, 113, 114, 116, 118, 119, 120, 121, 123, 124, 125, 134, 135, 148, 151, 152, 154, 157, 158, 159, 160, 163, 164, 165, 166, 176, 177, 179, 180, 184, 186, 189, 193, 194, 195, 196, 199, 209, 211, 212, 213, 214, 215, 218, 231, 242, 243, 274, 275, 276;

and/or having a 5-membered heterocyclic ring accoding to (A-6-g) and/or (A-6-h) forming an isooxazolyl or an isothiazolyl-ring such as Examples Nos.:
1, 2, 3, 4, 5, 6, 7, 8 and 280;

and/or having a 5-membered heterocyclic ring accoding to (A-6-e) and/or (A-6-f) forming a triazolyl-ring such as Examples Nos.:
169, 170, 181, 277.

Further, compounds with one of R^1/R^2 being a fluorine-substituted pyridinyl-group are preferred, such as Examples Nos.:
1, 2, 3, 4, 5, 6, 7, 8, 40, 94, 112, 113, 114, 118, 119, 120, 121, 125, 126, 127, 128, 134, 135, 148, 151, 152, 154, 157, 163, 164, 165, 166, 169, 176, 177, 179, 180, 181, 186, 193, 196, 199, 206, 208, 209, 211, 212, 213, 214, 218, 223, 226, 227, 228, 230, 231, 233, 239, 242, 243, 247, 249, 250, 251, 253, 255, 256, 257, 264, 265, 266, 267, 268, 269, 272, 273, 274, 275, 276, 277, 279 and 280.

Pharmaceutically acceptable salts of the compounds according to the invention include, for example, salts with suitable anions, such as carboxylates, sulfonates, sulfates, chlorides, bromides, iodides, phosphates, tartrates, methane sulfonates, hydroxyethane sulfonates, glycinates, maleates, propionates, fumarates, toluene sulfonates, benzene sulfonates, trifluoroacetates, naphthalenedisulfonates-1,5, salicylates, benzoates, lactates, salts of malic acid, salts of 3-hydroxy-2-naphthoic acid-2, citrates and acetates.

Pharmaceutically acceptable salts of the compounds according to the inventionfurther include, for example, salts with suitable pharmaceutically acceptable bases, such as, for example, salts with alkaline or alkaline-earth hydroxides, such as NaOH, KOH, $Ca(OH)_2$, $Mg(OH)_2$ etc., amine compounds such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, ethanolamine, diethanolamine, triethanolamine, methylglucamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine, N-methylpiperidin, 2-amino-2-methyl-propanol-(1), 2-amino-2-methyl-propandiol-(1,3), 2-amino-2-hydroxyl-methyl-propandiol-(1,3) (TRIS) etc..

Depending on their structure, the compounds according to the invention may exist in stereoisomeric forms (enantiomers, diastereomers) in the presence of asymmetric carbon atoms. The invention therefore includes the use of the enantiomers or diastereomers and the respective mixtures thereof. The pure-enantiomer forms may optionally be obtained by conventional processes of optical resolution, such as by fractional crystallisation of diastereomers thereof by reaction with optically active compounds. Since the compounds according to the invention may occur in tautomeric forms, the present invention covers the use of all tautomeric forms.

The compounds provided according to the invention may be present as mixtures of various possible isomeric forms, in particular of stereoisomers such as, for example, E- and Z-, syn and anti, as well as optical isomers. The E-isomers and also the Z-isomers as well as the optical isomers and any mixtures of these isomers are claimed.

The novel compounds of the present invention can be present in an amorphous, crystalline or partially crystalline form or they may also be present exist as hydrates.

The novel compounds according to formula (A-I) and its further embodiments, as defined above, have surprisingly been found to act as ferroportin inhibitors and are thus suitable for the use asa medicament, such as in particular for the use as ferroportin inhibitors.

As already explained above, ferroportin is the iron transport protein, which is responsible for the uptake of the released iron via the intestine and its transfer into the blood circulation, thereby conveying the iron to the appropriate tissues and organs. Inactivation or inhibition ofthe ferroportin disables the export of the iron, thereby reducing the absorption of iron in the intestine. Ferroportin inhibition in the sense of the present invention therefore includes the inhibition of iron transport from the cells into the blood circulation and the inhibition of iron absorption in the intestine. Therein, the inhibition of iron transport and/or iron reflux may be effected by different ways of mechanism, comprising for example inhibition of iron transport activity of ferroportin and thus inhibition of iron reflux, triggering internalization, degradation and/or reduction of ferroportin, administering hepcidin agonists, i.e. compounds which compete with hepcidin or by compounds, which inhibit the binding of hepcidin to ferroportin.

Ferroportin inhibition may be determined by measuring the inhibition of ferroportin mediated iron transport activity in an iron response assay (BLAzer-Assay), as described in more detail in the Examples below. Further, ferroportin inhibition may be determined by measuring ferroportin internalization and/or degradation in the Ferroportin Internalization and Degradation Assay (FACS) or by examining the Ferroportin Ubiquitination and Degradation, each as described in more detail in the Examples below. Further, ferroportin inhibition may be determined by measuring the activity as an hepcidin agonist, for example by determining the Hepcidin binding capacity to ferroportin in the Hepcidin Internalization Assay (J774), as described in more detail in the Examples below. Further, ferroportin inhibition may be determined by confirming the inhibition of hepcidin binding to ferroportin, for example in the Biophysical Ferroportin-Hepcidin Binding Assay (Hep Bind FP), as described in more detail in the Examples below. Further, ferroportin inhibition may be determined by determining the activity of a compound regarding its ability to block iron export via ferroportin, for example with a test for measuring inhibition of iron efflux, as described in more detail in the Examples below.

Ferroportin inhibition in the sense of the present invention can thus in particular be defined by exhibiting a ferroportin inhibiting activity in at least one of the aforementioned test methods, shown in particular by:

Inhibition of ferroportin mediated iron transport activity in an iron response assay (Blazer Assay): IC_{50} value [µm] of not more than 100 (≤ 100), preferably not more than 50 (≤ 50), more preferably below 50 (< 50).

Ferroportin Internalization and Degradation Assay (FACS): : EC_{50} value [µm] of not more than 100 (≤ 100), preferably not more than 50 (≤ 50), more preferably below 50 (< 50).

Ferroportin Ubiquitination and Degradation: visually inspected effed in Western blots of "+ comparable to hepcidin", "+/- intermediate effect" and "+ / +/- stronger intermediate effect", preferred is an effect "+" or "+ / + / -", most preferred is an effect "+" .

Hepcidin Internalization Assay (J774): IC_{50} value of not more than 100 (≤ 100), preferably not more than 50 (≤ 50), more preferably below 50 (< 50).

Biophysical Ferroportin-Hepcidin Binding Assay: : IC_{50} value of not more than 100 (≤ 100), preferably not more than 50 (≤ 50), more preferably below 50 (< 50).

Inhibition of Iron Efflux: IC_{50} value of not more than 100 (≤ 100), preferably not more than 50 (≤ 50), more preferably below 50 (< 50).

Ferroportin inhibition may further be determined in *in vivo* models, as described in more detail in the Examples below. Suitable *in vivo* models may comprise, for example, examination of hypoferremia in naïve mice via measurement of serum iron reduction; examination of prevention of iron absorption in anemic rats via measurement of serum iron inhibition; examination of correctionof hyperferremia in beta2-microglobulin deficient mice via measurement of serum iron reduction; examination of prevention of iron overload in beta2-microglobulin deficient mice via measurement of total iron in spleen or liver; examination of improvement of anemia, ineffective erythropoiesis and iron overload in a mouse model ofβ-thalassemia intermedia.

The activity of the compounds of the present invention as ferroportin inhibitors can in particular be determined by the methods as described in the Examples below.

As further already explained above, ferroportin inhibition may for example be effected by hepcidin, which is thus an essential regulating factor of iron absorption, inhibiting ferroportin and thus blocking iron transport from the cells into the blood circulation and iron absorption. It has further surprisingly been found that several of the compounds as defined herein act as hepcidin mimetics or hepcidin agonists, which is also included by ferroportin inhibition in the sense of the present invention.

Accordingly, the compounds as defined in the present invention are also suitable for use in the inhibition of iron transport from the cells into the blood circulation and the inhibition of iron absorption in the intestine, as well as for the use as hepcidin mimetics or hepcidin agonists.

Due to the activity of the compounds as defined herein asferroportin inhibitors, the compounds of the present invention are further particularly suitable for the use in the inhibition of iron transport mediated by ferroportin and thereby for the use in the prophylaxis and/or treatment of iron metabolism disorders leading to increased iron levels, of diseases related to or caused by increased iron levels, increased iron absorption or iron overload, such as in particular of tissue iron overload, of diseases associated with ineffective erythropoiesis, or of diseases caused by reduced levels of hepcidin. Further, the compounds of the present invention are suitable for the use in an adjunctive therapy bylimiting the amount of iron available to pathogenic microorganisms, such as the bacterium Vibrio vulnificus, therebypreventing or treating infections caused by said pathogenic microorganisms.

Therein, diseases being associated with, being related to, being caused by orleading to increased iron levels, increased iron absorption, iron overload (e.g. tissue iron overload) or ineffective erythropoiesis comprise thalassemia, hemoglobinopathy, such as hemoglobin E disease (HbE), hemoglobin H disease (HbH), haemochromatosis, hemolytic anemia, such as sickle cell anemia (sickle cell disease) and congenital dyserythropoietic anemia.

Diseases being associated with, being related to, being caused by or leading to increased iron levels, increased iron absorption, iron overload (e.g. tissue iron overload) further comprise neurodegenerative diseases, such as for example Alzheimer's disease and Parkinson's disease, wherein the compounds are considered to be effective by limiting the deposition or increase of iron in tissue or cells.

The compounds of the present invention are further suitable for the use in the prophylaxis and/or treatment of formation of radicals, reactive oxygen species (ROS) and oxidative stress caused by excess iron or iron overload as well as in the prophylaxis and/or treatment of cardiac, liver and endocrine damage caused by excess iron or iron overload, and further in the prophylaxis and/or treatment of inflammation triggered by excess iron or iron overload.

Diseases associated with ineffective erythropoiesis comprise in particular myelodysplastic syndromes (MDS, myelodysplasia) and polycythemia vera as well as congenital dyserythropoietic anemia.

Further diseases, disorders and/or diseased conditions comprise iron overload caused by mutations in genes involved in sensing the systemic iron stores, such as hepcidin (Hamp1), hemochromatosis protein (HFE), hemojuvelin (HJV) and transferrin receptor 2 (TFR2), such as in particular diseases related to HFE and HJV gene mutations, chronic hemolysis associated diseases, sickle cell diseases, red cell membrane disorders, Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), erythrpoietic porphyria, Friedrich`s Ataxia, as well as subgroups of iron overload such as transfusional iron overload, iron intoxication, pulmonary hemosiderosis, osteopenia, insulin resistense, African iron overload, Hallervordan Spatz disease, hyperferritinemia, ceruloplasmin deficiency, neonatal hemochromatosis and red blood cell disorders comprising thalassemia, including alpha thalassemia, beta thalassemia and delta thalassemia, thalassemia intermedia, sickle cell disease and myelodyplastic syndrome.

Further diseases and/or disorders and/or diseased conditions associated with elevated iron levels include, but are not limited to, diseases with elevated iron level, comprising ataxia, Friedrich's ataxia, age-related macular degeneration, age-related cataract, age-related retinal diseases and neurodegenrative disease, such as pantothenate kinase-associated neurodegeneration, restless leg syndrom and Huntington's disease,

The compounds of the present invention my further be suitable for the use in the prophylaxis and treatment of diseases caused by a lack of hepcidin.

In view thereof a further object of the present invention relates to a medicament containing one or more of the compounds as defined above, such as in particular a medicament for the prophylaxis and treatment in any of the indications, states, disorders or diseases as defined above.

A further object of the present invention relates to pharmaceutical compositions and medicaments comprising one or more of the compounds according to the invention as defined above as well as optionally one or more pharmacologically acceptable carriers and/or auxiliary substances and/or solvents. A further object of the present invention relates to pharmaceutical compositions and medicaments comprising one or more of the compounds according to the invention as defined above as well as optionally one or more further pharmaceutically effective compounds. The said pharmaceutical compositions contain, for example up to 99 weight-% or up to 90 weight-% or up to 80 weight-% or or up to 70 weight-% of the compounds of the invention, the remainder being each formed by pharmacologically acceptable carriers and/or auxiliaries and/or solvents and/or optionally further pharmaceutically active compounds.

Therein, the pharmaceutically acceptable carriers, auxiliary substances or solvents are common pharmaceutical carriers, auxiliary substances or solvents, including various orgaric or inorganic carrier and/or auxiliary materials as they are customarily used for pharmaceutical purposes, in particular for solid medicament formulations. Examples include excipients, such as saccharose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talcum, calcium phosphate, calcium carbonate; binding agents, such as cellulose, methylcellulose, hydroxypropylcellulose, polypropyl pyrrolidone, gelatine, gum arabic, polyethylene glycol, saccharose, starch; disintegrating agents, such as starch, hydrolyzed starch, carboxymethylcellulose, calcium salt of carboxymethylcellulose, hydroxypropyl starch, sodium glycol starch, sodium bicarbonate, calcium phosphate, calcium citrate; lubricants, such as magnesium stearate, talcum, sodium laurylsulfate; flavorants, such as citric acid, menthol, glycin, orange powder; preserving

agents, such as sodium benzoate, sodium bisulfite, paraben (for example methylparaben, ethylparaben, propylparaben, butylparaben); stabilizers, such as citric acid, sodium citrate, acetic acid and multicarboxylic acids from the titriplex series, such as, for example, diethylenetriaminepentaacetic acid (DTPA); suspending agents, such as methycellulose, polyvinyl pyrrolidone, aluminum stearate; dispersing agents; diluting agents, such as water, organic solvents; waxes, fats and oils, such as beeswax, cocoa butter; polyethylene glycol; white petrolatum; etc..

Liquid medicament formulations, such as solutions, suspensions and gels usually contain liquid carrier, such as water and/or pharmaceutically acceptable organic solvents. Furthermore, such liquid formulations can also contain pH-adjusting agents, emulsifiers or dispersing agents, buffering agents, preserving agents, wetting agents, gelatinizing agents (for example methylcellulose), dyes and/or flavouring agents, for example as defined above. The compositions may be isotonic, that is, they can have the same osmotic pressure as blood. The isotonicity of the composition can be adjusted by using sodium chloride and other pharmaceutically acceptable agents, such as, for example, dextrose, maltose, boric acid, sodium tartrate, propylene glycol and other inorganic or organic soluble substances. The viscosity of the liquid compositions can be adjusted by means of a pharmaceutically acceptable thickening agent, such as methylcellulose. Other suitable thickening agents include, for example, xanthan gum, carboxymethylcellulose, hydroxypropylcellulose, carbomer and the like. The preferred concentration of the thickening agent will depend on the agent selected.

Pharmaceutically acceptable preserving agents can be used in order to increase the storage life of the liquid composition. Benzyl alcohol can be suitable, even though a plurality of preserving agents including, for example, paraben, thimerosal, chlorobutanol and benzalkonium chloride can also be used.

The above-mentioned pharmaceutical compositions are suitable, for example, for intravenous, intraperitoneal, intramuscular, intravaginal, intrabuccal, percutaneous, subcutaneous, mucocutaneous, oral, rectal, transdermal, topical, intradermal, intragasteral or intracutaneous application and are provided, for example, in the form of pills, tablets, enteric-coated tablets, film tablets, layer tablets, sustained release formulations for oral, subcutaneous or cutaneous administration (in particular as a plaster), depot formulations, dragees, suppositories, gels, salves, syrup, granulates, suppositories, emulsions, dispersions, microcapsules, microformulations, nanoformulations, liposomal formulations, capsules, enteric-coated capsules, powders, inhalation powders, microcrystalline formulations, inhalation sprays, epipastics, drops, nose drops, nose sprays, aerosols, ampoules, solutions, juices, suspensions, infusion solutions or injection solutions etc..

A further object of the present invention relates to medicaments or combined preparations containing one or more of the compounds as defined above and at least one further pharmaceutically active compound, such as in particular a compound for the prophylaxis and treatment of iron overload and the associated symptoms, preferably an iron-chelating compound, or a compound for the prophylaxis and treatment of any of the states, disorders or diseases as defined above, such as in particular a pharmaceutically active compound for the prophylaxis and treatment of thalassemia, haemochromatosis, neurodegenerative diseases (such as Alzheimer's disease or Parkinson's disease) and the associated symptoms.

A further object of the present invention relates to the use of the compounds as defined above per se, in a combination therapy (fixed dose or free dose combinations for sequential use) with one or two other active ingredients (drugs). Such combination therapy comprises co-administration of the compounds of the present invention with the at least one additional pharmaceutically active compound (drug). Combination therapy in a fixed dose combination therapy comprises co-administration of the compounds of the present invention with the at least one additional pharmaceutically active compound in a fixed-dose formulation. Combination therapy in a free dose combination therapy comprises co-administration of the compounds of the present invention and the at least one additional pharmaceutically active compound in free doses of the respective compounds, either by simultaneous administration of the individual

compounds or by sequential use of the individual compounds distributed over a time period. The at least one additional pharmaceutically active compound (drug) comprises in particular drugs for reducing iron overload (e.g. Tmprss6-ASO) or iron chelators, in particular curcumin, SSP-004184, Deferitrin, deferasirox, deferoxamine and/or deferiprone, or antioxidants such as n-acetyl cysteine, anti-diabetics such as GLP-1 receptor agonists, antibiotics such as vancomycin (Van) or tobramycin, drugs for the treatment of malaria, anticancer agents, antifungal drugs, drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease (e.g. dopamine agonists such as Levodopa), anti-viral drugs such as interferon-α or ribavirin, or immunosuppressents (cyclosporine A or cyclosporine A derivatives), iron supplements, vitamin supplements, red cell production stimulators, anti-inflammatory biologies, anti-thrombolytics, statins, vasopressors and inotropic compounds .

A further object of the present invention relates to the use of the above combinations for the prophylaxis and/or treatment of diseases caused by a lack of hepcidin or iron metabolism disorders, such as particularly iron overload states such as in particular thalassemia and hemochromatosis and other disorders as described in the present application.

A further object of the present invention relates to the use of the compounds as definedherein per se or the hereinabove described combination therapies, in combination with Blood transfusion.

The compounds, medicaments and or combined preparations according to the present invention may be administered orally, parentally, as well as intravenously.

For this purpose, the compounds according to the invention are preferably provided in medicaments or pharmaceutical compositions in the form of pills, tablets, such as enteric-coated tablets, film tablets and layer tablets, sustained release formulations for oral administration, depot formulations, dragees, granulates, emulsions, dispersions, microcapsules, microformulations, nanoformulations, liposomal formulations, capsules, such as enteric-coated capsules, powders, microcrystalline formulations, epipastics, drops, ampoules, solutions, suspensions, infusion solutions or injection solutions or in the form of a preparation suitable for inhalation.

In a preferred embodiment of the invention the compounds are administered in the form of a tablet or capsule, as defined above. These may be present, for example, as acid resistant forms or with pH dependent coatings.

The compounds of the present invention as the active substance can be administered, for example, with a unit dose of 0.001 mg/kg to 500 mg/kg body weight, for example 1 to 4 times a day. However, the dose can be increased or reduced depending on the age, weight, condition of the patient, severity of the disease or type of administration.

Accordingly, a further object of the present invention relates to compounds, medicaments, compositions and combined preparations as defined above for the preparation of a medicament, particularly for the prophylaxis and treatment of any indication, state, disorder or disease as defined above, in particular for oral or parenteral administration.

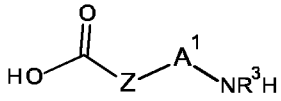
A further object of the present invention relates to a method for the prophylaxis and treatment as defined above, such as in particular for the prophylaxis and/or treatment of iron metabolism disorders being associated with or leading to increased iron levels and in particular iron overload, diseases related to or caused by increased iron levels or iron overload, iron storage diseases being associated with or leading to increased iron levels, and diseases being associated with ineffective erythropoiesis, the method comprising administering, to a patient (human or animal) in need thereof, a compound, a medicament, a composition or a combined preparation as defined above.

Therein, diseases being associated with, being related to, being caused by or leading to increased iron levels or iron overload are as defined above.

A further object of the present invention relates to the use of the compounds as defined above for the preparation of a medicament, particularly for the prophylaxis and treatment and of any indication, state, disorder or disease as defined above.

The compounds according to the invention of general structural formula (A-I) and (I) may basically be obtained by the processes described below and as shown in the general procedures (General Schemes). Accordingly, a further object of the invention is a process for the production of the compounds of general formula (A-I) as described herein, which includes:

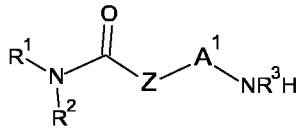
a) reacting compounds of formula (a)



(a)

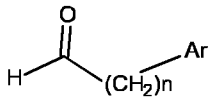
with compounds of formula (b) NH-R^1R^2,

to obtain compounds of formula (c)



(c), and

b) further reacting said compounds (c) with compounds of formula (d)



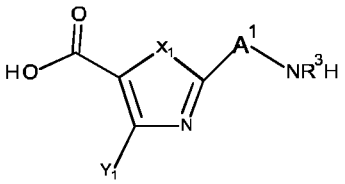
(d), with n = 0 to 7, preferably 0 to 5, preferably 0 to 1 or 2,

to obtain compounds of formula (A-I);

wherein R^1, R^2, Z, A^1, R^3 and Ar have the meaning as defined above. In principle the order of reaction steps is optional. It is further possible to start with the reaction of compounds (a) with compounds (d), followed by reaction with compound (b) to obtain compounds of formula (A-I). Further several intermediate steps are possible and several intermediate compounds are obtained as shown in the following Examples in detail. Several of the intermediate compounds are also novel compounds, which shall be covered from the present invention.

A further object of the invention is a process for the production of the compounds of general formula (I) as described herein, which includes:

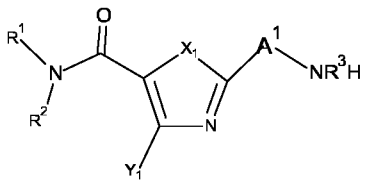
a) reacting compounds of formula (a)



(a)

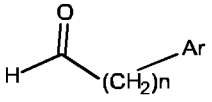
with compounds of formula (b) NH-R^1R^2,

to obtain compounds of formula (c)



(c), and

b) further reacting said compounds (c) with compounds of formula (d)

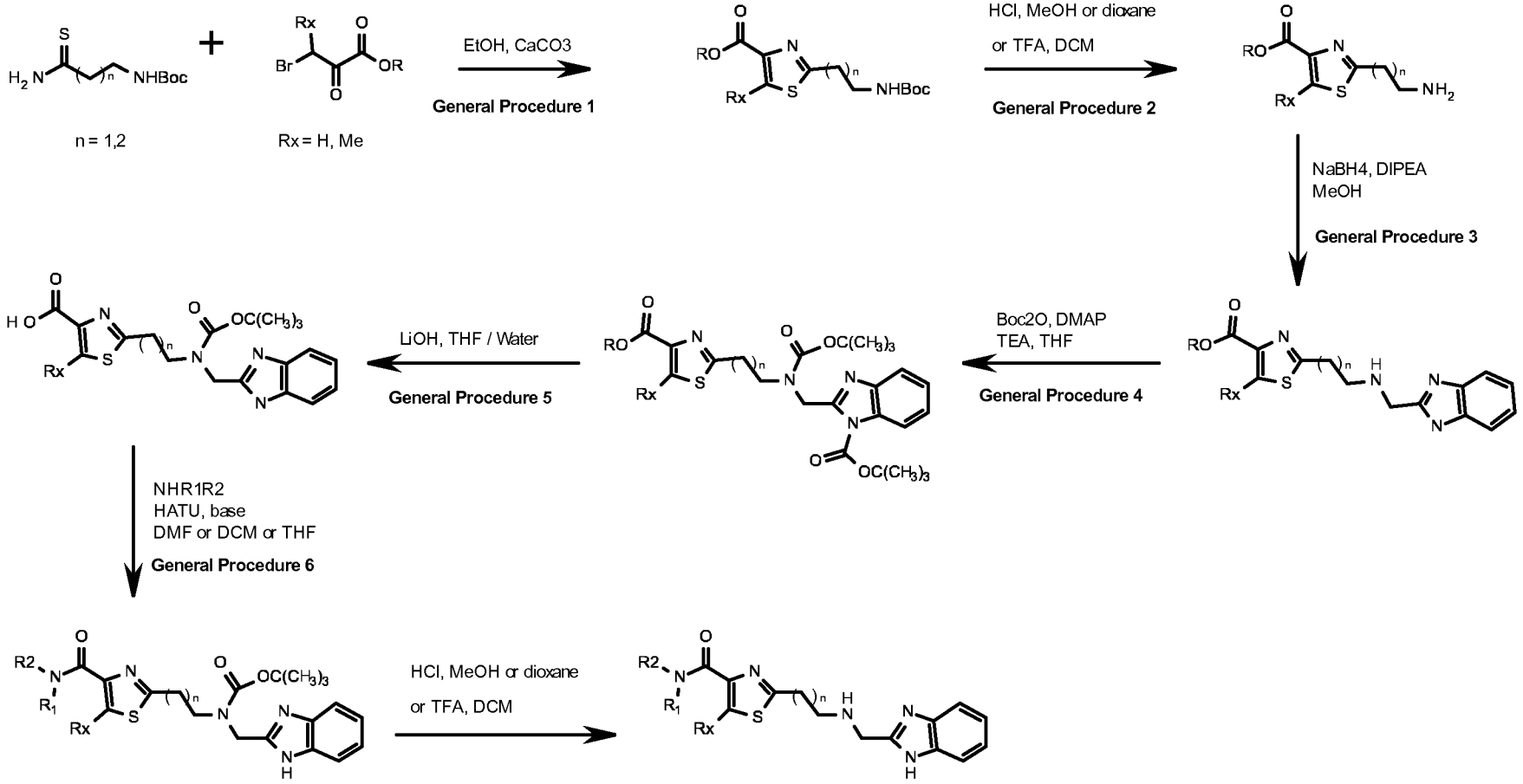


(d), with n = 0 to 7, preferably 0 to 5, preferably 0 to 1 or 2,

to obtain compounds of formula (I);

wherein X^1, Y^1, R^1, R^2, Z, A^1, R^3 and Ar have the meaning as defined herein. In principle the order of reaction steps is optional. It is further possible to start with the reaction of compounds (a) with compounds (d), followed by reaction with compound (b) to obtain compounds of formula (I). Further several intermediate steps are possible and several intermediate compounds are obtained as shown in the following Examples in detail. Several of the intermediate compounds are also novel compounds, which shall be covered from the present invention.

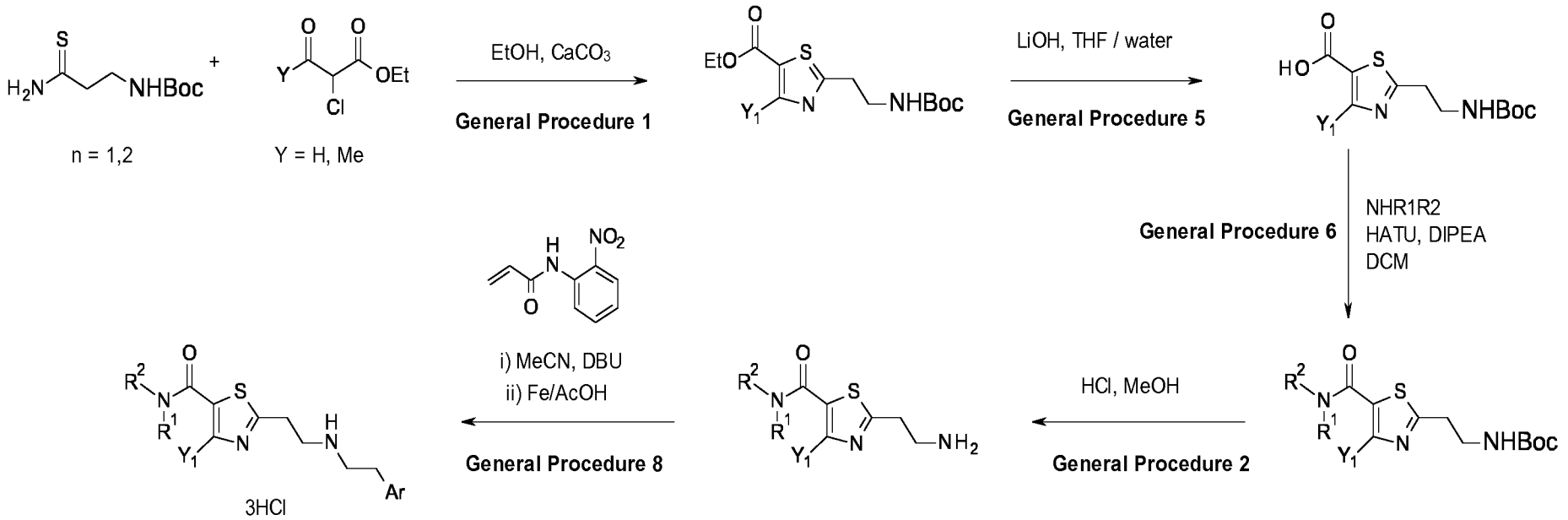
General Scheme 1



therein Rx indicates an optional substituent to X^4 and corresponds to Y^1

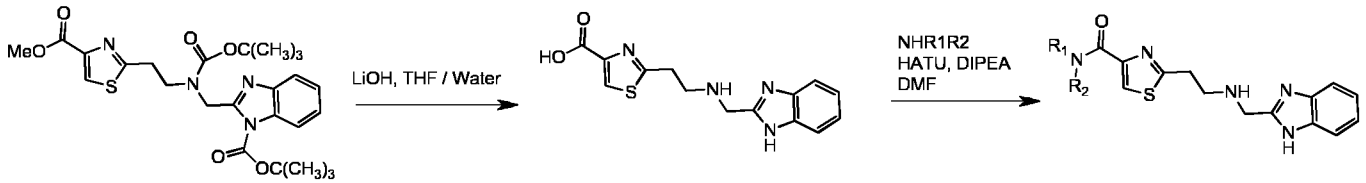
n indicates an integer as defined in context with A^1

General Scheme I-1

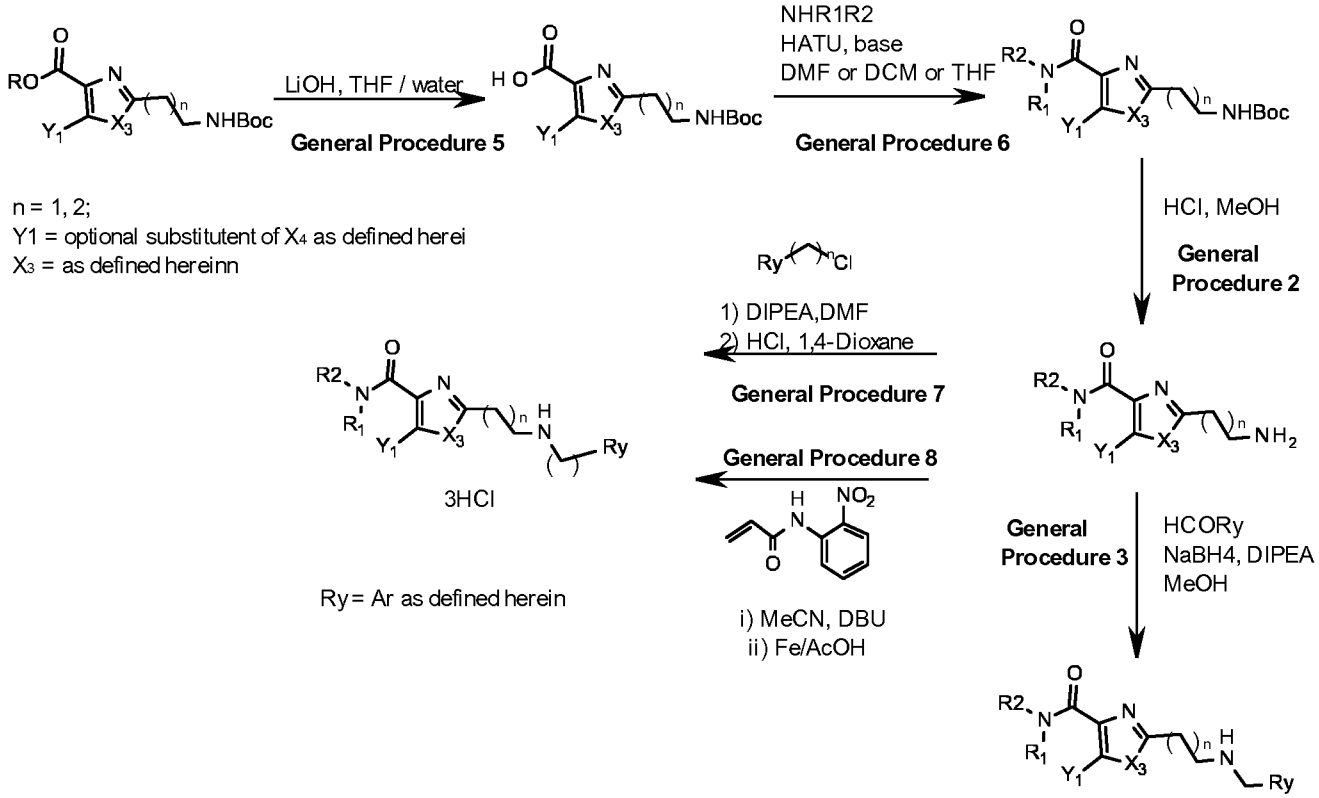


therein Ar has the meaning as defined herein and may correspond to Het2

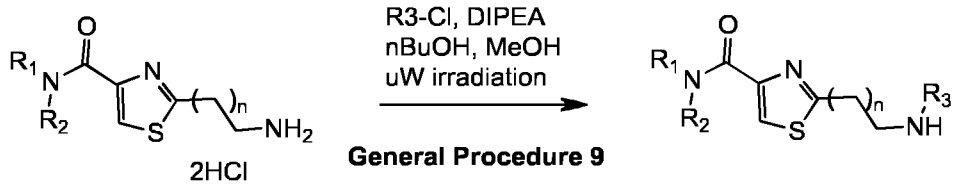
General Scheme 2



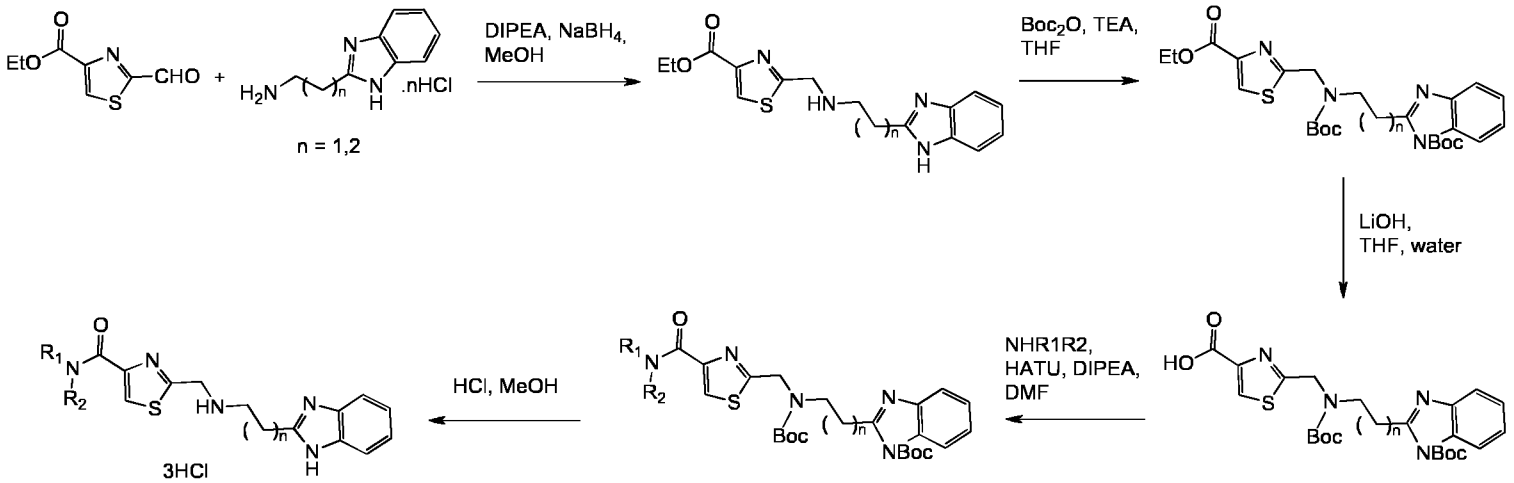
General Scheme 4



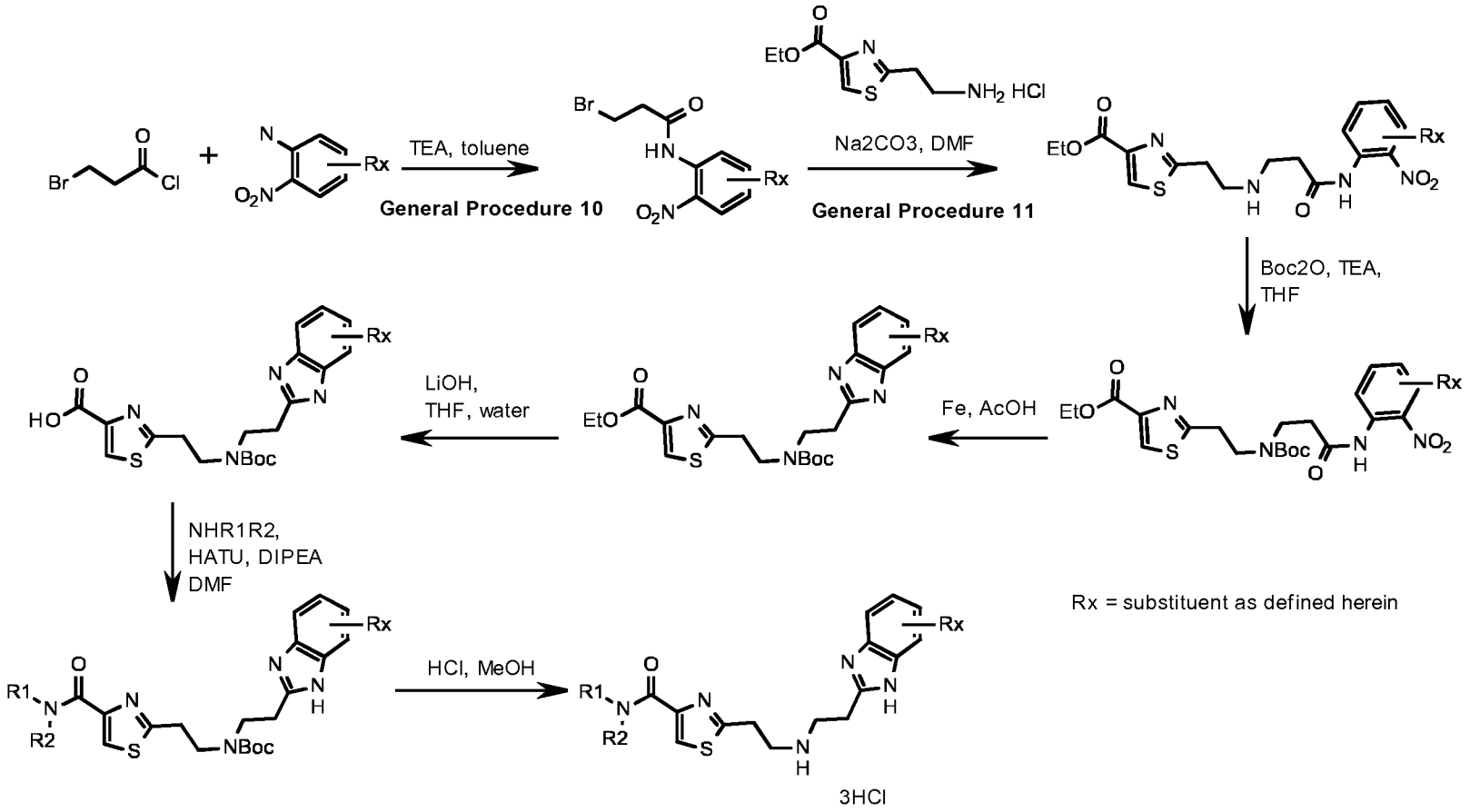
General Scheme 6



General Scheme 7

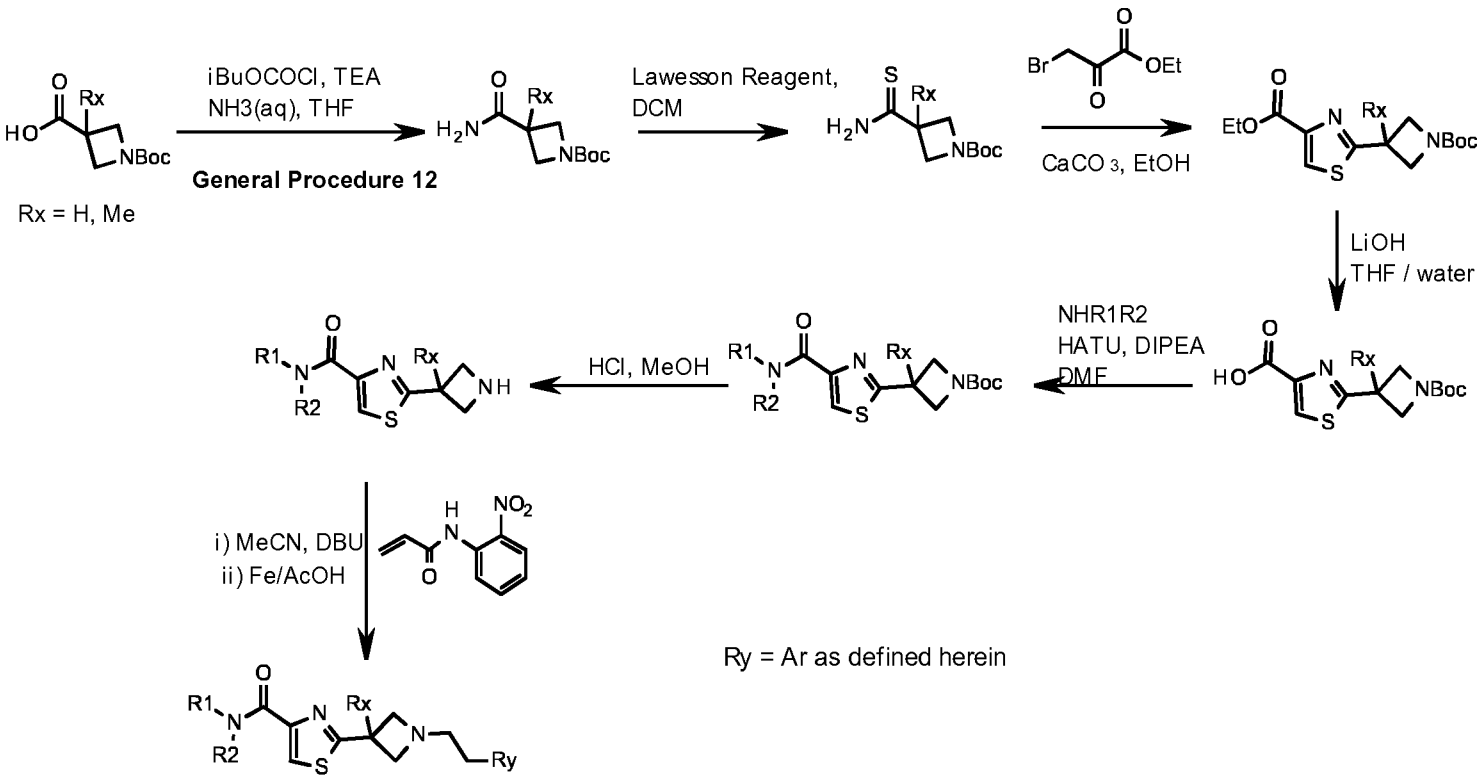


General Scheme 8



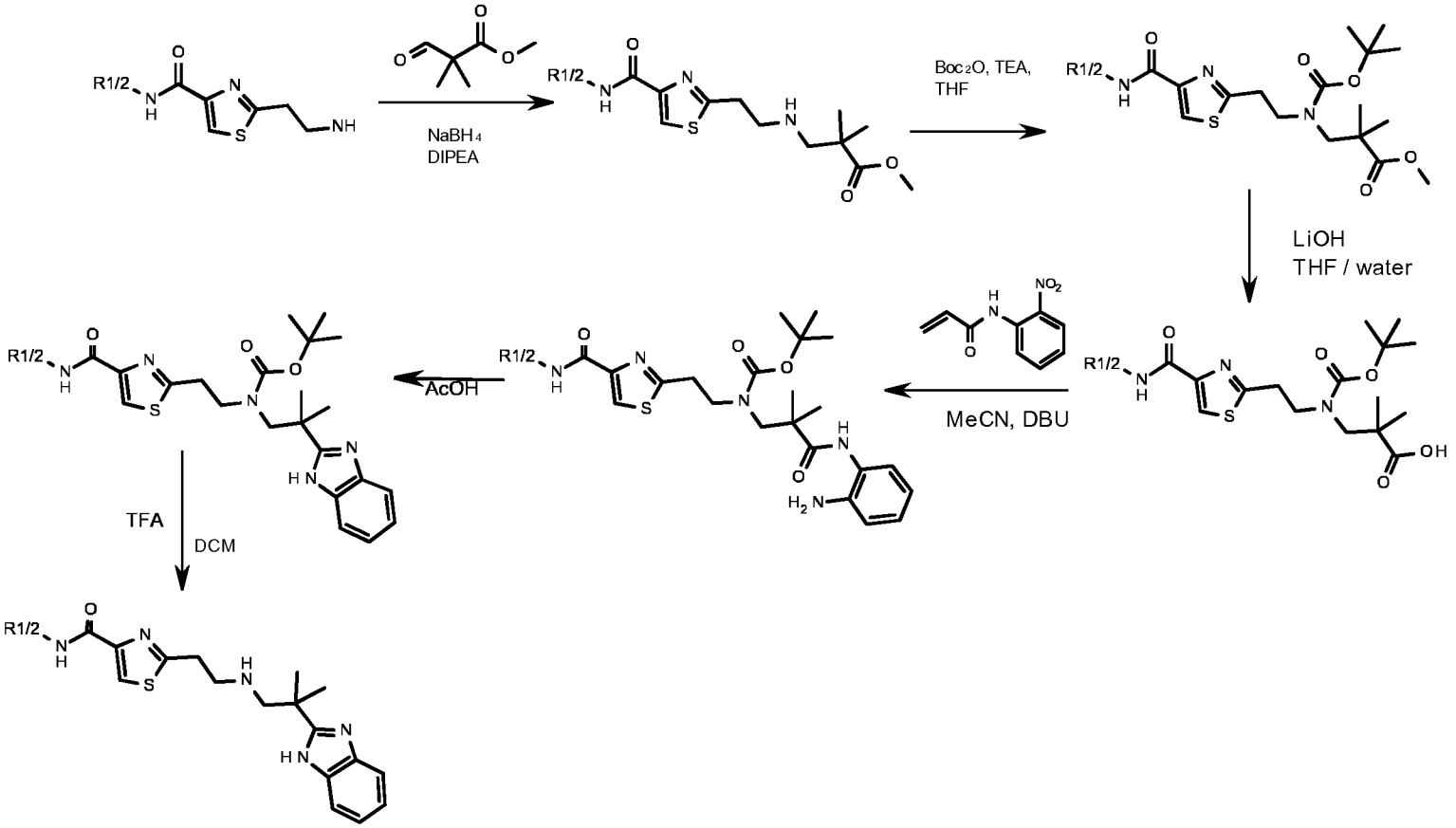
therein Rx indicates an optional substituent R^4 to Ar = Het-2 as defined herein

General Scheme 9

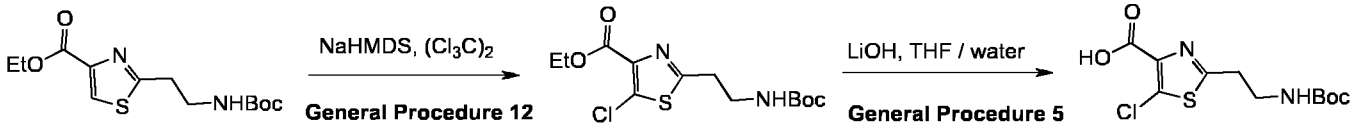


Ry = Ar has the meaning as defined herein and may correspond to Het-2

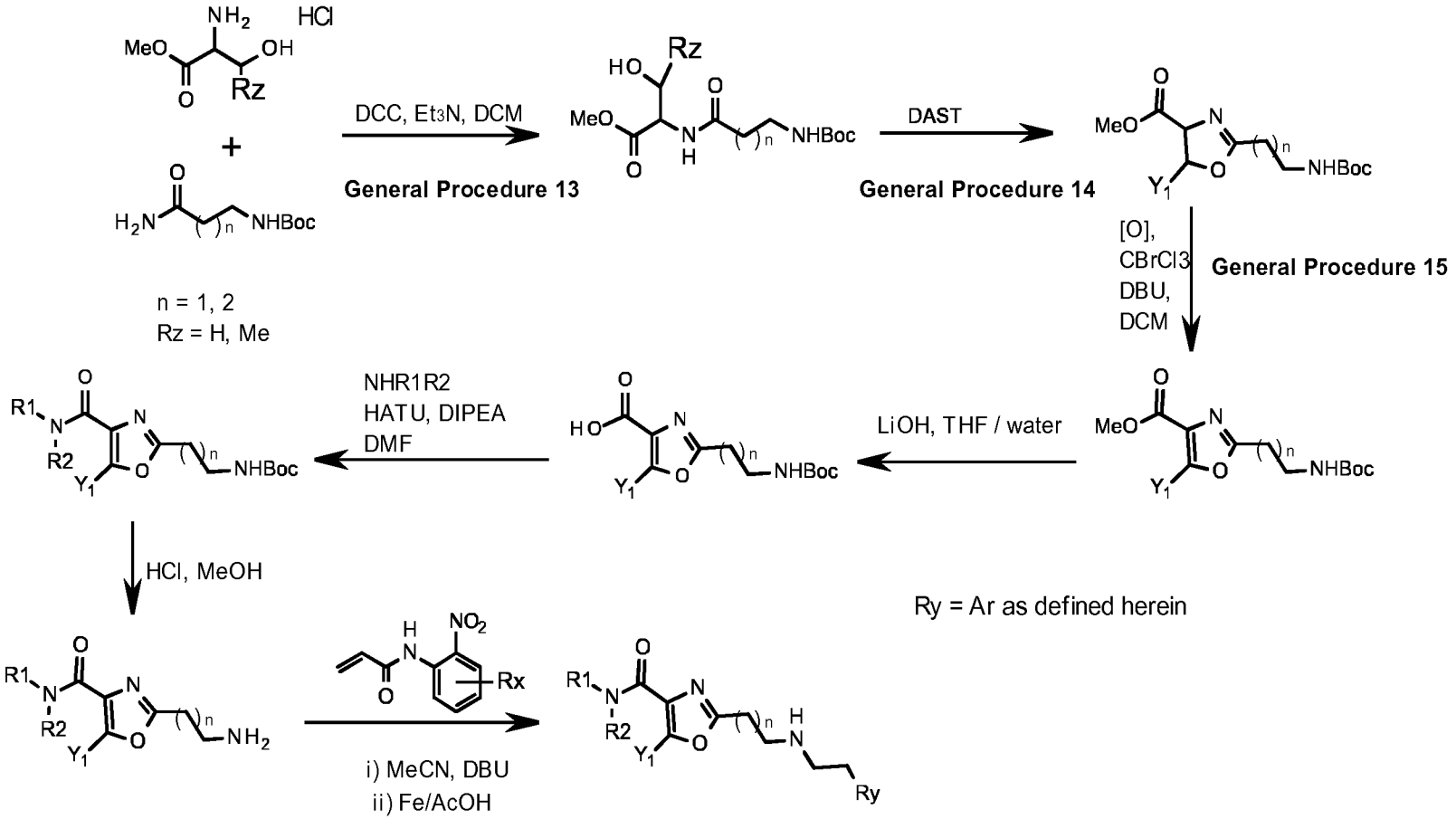
General Scheme 10



General Scheme 11



General Scheme 12

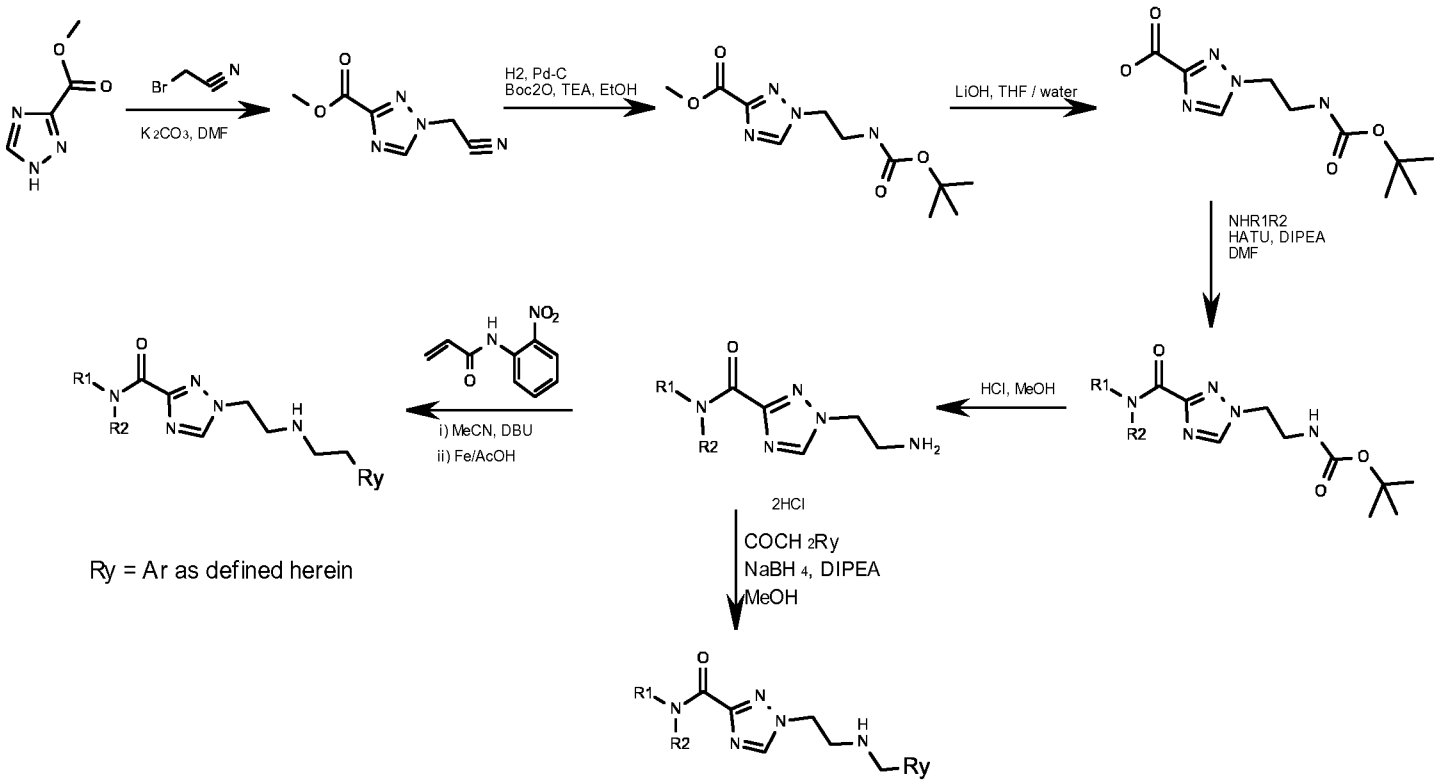


therein Y^1 indicates an optional substituent to X^4 as defined herein

Rx indicates an optional substituent to phenyl as defined herein

Ry = Ar has the meaning as defined herein and may correspond to Het-2

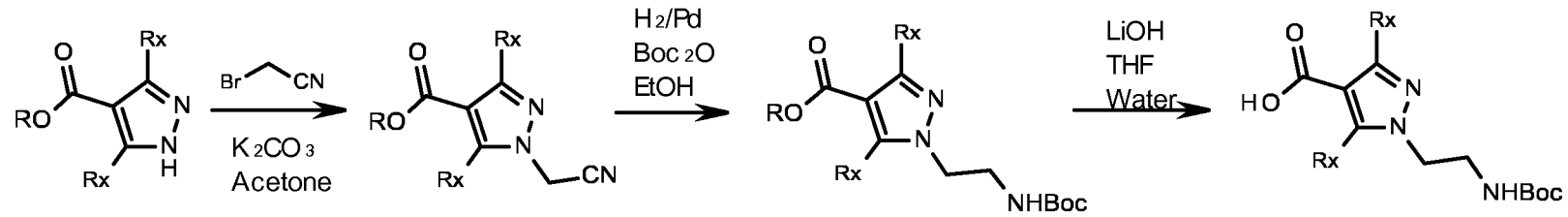
General Scheme 13



Ry = Ar as defined herein

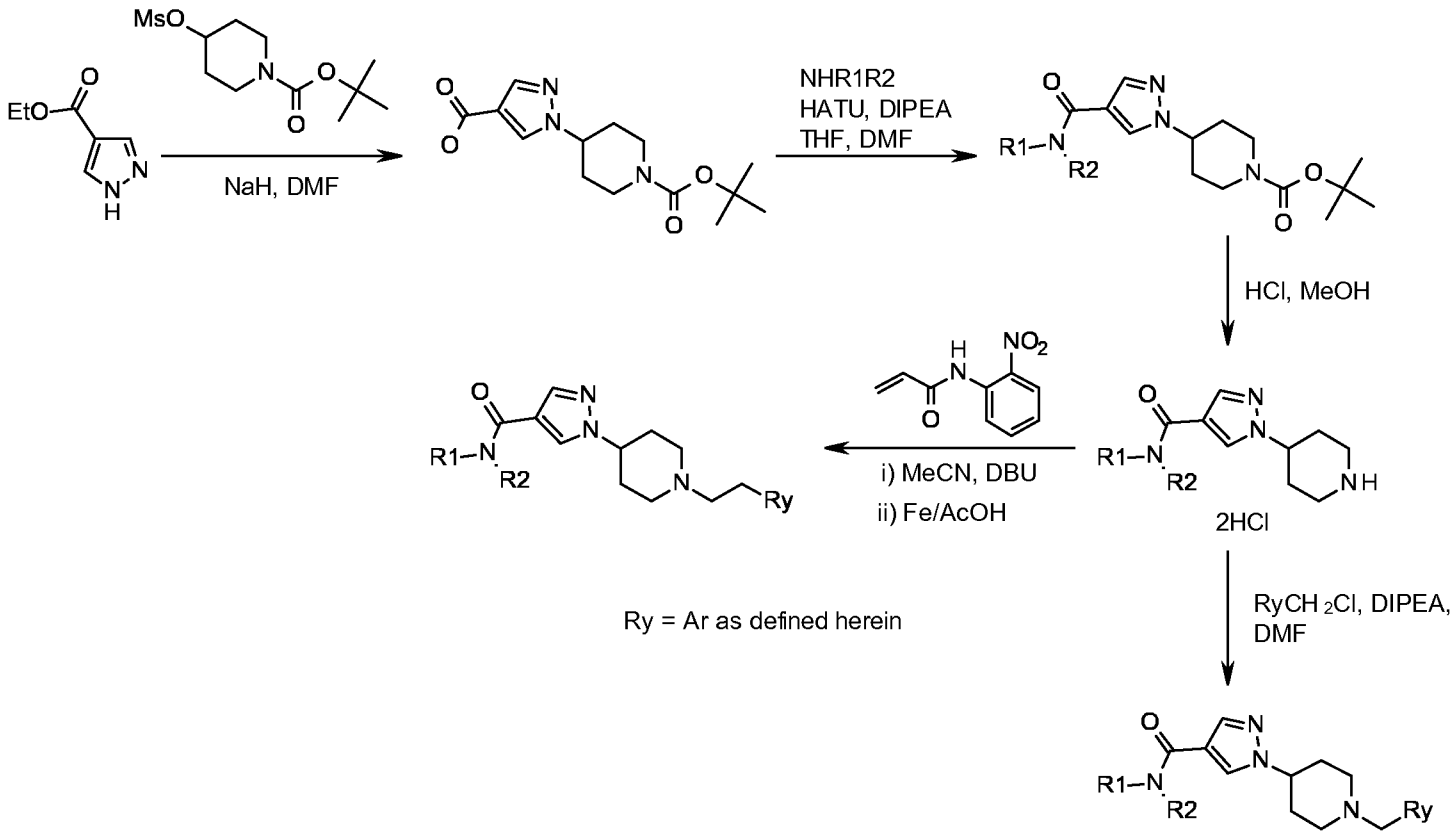
Ry = Ar has the meaning as defined herein and may correspond to Het-2

General Scheme 14



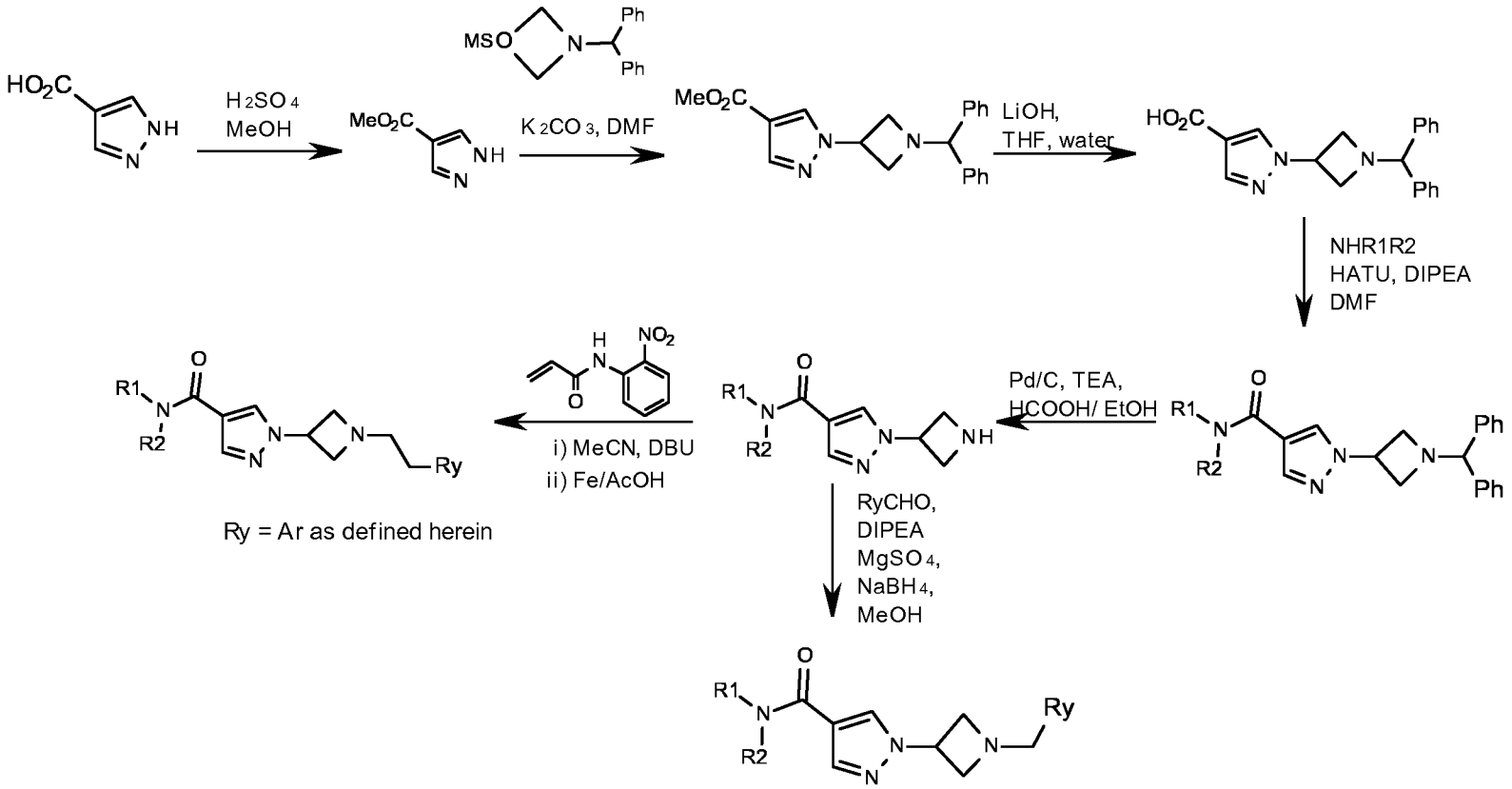
therein Rx indicates an optional substituent to X^1 or X^4 and corresponds to Y^1

General Scheme 15



Ry = Ar has the meaning as defined herein and may correspond to Het-2

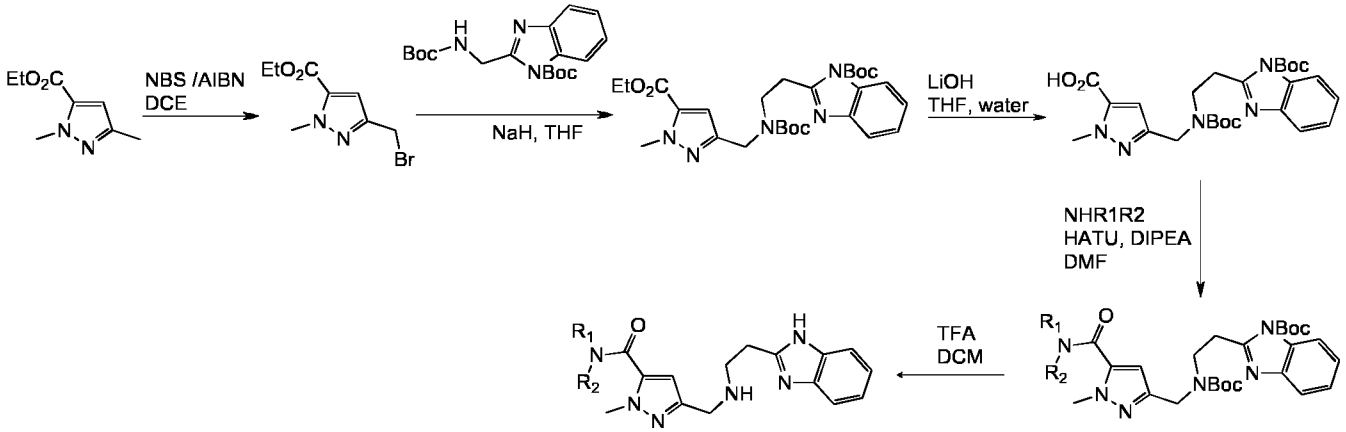
General Scheme 16



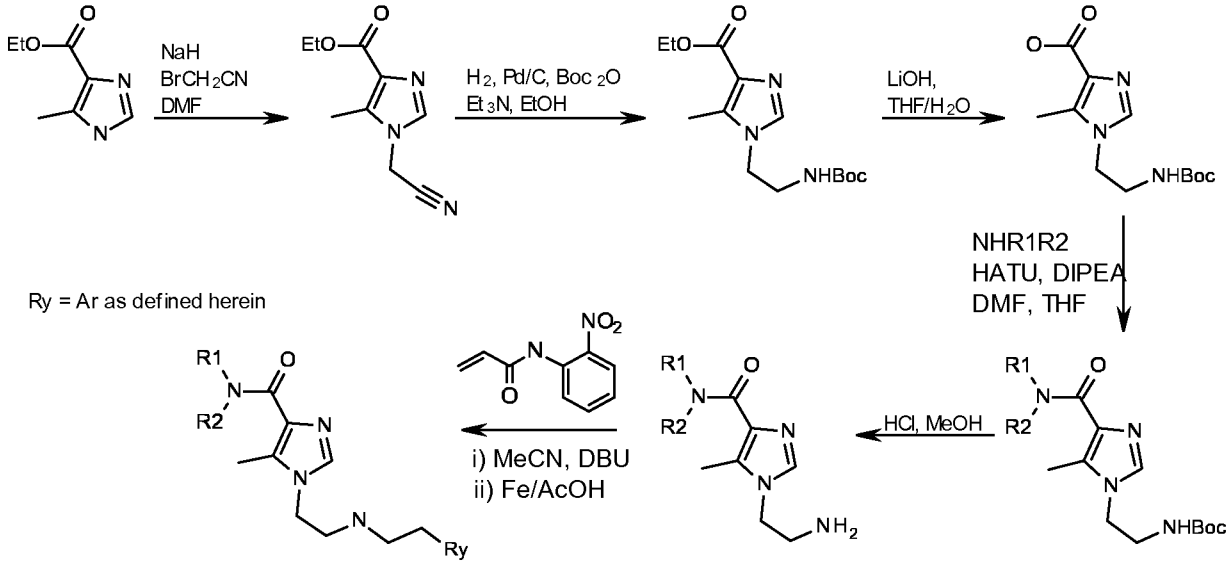
Ry = Ar as defined herein

Ry = Ar has the meaning as defined herein and may correspond to Het-2

General Scheme 18

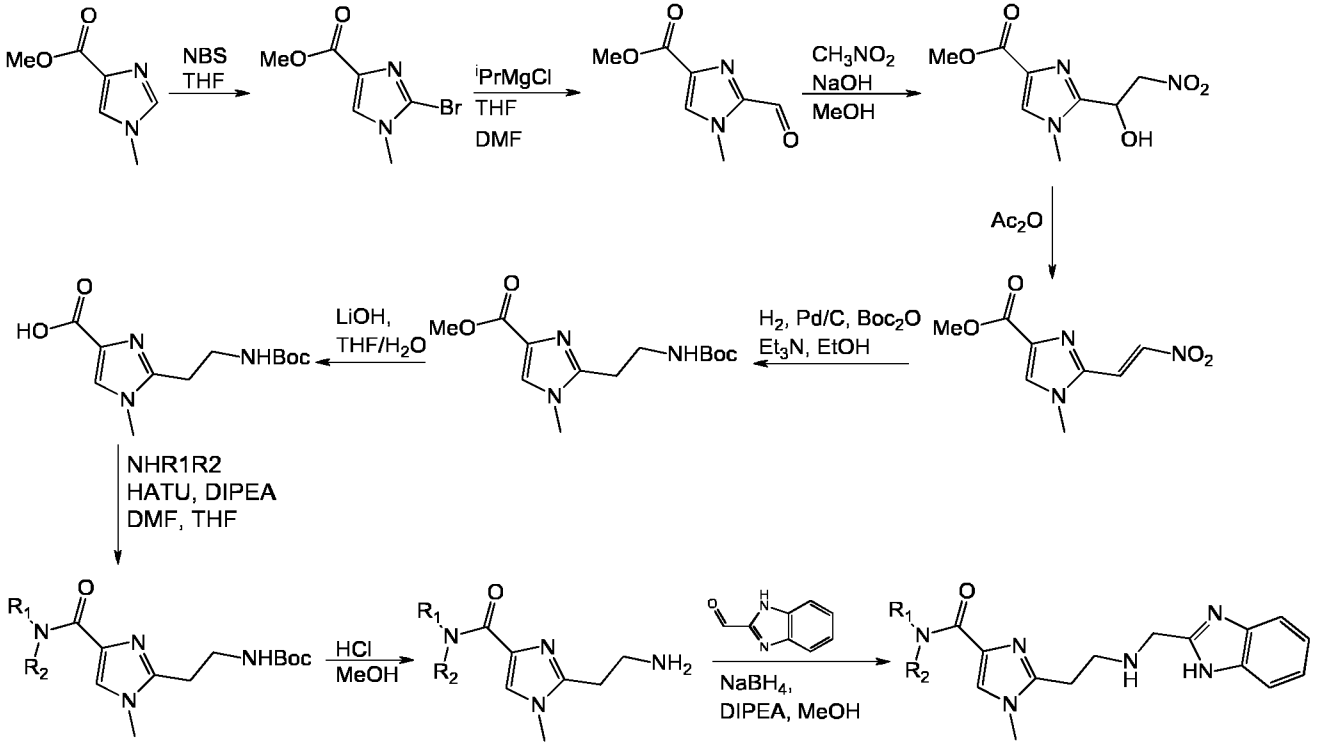


General Scheme 19

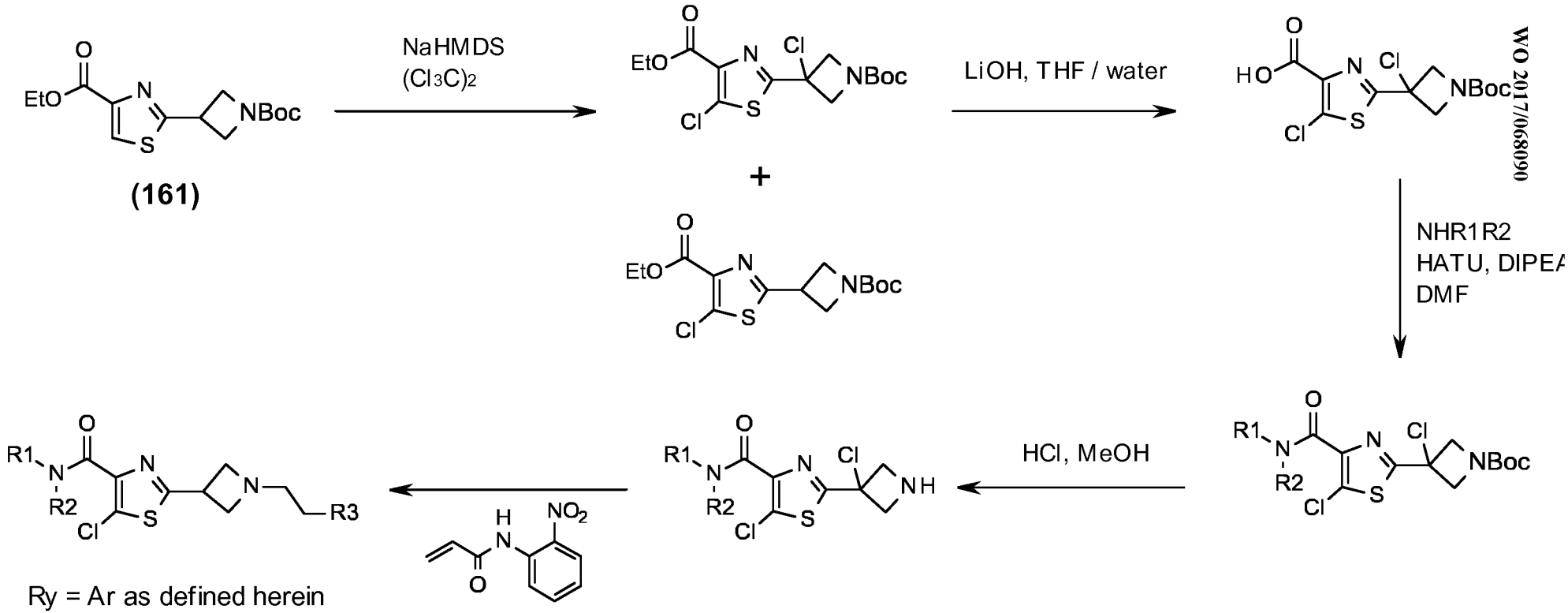


Ry = Ar has the meaning as defined herein and may correspond to Het-2

General Scheme 20

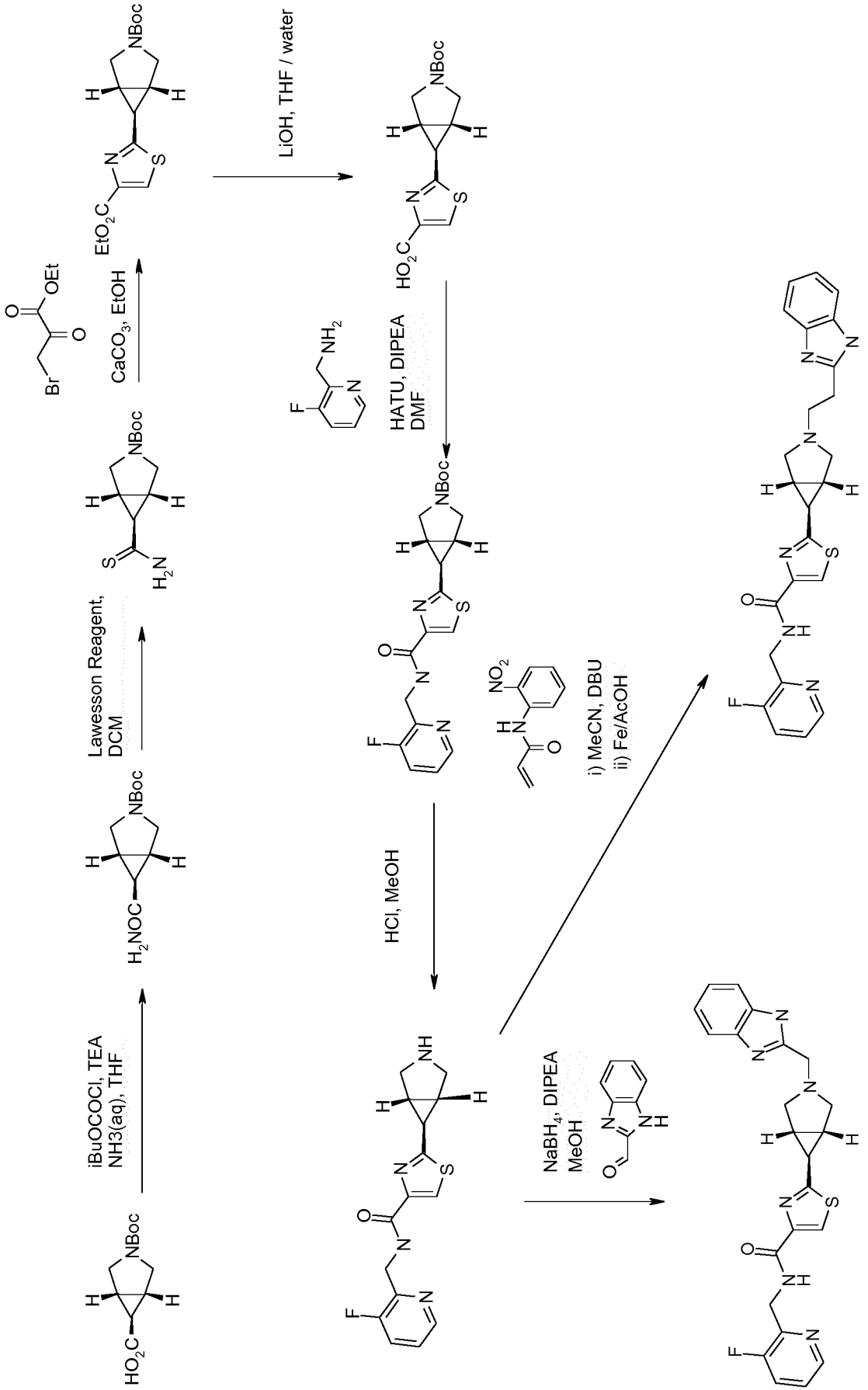


General Scheme 21

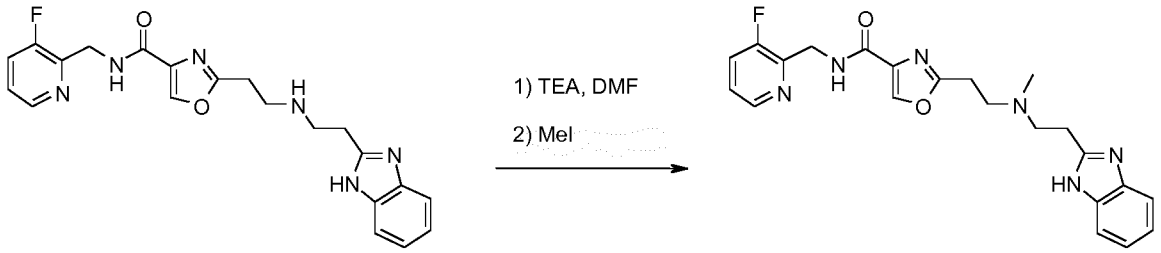


Ry = Ar has the meaning as defined herein and may correspond to Het-2

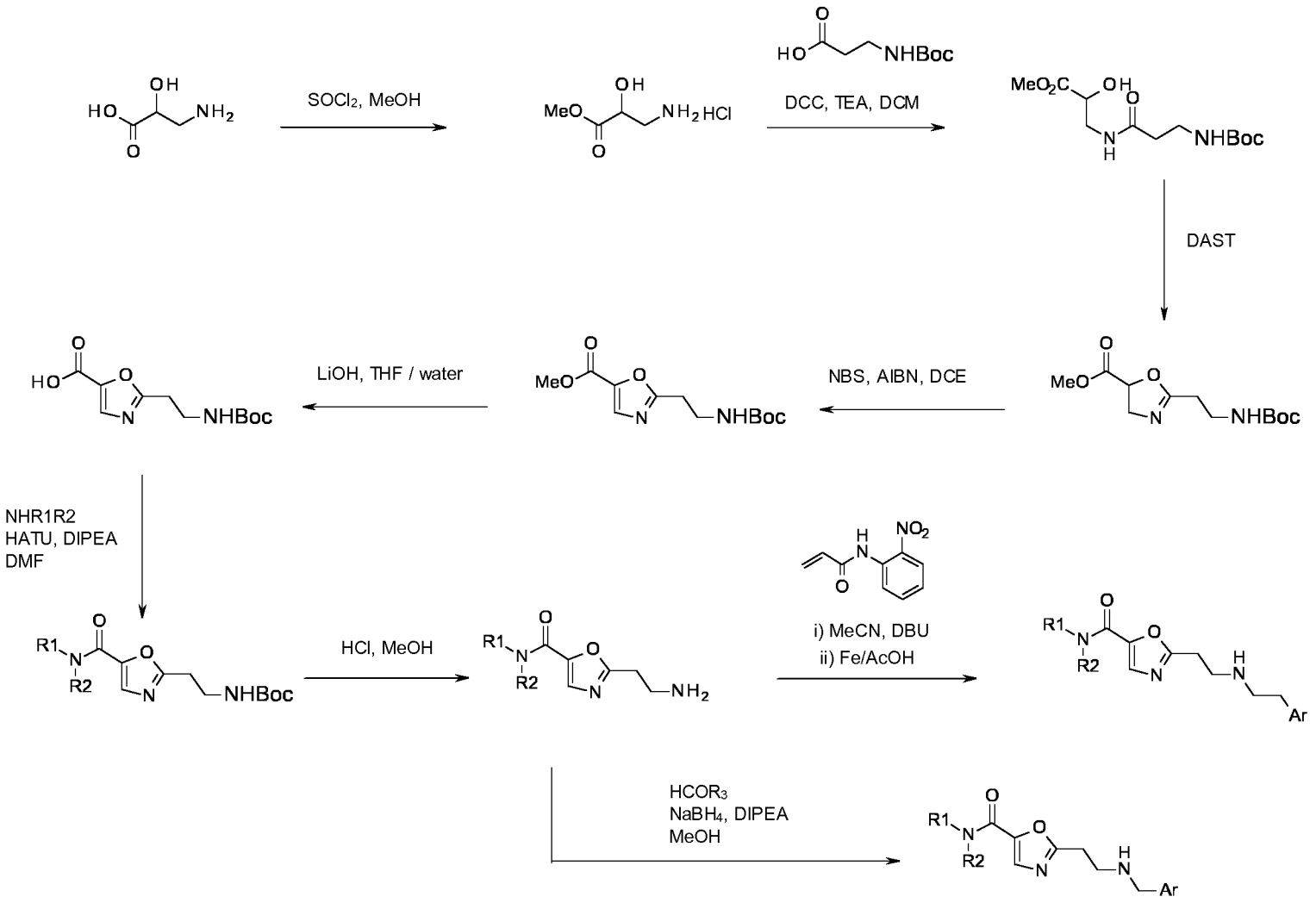
General Scheme 22



General Scheme 23

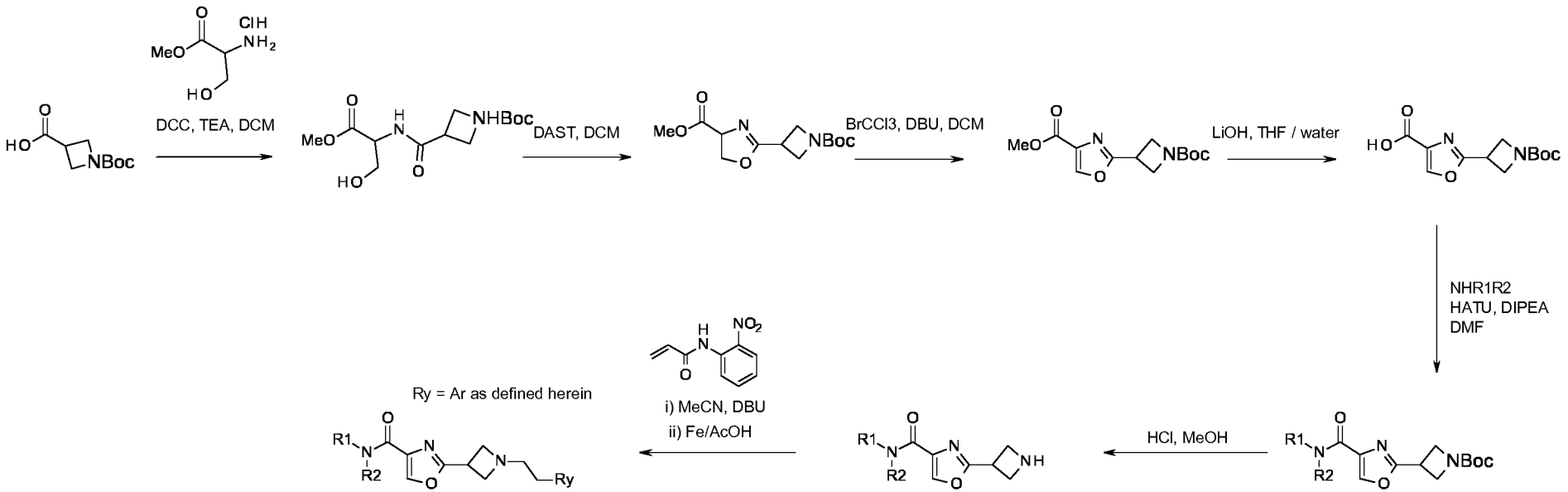


General Scheme 24



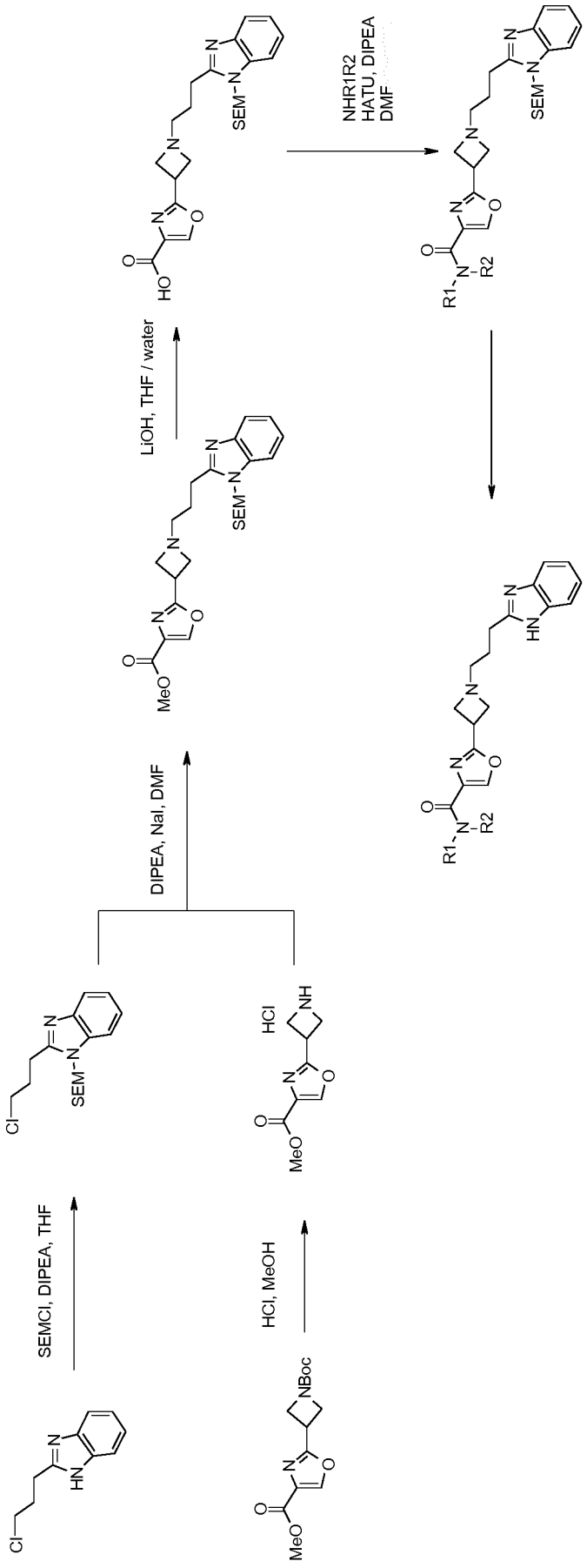
Ar has the meaning as defined herein and may correspond to Het-2

General Scheme 25

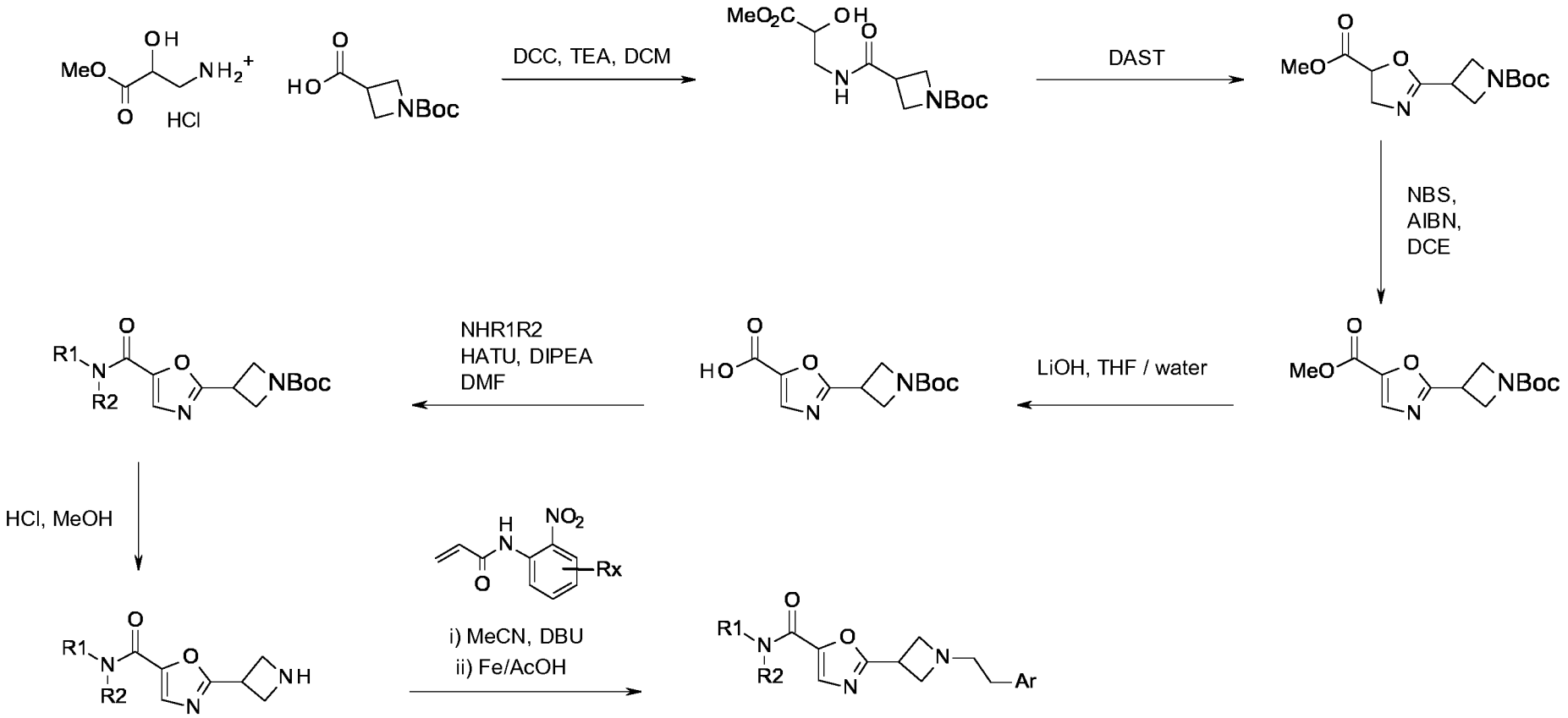


Ry = Ar has the meaning as defined herein and may correspond to Het-2

General Scheme 26



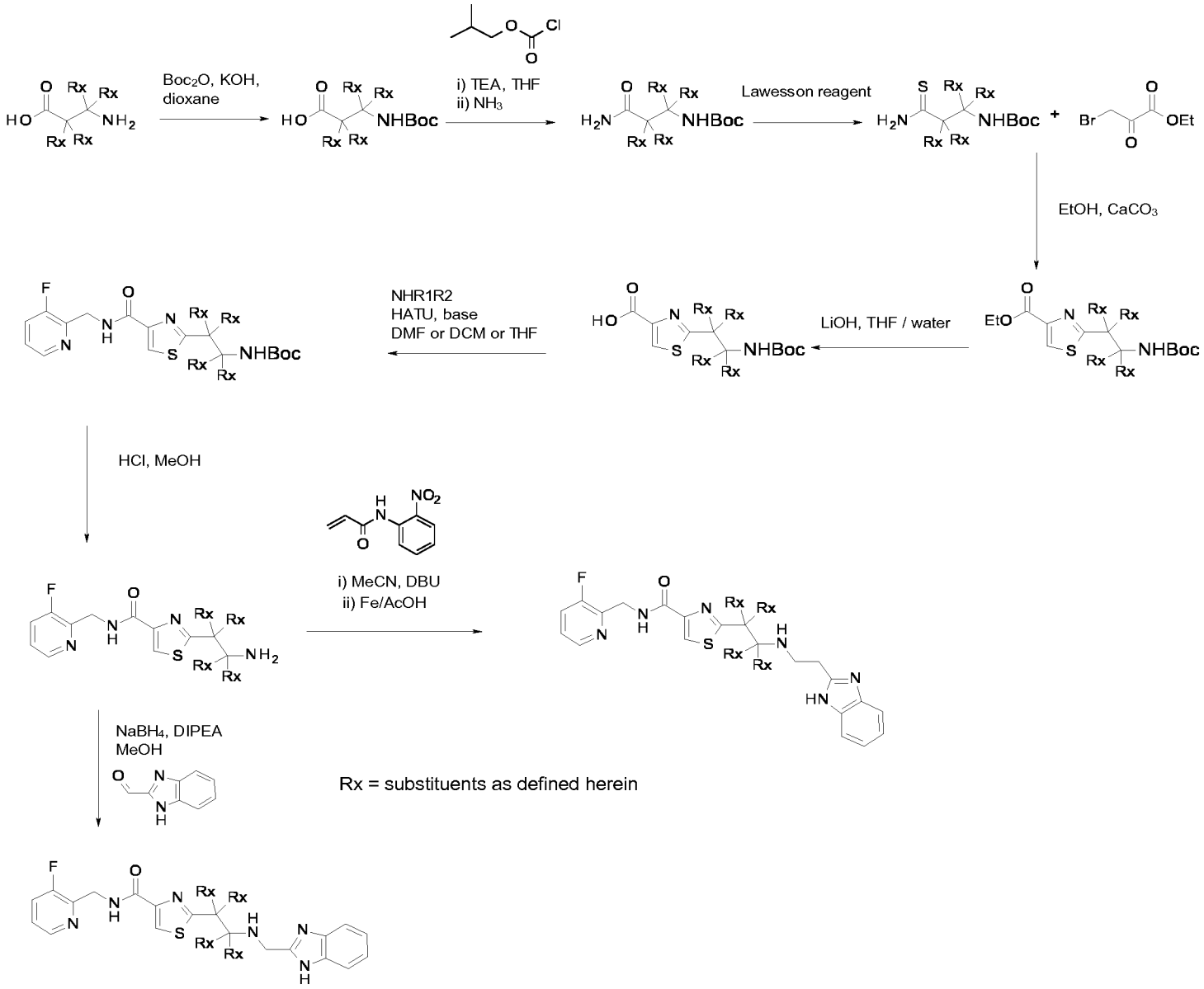
General Scheme 27



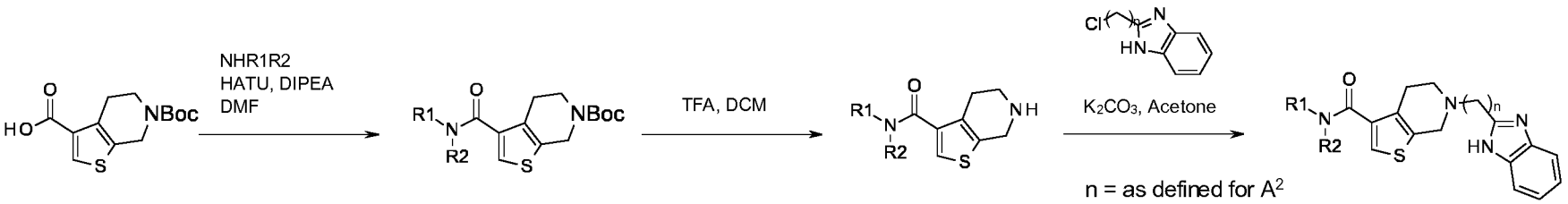
Ar has the meaning as defined herein and may correspond to Het-2

Rx = an optional substituent of phenyl as defined herein

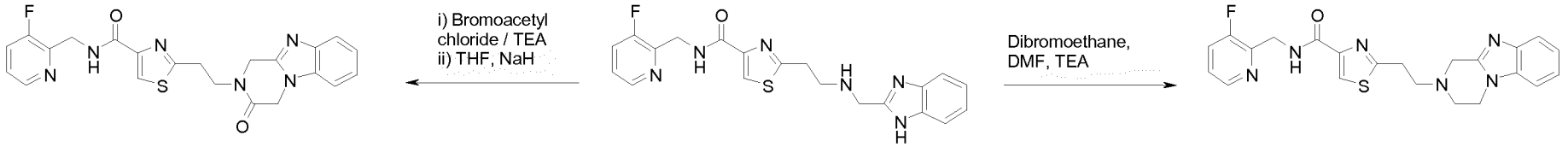
General Scheme 28



General Scheme 41

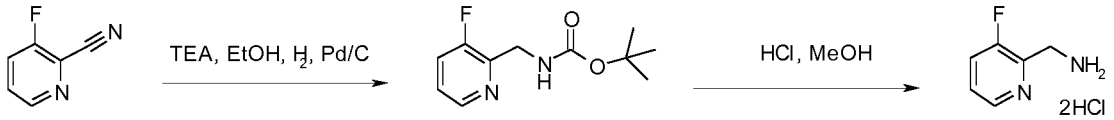


General Scheme 42



Intermediates

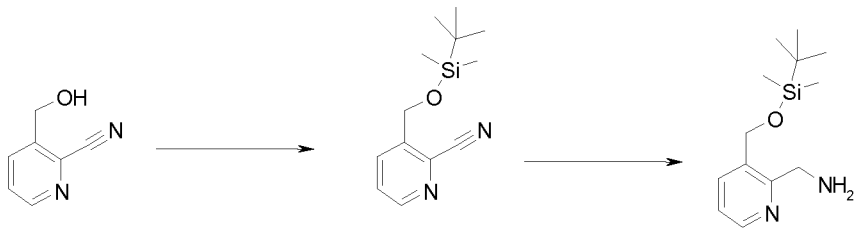
Scheme A



Scheme B

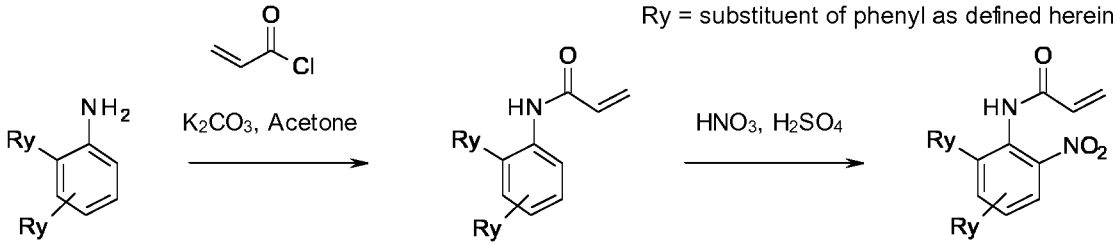


Scheme C

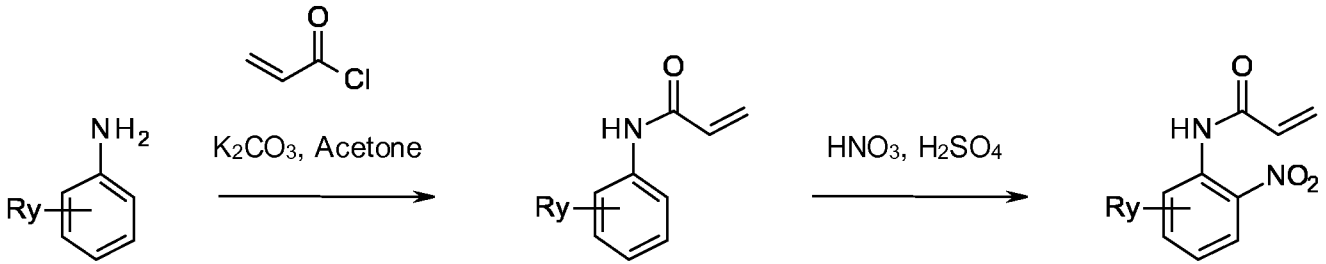


General Scheme K-I

Ry = substituent of phenyl as defined herein



General Scheme K-II



Ry = substituent of phenyl as defined herein

EXAMPLES

The invention is illustrated in more detail by the following examples. The examples are merely explanatory, and the person skilled in the art can extend the specific examples to further claimed compounds.

Pharmacological Assays

1. Hepcidin Internalization Assay (J774)

This cellular assay allows quantification of the binding of hepcidin to ferroportin (Fpn) through microscopic detection of internalization of a fluorescently labeled hepcidin into J774 cells. J774 is a mouse macrophage cell line which was shown to express Fpn endogenously uponincubation with iron (Knutson et al, 2005). Binding of hepcidin to Fpn triggers internalization and degradation of both hepcidin and Fpn. However, the TMR (6-carboxytetramethylrhodamine) fluorophore attached to hepcidin remains associated with the cell after degradation of the hepcidin peptide backbone. Therefore, microscopic detection of cell-associated TMR fluorescence is a measure of hepcidin binding to Fpn and internalization of hepcidin and Fpn. If TMR-hepcidin is prevented from binding to Fpn, cellular TMR fluorescence remains low (Dürrenberger et al, 2013). The effect of small molecular weight Fpn inhibitor compounds in this assay was evaluated in vitro as described below.

J774 cells, harvested from ca. 80% confluent cultures, were plated at $8x10^5$ cells/ml in complete medium (DMEM, 10% FBS, 1% Penicillin-Streptomycin) containing 200 µM Fe(III)NTA (nitrilotriacetic acid), 100 µl per well of 96 well MicroClear plates (Greiner; Cat. 655090) and grown at 37°C with 5% CO_2. After overnight incubation, cells were washed 3 times with pre-warmed DMEM w/o phenol red, 30 µl/well of DMEM w/o phenol red was added after the final wash and 10 µl/well of dilution series of test compounds were added in triplicates. J774 cells were pre-incubated with test compounds at 37°C with 5% CO_2 for 15 min. before TMR-hepcidin was added at 25 nM final concentration. Cells were incubated in a total volume of 50 µl at 37°C with 5% CO_2 for 2 hours, then Hoechst 33342 dye was added to a final concentration of 0.5 µg/ml to stain nuclei and further incubated for 10 min. at 37°C with 5% CO_2. Cells were washed 3 times with PBS and fixed in 100 µl of 4% paraformaldehyde in PBS for 15 min. at room temperature. After removal of the paraformaldehyde solution, cells were washed 3 times with PBS leaving 100µl per well and the plates were sealed with foil plate seal. TMR (530-550 nm excitation / 575-625 nm emission / 400 ms exposure time) and Hoechst 33342 (360-370 nm excitation / 420-460 nm emission / 10 ms exposure time) fluorescence images were acquired using a ScanR plate imager (Olympus) with a 20x high NA objective. Four pictures were acquired per well and fluorescence channel covering ca. 1500 cells per well. The acquired image data was analysed with the ScanR image analysis software. Image analysis included detection of nuclei (Hoechst 33342 fluorescence), identification of cell-associated regions, application of a virtual channel and thresholding for rolling-ball-type background reduction, followed by application of the Sum(Mean) algorithm to measure the TMR fluorescence associated with cells as a quantitative measure for internalized TMR- hepcidin. IC_{50} values were calculated with the Sum(Mean) raw data using "log(inhibitor) vs. response" curve fitting of Prism 5 software (GraphPad Software Inc., version 5.02). For each data set the fit of the "log(inhibitor) vs. response (three parameters)" model was compared to the fit of the "log(inhibitor) vs. response – Variable slope (four parameters)" model and the IC_{50} data of the preferred model was used. IC_{50} data of the Fpn inhibitors that were tested in the hepcidin internalization assay are listed in Table1. The IC_{50} of unlabeled hepcidin in this assay is 0.015 ± 0.011 µM.

Table 1 Average (AVE) IC_{50} data of Fpn inhibitors tested in the hepcidin internalization assay is shown for multiple measurements

Table 1

Exp. Comp. No.	J774 IC50 (uM)	Exp. Comp. No.	J774 IC50 (uM)	Exp. Comp. No.	J774 IC50 (uM)	Exp. Comp. No.	J774 IC50 (uM)	Exp. Comp. No.	J774 IC50 (uM)
1	0.012	72	1.36	114	0.118	161	0.361	210	4.913
2	0.035	74	0.21	115	>25.0 (< 50)	162	0.297	211	0.747
3	0.17	75	0.53	116	1.000	163	0.828	212	8.514
4	0.155	76	0.34	117	9.695	164	0.343	214	14.1
5	0.063	77	0.35	118	0.103	165	0.100	215	27.7
7	0.4	79	0.037	119	0.164	166	1.118	218	4.5
8	0.24	80	0.345	120	0.034	167	0.145	219	2.43
12	0.08	81	0.42	121	0.473	169	0.750	220	0.29
16	0.90	82	0.006	122	0.026	170	0.482	223	1.9
19	10.0	83	0.096	123	0.17	171	0.026	226	0.049
21	6.7	84	0.40	124	6.332	173	0.006	227	0.130
35	0.19	85	0.029	125	1.660	174	0.141	228	0.046
36	0.25	86	0.48	126	0.096	175	1.025	230	0.14
37	0.81	87	0.19	127	0.009	176	0.957	231	5.2
38	0.03	88	0.78	128	0.005	177	4.203	233	16
39	0.07	89	0.089	129	0.353	178	3.637	236	0.15
40	0.049	90	0.025	131	0.090	179	0.216	239	0.036
42	0.60	91	2.07	132	0.580	180	30.855	242	8.92
43	0.25	92	0.83	134	0.377	181	0.135	243	0.032
44	1.33	93	0.53	135	3.407	182	0.989	244	0.090
45	0.44	94	0.012	136	>10.49 (< 50)	183	0.131	247	0.082
46	0.59	95	7.23	137	0.514	184	0.063	249	0.040
47	0.72	96	2.97	138	0.179	186	0.30	250	0.014
49	30.58	97	0.27	139	4.794	187	87	251	0.062
54	0.46	98	1.85	140	3.727	188	1.16	253	0.226
55	0.015	99	2.99	141	0.167	189	0.060	256	0.081
56	0.41	100	0.46	142	21.606	191	0.33	257	0.035
57	0.10	101	0.28	144	0.012	192	13.56	258	0.152
58	0.01	102	0.058	145	0.385	193	0.287	261	0.554
59	0.05	103	2.37	148	2.085	194	0.72	265	0.070
60	2.39	104	0.90	151	0.111	195	0.21	273	0.228
61	0.56	105	0.077	152	0.004	196	1.13	274	0.145
63	0.61	106	1.52	154	0.0083	198	27.05	275	26.035
64	0.13	108	0.13	155	0.347	199	0.78	276	27.160
65	0.85	109	0.076	156	2.462	205	0.37	277	0.011
68	2.5	110	1.699	157	0.717	206	0.18	278	0.476
69	0.26	111	0.035	158	0.047	207	0.183	279	2.009
70	0.53	112	0.378	159	0.091	208	0.012	280	50.000
71	0.24	113	>25.0 (< 50)	160	0.256	209	0.379		

2. Biophysical Ferroportin-Hepcidin Binding Assay

This biophysical assay was developed to confirm inhibition of hepcidin binding to ferroportin (Fpn) more directly. Incubation of TMR-hepcidin with purified human Fpn isolated from *Pichia pastoris* yeast cells

expressing human Fpn with a C-terminal FLAG affinity tag (Bonaccorsi di Patti, 2014) leads to increased fluorescence polarization (FP) of the TMR-hepcidin ligand. Small molecular weight Fpn inhibitors were tested for inhibition of binding of TMR-hepcidin to Fpn, as detected by dose-dependent decrease of the TMR FP signal, as described in detail below.

A mixture of 1.3 μM human Fpn and 30 nM TMR-hepcidin in FP assay buffer containing 50 mM Tris-HCl pH 7.3, 200 mM NaCl, 0.02% DDM, 0.1% BSA was plated into a 384 well black low volume round bottom plate (Corning, Cat. 3677) at 16 μl per well. 8 μl of serial dilutions of test compounds were added in duplicates to reach final Fpn and TMR-hepcidin concentrations of 1 μM and 20 nM, respectively. Plates were incubated for 90 minutes at room temperature and parallel (S) and perpendicular (P) fluorescence was measured in a Synergy H1 fluorescence reader (BioTek). FP values were calculated in mP according to the following formula.

$$mP = \frac{F_{parallel} - F_{perpendicular}}{F_{parallel} + F_{perpendicular}} \times 1000$$

IC_{50} values were determined with the calculated mP values as described for the hepcidin internalization assay and are listed in Table 2. The IC_{50} of unlabeled hepcidin in this assay is 0.37 ± 0.067 μM.

Table 2 Average (AVE) IC_{50} data of Fpn inhibitors tested in the biophysical hepcidin-ferroportin binding assay is shown for multiple measurements.

Table 2

Exp. Comp. No.	FP IC50 (uM)
1	0.016
2	0.017
3	0.071
5	0.0511
7	0.18
8	0.282

Table 2 - continued

Exp. Comp. No.	FP IC50 (uM)	Exp. Comp. No.	FP IC50 (uM)	Exp. Comp. No.	FP IC50 (uM)	Exp. Comp. No.	FP IC50 (uM)	Exp. Comp. No.	FP IC50 (uM)
12	0.86	81	2.974	121	5.1	166	0.37	219	1.1
16	1.72	82	0.374	122	0.214	167	0.104	220	0.093
19	10.22	83	1.046	123	0.112	169	0.54	223	2.680
21	1.43	84	2.412	124	3.5	170	0.28	226	0.026
35	2.16	85	1.866	125	3.7	171	0.066	227	0.096
36	3.65	86	4.957	126	0.12	173	0.031	228	0.021
37	1.90	87	2.249	127	0.023	174	0.32	230	0.058
38	0.233	88	6.757	128	0.036	175	0.95	231	1.658
39	1.34	89	0.922	129	1.078	176	1.16	233	6.776
40	0.068	90	0.418	131	0.133	177	15.44	236	0.123
42	2.17	91	12.060	132	0.57	178	1.92	239	0.038
43	1.52	92	1.268	134	0.97	179	0.42	242	27.810
44	5.34	93	1.03	135	36.90	180	22.40	243	0.034
45	2.1	94	0.044	136	6.85	181	0.089	244	0.182
46	4.34	95	13.040	137	1.04	182	0.33	247	0.178
47	3.42	96	7.286	138	0.16	183	0.19	249	0.044
49	23.97	97	2.132	139	63.1	184	0.10	250	0.019
54	11.37	98	5.713	140	6.9	186	0.14	251	0.071
55	0.087	99	4.327	141	0.049	187	35.48	253	0.1481
56	0.566	100	1.419	142	10.5	188	0.63	256	0.046
57	0.43	101	0.315	144	0.073	189	0.047	258	0.194
58	0.076	102	0.258	145	0.35	191	0.52	257	0.038
59	0.270	103	2.525	148	7.3	192	49.26	261	0.4396
60	0.974	104	1.756	150	73	193	0.074		
61	1.690	105	0.420	151	0.089	194	0.73		
63	0.846	106	4.457	152	0.023	195	0.077		
64	1.237	108	0.478	153	57.77	196	0.87		
65	0.95	109	0.172	154	0.030	199	0.45		
68	4.056	110	3.422	155	0.46	205	0.29		
69	1.513	111	0.051	156	0.71	206	0.036		
70	1.065	112	1.035	157	4.27	207	0.047		
71	0.508	113	71.2	158	0.041	208	0.019		
72	0.931	114	0.23	159	0.035	209	0.038		
74	0.451	115	109	160	0.097	210	1.877		
75	1.830	116	0.058	161	0.26	211	0.154		
76	5.083	117	9.0	162	0.14	212	3.758		
77	2.813	118	0.25	163	2.97	214	3.188		
79	0.820	119	5.3	164	0.14	215	15.610		
80	2.276	120	0.071	165	0.061	218	2.2		

3. Inhibition of Ferroportin mediated Iron Export Activity in an Iron Response Assay

Intracellular iron levels are indirectly measured in this assay by monitoring the activity of a beta-lactamase (BLA) reporter gene fused to the human ferritin promoter and the associated iron regulatory element (IRE) contained within the 5' untranslated region of the ferritin mRNA. Expression of ferroportin (Fpn) in such a cell line leads to iron efflux and lower iron levels as reflected by lower activity of the reporter gene. On the

other hand, inhibition of Fpn-mediated iron efflux results in elevated cellular iron levels which is detected as increased reporter gene activity. Small molecular weight Fpn inhibitor compounds were tested for dose-dependent effects in this in vitro iron response assay as described below.

The HEK-293 cell line #354 was generated by stable integration of (i)a human Fpn-GFP fusion construct inserted in a derivative of the doxycycline-inducible pTRE-Tight-BI plasmid (Clontech, Cat. 631068) and (ii) a human ferritin promoter-BLA reporter gene into a derivative of the HEK-293 Tet-ON Advanced cell line (Clontech). To generate the ferritin-BLA reporter gene construct, a 1.4 kb fragment of the human ferritin H promoter was amplified by PCR from human genomic DNA (forward primer 5'-CAGGTTTGTGAGCATCCTGAA-3'; reverse primer 5'-GGCGGCGACTAAGGAGAGG-3') and inserted in front of the BLA gene present in the pcDNA™6.2/cGeneBLAzer™-DEST plasmid (Invitrogen, Cat. 12578-043) thereby replacing the original CMV promoter and placing the IRE that regulates translation of the ferritin gene ca. 170 bp upstream of the start codon of the reporter gene. #354 cellswere harvested from ca. 80% confluent cultures, seeded at $1.8x10^5$ cells/ml in DMEM/F12 GlutaMAX™ medium (Invitrogen, Cat. 31331-028) containing 10% FBS (Clontech, Cat. 631106), 1% Penicillin-Streptomycin, 200 µg/ml Hygromycin B (Invitrogen, Cat. 10687-010), Blasticidin 5 µg/ml, (Invitrogen, Cat. R210-01), 4 µg/ml doxycycline (Clontech, Cat. 631311), 50 µl per well of 384 well PDL-coated plates and grown at 37°C with 5% CO_2. After overnight incubation, 10 µl/well of dilution series of the test compounds were added in quadruplicates and plates were further incubated overnight at 37°C with 5% CO_2. Cells were washed 3 times with HBSS leaving 25 µl per well. BLA activity was detected by adding 5 µl/well of the GeneBlazer reagent CCF4-AM (Invitrogen, Cat. K1085) to the cells. After incubation of the plates in the dark at 18°C for 60 min., blue and green fluorescence signals were measured in a Safre2 fluorescence plate reader (Tecan) with excitation at 410 nm and emissions at 458 nm (blue) and 522 nm (green). The ratio of blue/green fluorescence as a measure for BLA activity was calculated and EC_{50} values were determined with the calculated blue/green fluorescence ratios as described for the hepcidin internalization assay. The EC_{50} data of the tested Fpn inhibitors is listed in Table 3. The EC_{50} of hepcidin in this assay is 0.096 ± 0.063 µM (n=37).

Table 3 Average (AVE) EC_{50} data of Fpn inhibitors tested in the iron response assay is shown for multiple measurements.

Table 3

Exp. Comp. No.	BLAzer EC50 (uM)
1	0.93
2	1.03
3	3.17
4	1.259
5	0.734
7	12.9
8	10.1

Table 3 - continued

Exp. Comp. No.	BLAzer EC50 (uM)	Exp. Comp. No.	BLAzer EC50 (uM)	Exp. Comp. No.	BLAzer EC50 (uM)	Exp. Comp. No.	BLAzer EC50 (uM)
12	8.27	93	20.55	140	>20.00 < 50	191	8.38
37	7.92	94	0.53	141	1.11	193	3.64
38	2.98	97	1.81	144	0.47	194	>3.22 < 50
39	2.90	99	22.80	145	4.7	195	3.55
40	1.45	100	6.56	151	0.72	196	12.72
42	36.26	101	2.92	152	0.17	199	5.70
43	30.95	102	1.85	154	0.74	205	3.83
44	18.31	105	2.63	155	8.17	206	3.26
46	38.67	108	4.12	156	16.13	207	2.76
55	1.23	109	2.62	158	0.62	208	0.50
56	10.38	111	0.62	159	1.16	209	3.38
57	2.11	112	13.47	160	1.91	211	6.1
58	1.72	114	4.45	161	17.18	220	17.0
59	1.38	116	2.79	162	4.37	226	2.34
61	37.46	118	2.69	164	2.11	227	24.90
64	4.53	120	1.60	165	2.59	228	2.12
65	32.33	122	4.33	167	2.84	230	6.38
68	10.40	123	3.04	169	8.23	236	12.72
71	1.79	126	1.26	170	3.96	239	0.88
75	6.00	127	0.42	171	1.23	243	1.40
79	0.84	128	0.097	173	0.10	244	3.86
82	0.76	129	10.56	174	7.73	247	3.15
84	13.15	131	0.75	179	25.94	249	1.55
85	18.69	132	13.94	181	3.72	250	0.46
86	22.34	134	4.09	182	6.84	251	2.27
87	16.56	135	>20.00 < 50	183	3.58	253	3.176
88	13.08	136	>20.00 <50	184	1.60	256	0.628
89	5.05	137	5.75	186	4.94	257	0.636
90	4.03	138	1.72	188	>39.07 < 50	258	2.525
92	17.78	139	>20.00 < 50	189	3.10	265	1.998
						273	3.604
						274	1.122
						277	0.17

4. Ferroportin Internalization and Degradation Assay

HEK-293 cell line #354 (described in example 3) was used to measure the capacity of the compounds to induce internalization and degradation of ferroportin (Fpn) by fluorescence activated cell sorting (FACS). Growing HEK-293 #354 cells in doxycycline containing media induced expression of human Fpn-GFP fusion protein on the cell surface. Data from 10 independent experiments showed that cultivation of HEK#354 cells for 48h in the presence of 4 µg/ml doxycycline induced in average 42.6% ± 6.4 % Fpn-

GFP-positive cells. Small molecular weight Fpn inhibitor compounds were tested for dose-dependent effects on the Fpn-GFP mean fluorescence intensity (MFI) on HEK-293 cell line #354, as described below. HEK#354 cells were harvested from ca. 80% confluent cultures, seeded at $0.6x10^6$ cells/ml in DMEM/F12 GlutaMAX™ medium (Invitrogen, Cat. 31331-028) containing 10% FBS (Clontech, Cat. 631106), 1% Penicillin-Streptomycin (Invitrogen, Cat. 15140-122), 200 µg/ml Hygromycin B (Invitrogen, Cat. 10687-010), Blasticidin 5 µg/ml, (Invitrogen, Cat. R210-01), 4 µg/ml doxycycline (Clontech, Cat. 631311), 50 µl per well of 384 well plates (Greiner; Cat. 781091) and grown at 37°C with 5% CO_2. After overnight incubation, 10 µl/well of dilution series of the test compounds were added in quadruplicates and plates were further incubated overnight at 37°C with 5% CO_2. Cells were washed once with FACS buffer (PBS containing 1% FBS, 2 mM EDTA and 0.05% NaN_3), harvested in FACS buffer with 0.5 µg/ml propidium iodide (Sigma, Cat. P4864) and analyzed in a flow cytometer (CANTO™ II, BD Biosciences) equipped with high throughput sampler. Live HEK#354 cells were gated as propidium iodide negative population and analyzed for expression of Fpn-GFP. MFI of Fpn-GFP of > 2000 live cells for each compound dilution was calculated using FlowJo (Tree Star's, Oregon) and the potency of the Fpn-inhibitors to induce internalization and degradation of Fpn-GFP was calculated as described for the hepcidin internalization assay. EC_{50} data of the Fpn inhibitors that were tested in the ferroportin internalization and degradation assay by FACS are listed in Table 4. The average EC_{50} value of hepcidin in this assay is 0.004 ± 0.002 µM.

Table 4 Average (AVE) EC_{50} data of Fpn inhibitors tested in the ferroportin internalization and degradation assayis shown for multiple measurements.

Table 4

Exp. Comp. No.	EC50 (uM)
1	0.22
2	0.63
3	1.84
4	1.198
5	0.549
7	1.89
8	1.13

Table 4 – continued

Exp. Comp. No.	EC50 (μM)	Exp. Comp. No.	EC50 (μM)	Exp. Comp. No.	EC50 (μM)	Exp. Comp. No.	EC50 (μM)
40	0.81	137	11.073	171	0.571	211	4.43
55	1.029	138	0.678	171-B	0.319	213 x 3 HCl	4.14
58	0.387	139	>20.0 < 50	173	0.071	220	3.82
82	0.689	140	>20.0 < 50	174	3.960	226	0.49
94	0.22	141	0.290	175	12.452	227	1.58
109	0.885	142	39.745	176	16.985	228	0.46
111	0.075	144	0.043	179	1.207	228-B	0.22
112	3.775	145	1.245	181	0.930	230	0.95
113	41.330	148	1.050	182	23.692	231	8.33
114	2.956	151	0.523	183	1.850	236	2.16
115	38.250	152	0.071	184	1.188	239	0.32
116	0.590	154	0.130	186	5.059	243	0.51
117	>25.0 < 50	155	3.954	188	35.985	244	1.69
118	4.908	156	12.110	189	0.679	247	2.18
120	0.530	157	7.862	191	2.512	249	0.95
122	3.015	158	0.325	193	3.946	250	0.60
123	4.507	159	0.757	193-B	1.391	251	1.42
126	0.757	160	1.287	194	8.050	253	1.828
127	0.081	161	5.300	195	1.459	256	0.736
128	0.006	162	1.412	196	24.845	257	0.518
129	4.464	163	7.411	199	2.966	258	1.231
131	0.194	164	3.207	205	11.115	265	1.196
132	2.148	165	0.587	206	2.072	273	1.721
134	5.194	166	>20.0 < 50	207	1.608	274	0.582
135	21.210	167	1.462	208	0.15	277	0.069
136	17.860	169	4.121	209	2.440		

5. Ferroportin ubiquitination and degradation

Exposure of cells expressing ferroportin (Fpn) to hepcidin is known to trigger ubiquitination and subsequent internalization and degradation of Fpn (Qiao, 2012). The potential of Fpn inhibitors to induceFpn ubiquitination and degradation was investigated with an immunoprecipitation assay using the J774 mouse macrophage cell line which expresses Fpn upon treatment with iron.

J774 cells (DSMZ, Cat. ACC170) were seeded at 0.8x106 cells/ml in 15 ml of medium(DMEM Gibco Cat. 11971-025, 10% heat inactivated FBS Gibco Cat. 10500-064, 1% Penicillin-Streptomycin Gibco Cat. 15140-122) containing 200µM Fe(III)-NTA into 10 cm tissue culture dishes (Greiner Cat. 664160) and grown overnight at 37°C with 5% CO_2. Cells were incubated with synthetic human hepcidin (Bachem, Cat. H-5926) or Fpn inhibitor compounds for 10 min or 120 min. Cells were washed and lysed with ice-cold lysis buffer (Pierce, Life Technoligies, Cat. 87787) including 1X HALT protease inhibitor cocktail (Life technologies, Cat. 78429) and 10 mM iodoacetamide (Sigma, Cat. I6125) to stabilize ubiquitinated proteins. Immunoprecipitation was done using the Pierce Classic IP Kit (Life Technologies, Cat. 26146) following the manufacturer's protocol. Briefly, 2 mg protein in 1.25 ml IP lysis buffer was incubated by mixing for 1h at 4°C with control agarose beads to pre-clear the lysate and reduce nonspecific signal. Unbound lysate was then incubated overnight with 12 µg per reaction of the affinity purified anti-Fpn antibody F308 that was raised against a GST fusion protein of mouse Fpn amino acids 224-308. Immune complexes were captured by pipetting 14µl settled Pierce Protein A/G Plus Agarose beads (Life Technologies, Cat. 20423) per reaction and the slurry was incubated for 1.5 h at 4°C with gentle end-over-end mixing. The beads were washed and immune complexes were eluted directly with 75 µl SDS NuPAGE LDS sample buffer (Life Technologies, Cat. NP0007) containing DTT (Life Technologies, Cat. NP0009). After immunoprecipitation samples were analyzed by Western blotting using a rabbit anti-mouse MTP1 antiserum (Alpha Diagnostic International, Cat. MTP11-A) and a mouse anti-mono- and polyubiquitinylated conjugates monoclonal antibody (Enzo Lifesciences, Cat. BML-PW8810) for detection of ferroportin and ubiquitin, respectively. Mouse monoclonal anti-rabbit IgG light chain (Abcam, Cat. ab99697) and anti-mouse IgG H&L (Abcam, Cat. ab6789) HRP conjugates were used as secondary antibodies.

A selection of eleven Fpn inhibitors were tested in this assay and compared to hepcidin. As shown in Fig. 1 and Table 5, treatment of cells with Fpn inhibitors lead to rapid ubiquitination within 10 minutes(Fig. 1 upper panel) and degradation after 2 hours of Fpn (Fig. 1 lower panel). The degree of Fpn degradation by the Fpn inhibitors was comparable to the effect of hepcidin. However, hepcidin treatment resulted in ubiquitinated Fpn with higher molecular weight compared to Fpn inhibitor treatment, suggesting poly-ubiquitination versus mono-ubiquitination by hepcidin versus Fpn inhibitors, respectively.

Table 5 Summary of Fpn inhibitors tested in the Fpn ubiquitination and degradation assay. The effects of treatment with Fpn inhibitors on Fpn degradation and Fpn ubiquitination were scored by visual inspection of Western blots (+ comparable to hepcidin; - no effect; +/- intermediate effect).

Table 5

Exp. Comp. No.	Concentration (uM)	Fpn Ubiquitination (10 min.)	Fpn Degradation (120 min.)
1	0.12	+	+
40	1.9	+	+
94	0.3	+	+
111	0.3	+	+
126	0.8	+/-	+
127	0.1	+	+
128	0.05	+	+
152	0.04	+	+/-
167	1.5	+	+
208	0.2	+	+
226	0.5	+	+
hepcidin	0.15	+	+

Figure 1 Fpn inhibitor trigger ubiquitination and degradation of Fpn expressed in a mouse macrophage cell line. J774 cells were incubated overnight with Fe(III)-NTA to induce expression of Fpn. Cells were then treated with ca. 10-fold IC_{50} concentrations, as determined in the hepcidin internalization assay (see Table 1), of hepcidin (Hepcidin, 150 nM) or Fpn inhibitors Example Compound No. 208 (210 nM), Example Compound No. 167 (1.5 µM), Example Compound No. 127 (120 nM), Example Compound No. 152 (40 nM) for 10 or 120 min before harvesting and immunoprecipitation with the anti-Fpn antibody F308. Mock treated cells were harvested after 120 min (Control).
Immunoblotting of immunoprecipitates with the anti-Fpn antibody MTP1 revealed disappearance of ferroportin 120 min after treatment with the Fpn inhibitors, to a similar extent as in the sample treated with hepcidin (upper panel). Rapid ubiquitination of Fpn was observed 10 min after treatment of cells with Fpn inhibitors and hepcidin. Protein molecular weight standards are indicated on the left in kD.

6. Inhibition of Iron Efflux by Ferroportin Inhibitors

The activity of hepcidin and ferroportin inhibitor compounds regarding their ability to block iron export via ferroportin was tested on T47D cells (ECACC, Cat. 85102201) as described below.
Cells were plated in 24-well plates (Greiner, Cat. 662160) containing 350'000 cells/well and incubated overnight with 100 µM ^{58}Fe (^{58}Fe(II)-Sulfate, Vifor Pharma Batch No. ROR 3085) in 500 µM L-Ascorbic Acid (Sigma Aldrich, Cat. 795437) containing growth medium. Cells were washed once with 500 µl iron uptake buffer (IUB; PIPES 40mM, Cat. P1851, Glucose Monohydrate 10 mM, Cat. 49158, Sodium Chloride 260 mM, Cat. 71379, Potassium Chloride 20 mM, Cat. P9541, Magnesium Sulfate 2 mM, Cat. 63138, Sigma Aldrich), then once with removal buffer (2 min incubation, BPDS 100 µM, Cat. 11890 and $Na_2S_2O_4$ 500 µM, Cat. 157953, Sigma Aldrich, in IUB) and again twice with IUB. A serial dilution of hepdicin (Bachem) or ferroportin inhibitors (4 µM-0.0064 µM, 5 fold dilution) was added in a total volume of 0.6 ml per well. Cells were incubated at 37°C with 5% CO2 for 20 h. Supernatants were collected and ^{58}Fe was measured using inductively coupled plasma mass spectrometry (ICP-MS, Thermo Scientific, Element 2). Pellets were harvested for protein concentration measurements. Results are plotted as ng ^{58}Fe in supernatant per mg protein in cell lysates. Example Compound No. 127 inhibited iron efflux with similar potency as the endogenous Fpn ligand hepcidin (Fig. 2).

Figure 2 Representative iron efflux inhibition of Hepcidin (IC_{50}: 0.086 µM) and Example Compound No. 127 (IC_{50}: 0.080 µM).

7. Hypoferremia in naïve mice

Injection of synthetic hepcidin in wild-type (WT) naïve mice resulted in a reduction of serum iron levels (40-50% from the vehicle control) with a maximal effect at 3-4 hours post treatment (Rivera, 2005; Fig. 3A). This data suggested that the injected hepcidin binds to and triggers the internalization of ferroportin (Fpn) on duodenal enterocytes and splenocytes, causing a rapid drop in serum iron. Similarly, orally administered small molecular weight Fpn inhibitors decreased the levels of serum iron of WT C57BL/6 mice in a dose-dependent manner (Fig. 3B) with an efficacy comparable to hepcidin. This data validated the use of WT mice as a simple and reliable model for testing the acute efficacy of Fpn inhibitors in vivo. Female C57BL/6 mice (Janvier, France) at age of 9 weeks were fed a standard diet (Harlan Provimi Kliba 3436) and treated per os (p.o.) with compounds or the corresponding amount of vehicle at a volume of 10 ml/kg body weight. Fpn inhibitors were formulated in 0.5% methylcellulose / water or 20% cremophor EL/ water and dosed p.o. in mice at 10, 30 or 100 mg/kg body weight. Three hours later, mice were pre-terminally anesthetized in isoflurane chambers and blood was collected by retro-orbital bleeding. Mice were sacrificed by cervical dislocation and spleens, livers and duodena were harvested and used for biomarker analysis. All experiments have been conducted in compliance with the license approved by the responsible veterinarian authorities. Serum was isolated by centrifugation of blood into gel-containing microtainers and serum iron was determined by the MULTIGENT Iron assay (Abbott Diagnostics, 6K95). Eight mice per group were used and one-way ANOVA with Bonferroni's multiple comparison test was performed to analyze the statistical differences between the experimental groups. The efficacy of selected Fpn inhibitors in WT C57BL/6 mice is shown in Table 6.

Figure 3 Serum iron reduction induced by hepcidin and ferroportin inhibitor according to Example Compound 94 (Example Compound No. 94).
A Kinetic of serum iron in naïve C57BL/6 mice injected with synthetic hepcidin (5 mg/kg) intraperitoneally (i.p.) for the indicated time. * - ***- indicate statistically significant serum iron reduction compared to PBS-treated mice.
B Serum iron levels in naïve C57BL/6 mice treated with the indicated amounts of either hepcidin (i.p.) or Example Compound 94 (Example Compound No. 94). (p.o.) for 3h.

Table 6 Efficacy of Fpn inhibitors tested in the naïve mouse hypoferremia model.
Serum iron reduction induced by selected ferroportin inhibitors dosed p.o. in naïve WT C57BL/6 mice at 10, 30 and 100 mg/kg. Relative serum iron reduction at 3h after dosing was calculated by subtracting the average of serum iron values of animals dosed with the Fpn inhibitor from that of vehicle-treated animals. The difference in average serum iron values between vehicle and compound treated groups was then divided by the average of serum iron of the vehicle control group and listed as percentage.

Table 6

	Serum Iron Reduction at 3h (%)		
Exp. Comp. No.	**Dose 10 mg/kg**	**Dose 30 mg/kg**	**Dose 100 mg/kg**
1	0	28	51
2	9	26	50
12	15	20	45
39	10	20	35
40	10	30	50
55	0	20	55
58	20	30	40
90	0	0	40

94	30	50	80
118	8	24	49
126	7	23	62
127	17	47	54
137	-2	14	25
154	13	35	56
159	4	26	60
167	19	17	34
171	10	42	61
193	13	11	31
208	50	65	73
228	13	26	55
239	12	20	51
250	5	18	40
277	6	21	54

8. Prevention of iron absorption in anemic rats

To assess the in vivo efficacy of ferroportin (Fpn) inhibitors to block iron absorption, a series of Fpn inhibitors were tested in an anemic rat model for iron absorption. Wistar rats (3-4 weeks old, n=5, Janvier Labs) were fed a low iron diet (Provimi-Kliba, Cat. 2039) until their hemoglobin (Hb) values reach 7 - 8 g/dl one day before dosing of the Fpn inhibitor compounds. One hour before oral application of 0.5 mg/kg of ferrous sulfate, test compounds formulated in methyl cellulose or Cremophor were dosed orally. Blood samples were taken by tail vein puncture one hour before administration of iron (-1h), immediately after dosing of the Fpn inhibitors (0h) and one hour (1h), three hours (3h) and occasionally up to 6 hours (6h) after dosing of the test compounds. Serum iron levels were measured (Abbott Diagnostics, Cat. 6K95) and inhibition of the rise of serum iron three hours after dosing of the test compound was calculated as a measure for efficacy of the Fpn inhibitors in blocking iron absorption (Table 7). As shown in Fig. 4, oral administration of the Fpn inhibitor Example Compound No. 55 at 3 mg/kg, 10 mg/kg or 30 mg/kg reduced serum iron levels by 54%, 72% and 89%, respectively, three hours after iron dosing when compared to serum iron levels of vehicle-control animals before iron dosing and corrected for the baseline serum iron levels in vehicle-treated animals that did not receive a dose of iron.

Table 7 Fpn inhibitors tested in the anemic rat model for inhibition of iron absorption. Relative inhibition values (%) of serum iron levels are shown, corrected for average baseline serum iron levels of the control group which did not receive a dose of oral iron, compared to control groups treated with vehicle before iron dosing. Average values of groups (n=5) treated with the indicated doses of Fpn inhibitor are shown. Statistically significant (2-way ANOVA with Bonferroni post test) differences observed between compound-treated and vehicle-treated groups are indicated (*** $p<0.001$; ** $p<0.01$, * $p<0.05$).

Figure 4 Dose-dependent block of iron absorption in anemic rats by Fpn inhibitor Example Compound No. 55. One hour before oral administration of a dose of ferrous sulfate (0.5 mg/kg), Example Compound No. 55 was orally administered either at 3 mg/kg (light blue line), 10 mg/kg (green line) or 30 mg/kg (dark blue line). Dosing of Example Compound No. 55 led to statistically significant ($p<0.001$) and dose-dependent inhibition of the increase in serum iron observed 3 hours after iron dosing in animals treated with vehicle (red line). Baseline serum iron levels in the vehicle-treated group that did not receive a dose of iron are also shown (black line). Averages with standard deviations are plotted for each treatment group and time point.

Table 7

	Serum Iron Inhibition (%) at 3h				
Exp. Comp. No.	Dose 1 mg/kg	Dose 3 mg/kg	Dose 10 mg/kg	Dose 30 mg/kg	Dose 100 mg/kg
1	nd	2.1	42.6**	64.9***	nd
2	nd	-3	29**	57***	nd
40	nd	nd	32**	53***	97***
55	nd	54***	72***	91***	109***
58	nd	nd	nd	64***	95***
94	59***	0	70***	nd	nd
127	nd	-8	47***	79***	nd
154	nd	22*	16	58***	nd
159	nd	21**	32***	71***	nd
167	nd	-39***	-34***	47***	nd
171	nd	-3	16**	34***	nd
208	nd	59***	86***	109***	nd

9. Correction of hyperferremia in beta2-microglobulin deficient mice

Mutations in genes involved in sensing the systemic iron stores, such as hepcidin (Hamp1), hemochromatosis protein (HFE), hemojuvelin (HJV) and transferrin receptor 2 (TFR2) cause iron overload in mice and men. HFE, HJV and TFR2 molecules on hepatocytes are necessary for signalingof appropriate hepcidin production and their deficiency results in pathophysiologically low hepcidin levels and excessive iron absorption. HFE mutations is the most frequent cause of hereditary hemochromatosis (HH) in Caucasian adults. HFE is a MHC class I-like membrane molecule that associates with beta 2-microglobulin and participates in hepcidin transcriptional regulation through the bone morphogenetic protein receptor (BMPR) pathway. HFE-/- mice have decreased hepcidin levels, develop hyperferremia and high hepatic iron levels, which makes them a suitable animal model for studying iron overload in humans (Zhou, 1998). Mice deficient in beta 2-microglobulin (b2m-/-) develop hyperferremia and hemochromatosis similarly to HFE-/- animals, as beta 2-microglobulin is necessary for the cell-surface expression and function of HFE (Rothenberg and Voland, 1996). Due to the unavailability of HFE-/- mice, b2m-/- mice were used as a model of iron overload. A pilot study confirmed that HFE-/- and b2m-/- mice have similar iron metabolism-related parameters.

Female and male homozygous b2m-/- mice were supplied from Jackson Laboratories (B6.129P2-B2mtm1Unc/J, Stock Number: 002087) at age of 6 to 7 weeks and fed standard diet (Harlan Provimi Kliba 3436) ad libitum. Age and gender matched WT C57BL/6 mice are supplied by Charles River. To study the acute effects of ferroportin (Fpn) inhibitors in iron overload b2m-/- mice were treated with compounds or the corresponding amount of vehicle at a volume of 10 ml/kg body weight. Fpn inhibitor compounds were formulated in 0.5% methylcellulose / water or 20% cremophor EL/ water and dosed p.o. in mice at 50 mg/kg body weight. WT controls received only vehicle. Three hours later, mice were pre-terminally anesthetized in isoflurane chambers and blood was collected by retro-orbital bleeding. Mice were sacrificed by cervical dislocation and spleens, livers and duodena were harvested and used for biomarker analysis. All experiments have been performed in compliance with license approved by the responsible veterinarian authorities. Serum was isolated by centrifugation of blood into gel-containing microtainers (BD Biosciences) and serum iron was determined by the MULTIGENT Iron assay (Abbott Diagnostics, Cat. 6K95). Four to nine mice per group were used and one-way ANOVA with Bonferroni's multiple comparison test was applied to analyze the statistical differences between the experimental groups.

To investigate the effects of Fpn inhibitors Example Compound No. 40 and Example Compound No. 94 in conditions of iron overload b2m-/- mice or WT controls were dosed with Fpn inhibitors or vehicle for 3h.

Due to their genetic deficiency, b2m-/- mice treated with vehicle showed significantly higher serum iron levels compared to WT mice (Fig. 5, group average of 60 µM in A and 56 µM in B). Treatment of b2m-/- mice with Example Compound No. 40 or Example Compound No. 94 at 50 mg/kg for 3h corrected the elevated serum iron to the levels observed in WT controls .These data demonstrated the acute efficacy of small molecular weight ferroportin inhibitors in a disease relevant model.Serum iron correction was observed in further studies as summarized in Table 8.

Fig. 5 Complete correction of the elevated serum iron levels in b2m-/- mice by treatment with the ferroportin inhibitors Example Compound No. 40 / methylcellulose (A.) and Example Compound No. 94 / cremophor EL (B.) for 3h.

Table 8 Fpn inhibitors tested in the beta2-microglobulin deficient mouse model for lowering elevated serum iron levels

Blood was collected 1 (#) or 3 (##) hours after oral administration of the indicated doses of Fpn inhibitors to beta2-microglobulin deficient mice and serum iron concentrations were measured.Relative reduction (%) of serum iron levels are shown, which were calculated by subtracting the average of serum iron values of animals dosed with the Fpn inhibitor from that of vehicle-treated animals. The difference in average serum iron values between vehicle and compound treated groups was then divided by the average of serum iron of the vehicle control group and listed as percentage. Values are listed separately for female (♀) and male (♂) animals, because a marked sex-dependent difference in efficacy was noted. Statistically significant (2-way ANOVA with Bonferroni post test) differences observed between compound-treated and vehicle-treated groups are indicated (*** p<0.001; ** p<0.01, * p<0.05).

Table 8

		Serum Iron Reduction (%)	
Exp. Comp. No.		**Dose 20 mg/kg**	**Dose 60 mg/kg**
1	♀	31**	52**
	♂	31**	59**
2	♀	27	57**
	♂	29	66**
40#	♀	0	13
	♂	35**	32**
40#	♀	nd	10
	♂	nd	58**
94##	♀	nd	47
	♂	nd	67
127	♀	47***	74***
	♂	21	83**
208##	♀	9	49***
	♂	44	67**

10. Prevention of iron overload in beta2-microglobulin deficient mice

As a result of decreased hepcidin levels and increased iron absorption in the gut beta2-microglobulin deficient (b2m-/-) mice on a standard diet accumulate excessive amounts of iron in liver, heart and

pancreas. A pilot study showed that liver iron loading in b2m-/- starts at age of 3-4 weeks and that liver iron levels reaches up to 4 fold the liver iron content of wild-type (WT) mice at age of 6 weeks. In addition, feeding 3 week old b2m-/- mice a diet with low iron content (LID) immediately after weaning prevented liver iron loading by age of 6-7 weeks. The efficacy of the Fpn inhibitors to prevent liver iron accumulation in b2m-/- mice was investigated. Three weeks old b2-/- mice fed LID were dosed with either Fpn inhibitor or vehicle (methylcellulose; 10 ml/kg). Mice had access to drinking water supplemented with 1mM ^{58}Fe(II)-sulfate and 10 mM ascorbic acid. Dosing of Fpn inhibitor or vehicle followed by exposure to iron-containing water was repeated for 14 days. Mice are euthanized and the liver and spleen iron contents were analyzed by ICP-OES (all iron isotopes) and liver tissue is also analyzed for ^{58}Fe concentration (ICP-MS). The data summarized in Table 9 illustrates that oral dosing of Fpn inhibitors for two weeks prevented liver iron loading in b2m-/- mice and increased spleen iron concentrations, indicating inhibition of ferroportin both in the intestine and in the spleen.

These data demonstrated the efficacy of a small molecular weight ferroportin inhibitor to prevent liver iron loading in b2-/- mice, which provides a proof of concept in a disease-relevant model.

Table 9 Fpn inhibitors tested in the beta2-microglobulin deficient mouse model for inhibition of liver iron overload.

Livers and spleens were collected after 14 day treatment (p.o.; b.i.d) of beta2-microglobulin deficient mice with the indicated doses of Fpn inhibitors. Total liver and spleen tissue iron concentrations were measured using ICP-OES and ^{58}Fe liver concentrations were determined with ICP-MS. Relative changes (%) of tissue iron levels are shown, which were calculated by normalizing the difference between the averages of tissue iron values of animals dosed with the Fpn inhibitors and those of vehicle-treated animals with the average of vehicle controls. Values are listed separately for female (♀) and male (♂) animals, because a marked sex-dependent difference in efficacy was noted. Statistically significant (2-way ANOVA with Bonferroni post test) differences observed between compound-treated and vehicle-treated groups are indicated (*** p<0.001; ** p<0.01, * p<0.05). nd, not determined; na, not available.

Table 9

Exp. Comp. No.		Total Spleen Iron Increase (%)		Total Liver Iron Reduction (%)		^{58}Fe Liver Iron Reduction (%)	
		Dose (mg/kg)					
		20	60	20	60	20	60
1	♀	21	65	-1	15	4	59
	♂	28	49	16	25	-8	22
2	♀	13	1	26	45	60**	77***
	♂	18	-20	10	28	24	70
40	♀	50*	85***	32	67*	44	80*
	♂	25	24	31	69***	53*	81***
40	♀	nd	9	nd	66	nd	67
	♂	nd	36	nd	85**	nd	95**
94	♀	nd	65	nd	57	nd	na
	♂	nd	41	nd	79	nd	na
127	♀	71*	51	-38	2	34	63***
	♂	-7	-16	50**	65***	71***	73***
208	♀	56**	150***	15	8	71*	87**
	♂	21	43	41	84**	58	94**

11. Improvement of anemia, ineffective erythropoiesis and iron overload in a mouse model of β-thalassemia intermedia

β-thalassemia is inherited anemia caused by mutations in the β -globin gene of hemoglobin resulting in abnormal red blood cells with decreased life span. The most severe form, thalassemia major, requires blood transfusions which result in secondary iron overload. Patients with thalassemia intermedia have a moderate transfusion-independent anemia but still develop iron overload due to inefficient erythropoiesis and chronic repression of hepcidin production.

As shown in the previous examples, oral ferroportin (Fpn) inhibitors similarlyto hepcidin blocked ferroportin mediated export of iron from cells *in vitro* and upon dosing in wild- type mice transiently reduced serum iron. Based on these findings and published studies (Schmidt PJ, et al , Blood 2013, Guo S, et al, JCI, 2013 and Casu C. et al, Blood, 2016) Fpn inhibitors were examined with respect to its capacity to prevent iron loading and improve erythropoiesis in thalassemia intermedia by restricting iron absorption and reutilization from senescent erythrocytes. The efficacy of Fpn inhibitors was investigated using a mouse model of transfusion-independent β -thalassemia. Mice with heterozygous deletion of β 1 and β 2 globin genes (called Hbb th3/+ mice) develop transfusion-independent anemia, ineffective erythropoiesis, splenomegaly and secondary iron overload in spleen, liver and kidneys. Heterozygous Hbbth3/+ mice were supplied from Jackson Laboratories (B6;129P-Hbb-b1tm1Unc Hbb-b2tm1Unc/J, Stock Number: 002683) at age of 8-18 weeks and during experiments fed a low iron diet (Harlan Provimi Kliba 2039, 13.4 ppm Fe) ad libitum. Hbb th3/+ mice were dosed twice daily with either compound at 20 or 60 mg/kg or with methylcellulose (10 ml/kg, Sigma, Cat. 274429) as a vehicle. Between both doses mice had access to drinking water supplemented with 1 mM ^{58}Fe(II)-sulfate (Vifor Pharma, Batch No. ROR 3096) and 10 mM ascorbic acid (Sigma, Cat. 795437) for 6h. The concentration of ^{58}Fe(II)-Sulfate supplied in the drinking water has been adjusted to substitute for intake of standard rodent diet with iron content of 250 ppm. Water without ^{58}Fe(II)-Sulfate and ascorbic acid was provided during the remaining 18h. Dosing of Fpn inhibitors or vehicle followed by exposure to iron-containing water was repeated for 20 to 46 days in individual experiments.

As previously shown in wild-type and b2m-/- mice, Fpn inhibitors dosed for 3h in Hbb th3/+ mice reduced efficiently serum iron levels also in this mouse strain (Table 10), demonstrating the ability of these small molecules to cause iron restriction.

Hbb th3/+ mice are anemic with hemoglobin levels in the range of 70-80 g/L. Oral administration of Fpn inhibitors in Hbb th3/+ mice for two weeks increased significantly hemoglobin levels compared to vehicle treated mice (Table 10). The change of hemoglobin levels in compound-dosed compared to vehicle-treated group reached 19-22 g/L by the study end. Additional hematologic parameters were measured in terminal blood using automated blood cell analyzer. Treating Hbb th3/+ mice with Fpn inhibitors increased red blood cell counts, hematocrit and decreased reticulocyte concentration and red cell distribution width (RDW), indicating improved erythropoiesis. In addition, Hbb th3/+ mice receiving Fpn inhibitors had significantly lower leucocyte counts in blood compared to the vehicle group, further demonstrating the beneficial effect of Fpn inhibitors in correcting pathologically altered parameters in the disease model. Therefore, Fpn inhibitors improved significantly anemia and corrected blood composition in the mouse model of thalassemia intermedia.

The inefficient erythropoiesis of Hbb th3/+ mice causes excessive proliferation of erythroid precursors in spleen, leading to splenomegaly. Treatment of Hbb th3/+ mice with Fpn inhibitors resulted in significant reduction in spleen weight, therefore highlighting the potential of Fpn inhibitors torevert splenomegaly (Table 10).

The effect of Fpn inhibitors on erythropoiesis was studied by analyzing the percentage of differentiating erythroid precursors in bone marrow and spleen using flow cytometry and Ter119 (eBioscience, Cat. 17-5921) and CD44 (BioLegend, Cat. 103028) markers. Bone marrow or spleen cells isolated from Hbb th3/+ mice treated with Fpn inhibitors contained significantly reduced percentage of the early erythroid

precursors proerythroblasts, basophilic, and polychromatic erythroblastand increased percentage of mature erythrocytes compared to vehicle-treated Hbb th3/+ mice (Table 10). These data demonstrated that Fpn inhibitors ameliorated the inefficient erythropoiesis in Hbb th3/+ mice and are in agreement with the improved hematological parameters in blood.

Serum erythropoietin levels in Hbb th3/+ mice and patients with thalassemia are upregulated due to a feedback response to anemia, hypoxia and inefficient erythropoiesis (Guo et al. JCI, 2013). Hbb th3/+ mice treated with Fpn inhibitors produced significantly less serum erythropoietin (DuoSet ELISA R&D Systems, Cat. DY959) compared to the vehicle group, most likely as a consequence of partially corrected anemia and improved erythropoiesis (Table 10).

Elevated erythropoietin levels in Hbb th3/+ mice induced overexpression of erythroferrone, an erythroid regulator hormone known to suppress hepcidin (Kautz L. et al , Nat. Genet., 2014). In agreement with reduced serum erythropoietin, erythroferrone mRNA expression was significantly reduced in spleens of Fpn inhibitor-treated Hbb th3/+mice compared to those administered with vehicle alone (Table 10). Erythroferrone is produced by erythrocyte precursors proliferating massively in spleens of Hbb th3/+ mice as a consequence of extramedullar erythropoiesis. Therefore, the effect of Fpn inhibitors on erythroferrone expression in spleen is mediated by the improved erythropoiesis.

Increased iron demand due to inefficient erythropoiesis and chronically low hepcidin levels in patients with thalassemia causes organ iron loading and associated morbidities, such as hepatocellular carcinoma and heart failure (Rivella S. Haematologica, 2015). Hbb th3/+ mice absorb excessive amounts of iron as a consequence of inadequately low hepcidin levels relative to the high iron content in liver, spleen and kidney and increased ferroportin expression in duodenum (Gardenghi S., Blood, 2007). Total liver iron and ^{58}Fe content in organs of Hbb th3/+ mice treated with either vehicle or Fpn inhibitors were analyzed by inductively coupled plasma optical emission spectrometry (ICP-OES) and inductively coupled plasma mass spectrometry (ICP-MS), respectively. ^{58}Fe concentrations in livers and spleens of Hbb th3/+ mice dosed with Fpn inhibitors were significantly lower compared to those of vehicle treated mice, indicating that Fpn inhibitors prevent organ iron accumulation (Table 10).

As Fpn inhibitors are systemically available, they are able to block iron export in all ferroportin expressing tissues, including duodenum, spleen and liver. Accordingly, Fpn inhibitors are expected to prevent iron absorption from duodenum, however, they could not remove pre-existing iron in liver and spleen. Indeed, total liver iron in mice treated with Fpn inhibitor or vehicle remained unchanged (not shown). Importantly, Fpn inhibitors reduced significantly ^{58}Fe concentration in spleens and livers of Hbb th3/+ mice, demonstrating the ability of these small molecules to prevent iron loading.

Additionally, reactive oxygen species (ROS) were detected in bone marrow cells using a fluorescent indicator, CM-H_2DCFDA (Thermo Fisher Scientific, Cat. C6827). Flow cytometric analysis showed that Fpn inhibitors decreased significantly ROS in mature erythroid cells compared to vehicle treated Hbb th3/+ mice (Table 10).

These data demonstrated the disease-modifying capacity of orally administered small molecular weight ferroportin inhibitors in improving anemia and ineffective erythropoiesis, as well in reducing splenomegaly and preventing further liver and spleen iron loading in a disease model of β -thalassemia intermedia.

Table 10

Parameter	Exp. Comp. No.1	Exp. Comp. No. 2	Exp. Comp. No. 40	Exp. Comp. No. 127
Decrease in serum iron by 20 / 60 mg/kg compound	49 / 66%	50 / 69%	28 / 58%	68 / 81%
Correction of anemia at day 20-48 by 20 / 60 mg/kg	6 / 20 g/d	3 / 11 g/L	6 /13 g/L	12 / 20 g/L

Increase in blood erythrocyte counts by 20 / 60 mg/kg compound	4 / 8%	0 / 33%	2 / 22%	0 / 36%
Decrease in blood reticulocyte counts by 20 / 60 mg/kg compound	8 / 39%	0 / 11%	19 / 43%	16 / 61%
Increase in hematocrit by 20 / 60 mg/kg compound	0 / 4%	0 / 15%	0 / 1%	3 / 20%
Decrease in RDW by 20 / 60 mg/kg compound	3 / 16%	0 / 15%	NA / NA	19 / 25%
Decrease in leukocyte counts by 20 / 60 mg/kg compound	32 / 44%	29 / 55%	0 / 36%	46 / 66%
Decreased in ROS in bone marrow erythrocytes	20 / 45%	13 / 65%	NA/ NA	NA/ 75%
Decrease in relative spleen weight by 20 / 60 mg/kg	23 / 59%	16 / 47%	23 / 48%	40 / 61%
Decrease in ^{58}Fe spleen iron content by 20 / 60 mg/kg compound	14 / 48%	13 / 40%	19 / 51%	43 / 68%
Prevention of liver ^{58}Fe loading by 20 / 60 mg/kg	12 / 40%	14 / 47%	20 / 48%	39 / 59%
Decrease in serum erythropoietin by 20 / 60 mg/kg compound	64 / 78%	4 / 27%	6 / 37%	32 / 33%
Decrease in spleen erythroferrone mRNA by 20 / 60 mg/kg compound	82 / 292%	461 / 639%	NA/ NA	1012 / 3031%

Table 10. Efficacy of Ferroportin inhibitors in a mouse model of thalassemia intermedia (Hbb th3/+ mice). The indicated Fpn inhibitors were dosed twice daily for 20 days (Example Compound 1 and 2), 27 days (Example Compound 127) or 46 days (Example Compound 40). Data are expressed as difference to the vehicle control group for hemoglobin and as % change to the vehicle control group for all other parameter shown

Preparation of Example Compounds

General Experimental Details

Commercially available reagents and solvents (HPLC grade) were used without further purification. ^{1}H NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer, a Bruker DPX 250 MHz spectrometer or a Bruker Avance spectrometer 400 MHz in deuterated solvents. Chemical shifts (δ) are in parts per million.

Compounds were purified by flash column chromatography on normal phase silica on Biotage Isolera systems using the appropriate SNAP cartridge and gradient. Alternatively compounds were purified on reverse phase using Biotage Isolera systems with the appropriate C18 SNAP cartridge and reversephase eluent or by preparative HPLC (if stated otherwise).

Analytical HPLC-MS

Method A (MET/CR/1673)

Column	Supelco Ascentis Express (Part No. 53802-U) 2.1 x 30 mm, 2.7 µm	
Column Temp	40°C	
Mobile Phase	A, Water + 0.1% Formic acid	
	B, Acetonitrile + 0.1% Formic acid	
Gradient	Time (mins)	% organic
	0	5
	1.5	100
	1.6	100
	1.61	5
Flow rate	1 ml / min	
Injection Vol	3 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm step: 1 nm	
MSD Signal settings	Scan Pos (Shimadzu): 100-1000 Scan Pos (MS14): 130-850	

Method B (MET/CR/1600)

Column	Phenomenex Gemini–NX C18 (Part No. 00D-4453-B0) 2.0 x100 mm, 3 µm column	
Column Temp	40°C	
Mobile Phase	A, 2 mM amm. bicarbonate, buffered to pH 10	
	B, Acetonitrile	
Gradient	Time (mins)	% organic
	0.00	5
	5.50	100
	5.90	100
	5.92	5
Flow rate	0.5 ml / min	
Injection Vol	3 µl	
Detection		
Signal	UV 215	

PDA Spectrum	Range: 210-420 nm step: 1 nm
MSD Signal settings	Scan Pos: 100-1000

Method C (MET/CR/1416)

Column	Waters Atlantis dC18 (Part No. 186001295) 2.1 x 100 mm, 3 µm	
Column Temp	40ºC	
Mobile Phase	A, Water + 0.1% Formic acid	
	B, Acetonitrile + 0.1% Formic acid	
Gradient	Time (mins)	% organic
	0.00	5
	5.00	100
	5.40	100
	5.42	5
Flow rate	0.6 ml / min	
Injection Vol	3 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm step: 1 nm	
MSD Signal settings	Scan Pos: 100-1000	

Method D – (MET/uPLC/AB101)

Column	Phenomenex Kinetix-XB C18 (Part No.00D-4498-AN) 2.1 x 100 mm, 1.7 µm	
Column Temp	40ºC	
Mobile Phase	A, Water + 0.1% Formic acid	
	B, Acetonitrile + 0.1% Formic acid	
Gradient	Time (mins)	% organic
	0.00	5
	5.30	100
	5.80	100
	5.82	5
Flow rate	0.6 ml / min	
Injection Vol	1 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 200-400 nm step: 1 nm	
MSD Signal settings	Scan Pos: 150-850	

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Method E - (MET/CR/1278)

Column	Waters Atlantis dC18 (Part No. 186001291) 2.1 x 50 mm, 3 µm
Column Temp	40ºC
Mobile Phase	A, Water + 0.1% Formic acid

	B, Acetonitrile + 0.1% Formic acid	
Gradient	Time (mins)	% organic
	0.00	5
	2.50	100
	2.70	100
	2.71	5
	3.50	5
Flow rate	1 ml / min	
Injection Vol	3 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm step: 1 nm	
MSD Signal settings	Scan Pos (Shimadzu): 100-1000 Scan Pos (MS14): 130-850	

Method F - MET/CR/0990

Column	Phenomenex Gemini-NX C18 (00B-4453-B0) 2.0 x 50mm, 3um	
Column Temp	40°C	
Mobile Phase	A, 2 mM Ammonium bicarbonate, buffered to pH 10	
	B, Acetonitrile	
Gradient	Time (mins)	% organic
	0.00	1
	1.80	100
	2.10	100
	2.30	1
	3.50	1
Flow rate	1 ml / min	
Injection Vol	3 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm step: 1 nm	
MSD Signal settings	Scan Pos: 150-850	

Method G - MET/CR/2044

Column	Thermofisher Hypercarb™ Porous Graphitic Carbon 2.1 mm x 50 mm, 3µm	
Column Temp	40°C	
Mobile Phase	A, 25 mM Ammonium acetate in HPLC grade water pH~5	
	B, 25 mM Ammonium acetate in HPLC grade acetonitrile	
Gradient	Time (mins)	% organic
	0.00	2
	4	100
	5	100
	6	2
	6.5	2

Flow rate	0.5 ml/min
Injection Vol	3 µl
Detection	
Signal	UV 215
PDA Spectrum	Range: 210-420nm step: 1nm
MSD Signal settings	Scan Pos: 150-850

Method H - METUPLCMS-A-004

Column	Acquity UPLC BEH C18 2.1 mm X 50 mm, 1.7 µM	
Column Temp	Ambient	
Mobile Phase	A, Water /acetonitrile, 9:1 + 0.1% formic acid	
	B, Acetonitrile / water, 9:1 + 0.1% formic acid	
Gradient	Time (mins)	% organic
	0.00	5
	1.5	100
	1.7	100
	1.8	5
	2.0	5
Flow rate	0.7 ml/min	
Injection Vol	4 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420nm	
MSD Signal settings	Scan Pos: 150-800	

Method I - METUPLCMS-A-006

Column	Acquity UPLC HSS T3 2.1 mm X 100 mm , 1.8 µm	
Column Temp	40°C	
Mobile Phase	A, Water /acetonitrile, 9:1 + 0.1% formic acid	
	B, Acetonitrile / water, 9:1 + 0.1% formic acid	
Gradient	Time (mins)	% organic
	0.00	5
	5.30	100
	5.80	100
	5.82	5
	6.00	5
Flow rate	0.7 ml/min	
Injection Vol	4 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm	
MSD Signal	Scan Pos: 150-800	

settings	

Method J - METUPLCMS-A-007

Column	Acquity UPLC BEH C18 2.1 X 100 mm , 1.7 µm	
Column Temp	40°C	
Mobile Phase	A, 2 mM Ammonium Bicarbonate	
	B, Acetonitrile : 2 mM Ammonium Bicarbonate (95 : 5)	
Gradient	Time (mins)	% organic
	0.00	5
	5.30	100
	5.80	100
	5.82	5
	6.00	5
Flow rate	0.6 ml/min	
Injection Vol	4 µl	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420 nm	
MSD Signal settings	Scan Pos: 150-800	

Method K – MET/UPLCMS-A/013

Column	Acquity UPLC HSS T3 2.1 X 100 mm , 1.8 µm	
Column Temp	40°C	
Mobile Phase	A, Water + 0.1% formic acid, acetonitrile + 0.1% formic acid (90:10)	
	B, Acetonitrile + 0.1% formic acid, water + 0.1% formic acid (90:10)	
Gradient	Time (mins)	% organic
	0.00	30
	5.30	100
	5.80	100
	5.82	30
	6.00	30
Flow rate	0.6 ml/min	
Detection		
Signal	UV 215	
PDA Spectrum	Range: 210-420nm	
MSD Signal settings	Scan Pos: 150-800	

Method L – MET-THERMOMS-B-015

Column	X-bridge C-18

	250 X 4.6 mm , 5 µm	
Column Temp	NA	
Injection Vol.	10 µl	
Mobile Phase	A, 2mM Ammonium Bicarbonate (pH-10)/ pH 10 adjusted using liq. NH_3	
	B, Acetonitrile	
Gradient	Time (mins)	% organic
	0.0	5
	10.0	100
	10.5	100
	11.0	5
	12.0	5
Detection		
Signal	UV 215	
MSD Signal settings	Scan Pos: 50-1000	

Method M - MET/CR/1410

Column	**Phenomenex Kinetex Core-Shell C18 (Part No. 00D-4601-AN) 2.1 x 50 mm, 5 µm**	
Column Temp	**40°C**	
Mobile Phase	**A, Water + 0.1% Formic acid**	
	B, Acetonitrile + 0.1% Formic acid	
Gradient	**Time (mins)**	**% organic (B)**
	0.00	**5**
	1.20	**100**
	1.30	**100**
	1.31	**5**
Flow rate	**1.2 ml / min**	
Injection Vol	**3 µl**	

Preparative HPLC – neutral pH method

Column	Waters Sunfire C18 (Part no.186003971) 30 x 100mm, 10um	
Column Temp	Room temperature	
Mobile Phase	A, Water	
	B, Acetonitrile	
Gradient	Time (mins)	% organic
	0	10
	2	10
	2.5	15
	14.5	100
	15.5	100
	16	10
	17	10

Flow rate	40ml/min
Injection Vol	1500µl
Detection	
Signal	UV 215

Preparative HPLC - low pH prep method (acid)

Column	Waters Sunfire C18 (Part no.186003971) 30 x 100mm, 10µm	
Column Temp	Room temperature	
Mobile Phase	A, Water + 0.1% Formic acid	
	B, Acetonitrile + 0.1% Formic acid	
Gradient	Time (mins)	% organic
	0	5
	2	5
	2.5	10
	14.5	100
	15.5	100
	16	5
	17	5
Flow rate	40ml/min	
Injection Vol	1500µl	
Detection		
Signal	UV 215	

Preparative HPLC - high pH prep method (basic)

Column	Waters Xbridge C18 (Part no.186003930) 30 x 100mm, 10µm	
Column Temp	Room temperature	
Mobile Phase	A, Water+ 0.2%Ammonium hydroxide	
	B, Acetonitrile + 0.2% Ammonium hydroxide	
Gradient	Time (mins)	% organic
	0	5
	2.5	5
	16.05	95
	18.2	95
	19.1	5
	20	5
Flow rate	40ml/min	
Injection Vol	1500µl	
Detection		
Signal	UV 215	

Abbreviations

AcOH	Acetic acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
BH_3	Borane
Boc_2O	Di-*tert*-butyl dicarbonate

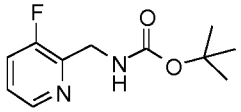
$CaCO_3$	Calcium carbonate
CBz	Benzyloxy carbamate
CDI	1,1'-Carbonyldiimidazole
$CHCl_3$	Chloroform
d	Day(s)
DAST	N-ethyl-N-(trifluoro-lambda-4-sulfanyl)ethanamine
DBU	1,8-Diazabicycloundec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-diisoproylethylamine
DMAP	*N,N*-dimethylpyridin-4-amine
DMF	*N,N*-dimethylformamide
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour(s)
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-Oxide Hexafluorophosphate
HCl	Hydrochloric acid
HPLC	High Performance Liquid Chromatography
IPA	Isopropyl alcohol
K_2CO_3	Potassium carbonate
KO^tBu	Potassium *tert*-butoxide
KHMDS	Potassium 1,1,1,3,3,3-hexamethyldisilazan-2-ide
$KHSO_4$	Potassium bisulfate
$LiAlH_4$	Lithium Aluminium Hydride
LiCl	Lithium chloride
LiOH	Lithium hydroxide
MeCN	Acetonitrile
MeI	Methyl iodide
MeOH	Methanol
min	Minute(s)
MW	Molecular weight
$NaBH_4$	Sodium borohydride
$NaHCO_3$	Sodium hydrogen carbonate
NaH	Sodium Hydride (60% in mineral oil)
NaOH	Sodium hydroxide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NH_4Cl	Ammonium chloride
Pd/C	Palladium on carbon
$PdCl_2(dppf)$	Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
Pd_2dba_3	Tris(dibenzylideneacetone)dipalladium(0)
PPh_3	Triphenylphosphine
PTSA	p-Toluenesulfonic acid
TBME	*tert*-butyl methyl ether

TBSCl	tert-Butyldimethylsilyl chloride
TEA	Triethylamine
TFA	Trifluoroacetic acid
TMOF	Trimethyl orthoformate
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Intermediates

Scheme A above:

Tert-butyl N-[(3-fluoropyridin-2-yl)methyl]carbamate (A1)

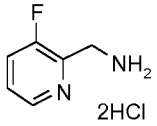


A suspension of 3-fluoropyridine-2-carbonitrile (8.0 g, 6.55 mmol), di-tert-butyl dicarbonate (15.7 g, 72.07 mmol), TEA (10.05 ml, 72.07 mmol) in EtOH (300 ml) was purged with N_2. Pd/C (10% wt., 0.7g, 6.55 mmol) was added and the reaction mixture was stirred under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through celite, rinsed with MeOH (100 ml) and the filtrates were removed *under vacuum* to afford the crude product. Purification by flash column chromatography (gradient elution 0-70% EtOAc / heptane) afforded the title compound (11.3 g, 72%) as an off-white solid.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.41 - 8.31 (m, 1H), 7.65 (ddd, J = 10.1, 8.3, 1.3 Hz, 1H), 7.38 (dt, J = 8.5, 4.4 Hz, 1H), 7.18 (s, 1H), 4.30 (d, J = 5.4 Hz, 2H), 1.37 (s, 9H)

HPLCMS (Method A): [*m/z*]: 226.9 $[M+H]^+$

(3-Fluoropyridin-2-yl)methanamine dihydrochloride (A2)



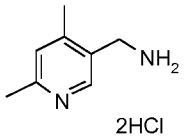
In a similar fashion to general procedure 2, tert-butyl N-[(3-fluoropyridin-2-yl)methyl]carbamate **(A1)** (11.3 g, 47.45 mmol) and 12M HCl (59.3 ml, 711.72 mmol) in MeOH (150 ml) at 40°C for 2 h, gave the title compound (9.7 g, 100%) as an off-white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.48 (dt, J = 4.7, 1.3 Hz, 1H), 7.69 (ddd, J = 9.7, 8.5, 1.2 Hz, 1H), 7.50 (dt, J = 8.8, 4.5 Hz, 1H), 4.37 (s, 2H)

HPLCMS (Method A): [*m/z*]: 126.9 $[M+H]^+$

Scheme B above:

(4, 6-Dimethylpyridin-3-yl)methanamine hydrochloride (B1)



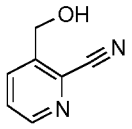
4,6-dimethylpyridine-3-carbonitrile (0.15 g, 1.135 mmol) in MeOH (150 ml) was subjected to the H-Cube with 10% palladium on carbon at a flow rate of 1 ml / min using H_2 at 50 bar and room temperature into a solution of 1M HCl (1 ml). The solvent was evaporated *in vacuo* to give the title compound (190 mg, 64%) as a white solid. Used without purification.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.74 - 8.66 (m, 1H), 8.62 - 8.42 (m, 3H), 7.76 - 7.64 (m, 1H), 4.23 - 4.13 (m, 2H), 2.66 - 2.63 (m, 3H), 2.58 - 2.54 (m, 3H)

HPLCMS (Method E): [*m/z*]: 136.9 $[M+H]^+$

Scheme C above:

2-(Hydroxymethyl)benzonitrile (C1)

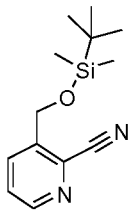


1M BH_3 in THF (1.51 ml) was added to an ice-cooled (0°C) solution of 3-formylpyridine-2-carbonitrile (200 mg, 1.51 mmol) in THF (5 ml). The reaction was allowed to warm to room temperature and stirred for 15 h. The reaction was poured onto ice/water (25 ml). The aqueous layer extracted with EtOAc (3 x 20ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent evaporated to give a brown oil. Purification by flash column chromatography (eluting with a gradient 20-100% EtOAc / heptane) gave the titled compound (45.5 mg, 22.4%) as a yellow solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.55 (dd, J = 4.7, 1.4 Hz, 1H), 8.01 - 7.95 (m, 1H), 7.49 (dd, J = 8.0, 4.7 Hz, 1H), 4.89 (s, 2H)

HPLCMS (Method A): [*m/z*]: 134.85 $[M+H]^+$

2-{[(Tert-butyldimethylsilyl)oxy]methyl}benzonitrile (C2)

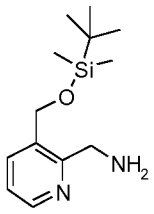


1M TBSCl in DCM (0.369 ml, 0.369 mmol) was added dropwise to a solution of 3-(hydroxymethyl)pyridine-2-carbonitrile **(C1)** (45 mg, 0.335 mmol) and imidazole (46 mg, 0.671 mmol) in DMF (2 ml). The reaction was stirred at room temperature for 15 h. The solvent was evaporated and the crude product purified by flash column chromatography (eluting with a gradient of 0-50% EtOAc-heptane) to give the titled compound (44 mg, 52.8%) as a yellow oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.60 - 8.58 (m, 1H), 8.10 - 7.96 (m, 1H), 7.53 (dd, J = 8.0, 4.7 Hz, 1H), 4.94 (s, 2H), 0.95 (s, 9H), 0.15 (s, 6H)

HPLCMS (Method A): [*m/z*]: 249.00 $[M+H]^+$

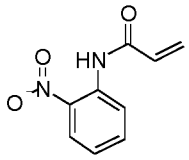
(3-{[(Tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)methanamine (C3)



2M $LiAlH_4$ in THF (0.09 ml) was added dropwise to an ice-cooled solution (0°C) of 3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridine-2-carbonitrile **(C2)** (44 mg, 0.18 mmol) in THF (3 ml). The reaction was allowed to warm to room temperature and stirred for 2 h. Diethyl ether (5 ml) was added followed by H_2O (1 ml), then 20% w/w NaOH (1 ml) and water (3 ml). The layers separated. The aqueous layer was extracted with EtOAc (3 x 10 ml). The combined organic layers were dried (Na_2SO_4), filtered and the solvent evaporated. The crude product was purified by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) to give the title compound (10 mg, 22.4%) as a yellow oil.

HPLCMS (Method A): [*m/z*]: 252.95 $[M+H]^+$

N-(2-Nitrophenyl)prop-2-enamide (D)

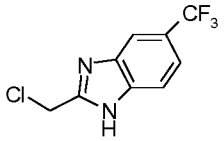


To a stirring suspension of 2-nitroaniline (5.0 g, 36.2 mmol) and K_2CO_3 (15.01 g, 108.6 mmol) in acetone (100 ml) at room temperature was added acryloyl chloride (11.8 ml, 145 mmol) and the mixture stirred for 16 h. The reaction mixture was filtered and concentrated in vacuo to give the crude product. Purification by flash column chromatography (gradient elution 10-15% EtOAc / heptane) afforded the title compound (6.95 g, 78%) as a yellow solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 10.59 (s, 1H), 8.90 (dd, J = 8.6, 1.3 Hz, 1H), 8.25 (dd, J= 8.5, 1.6 Hz, 1H), 7.68 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.21 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 6.54– 6.28 (m, 2H), 5.89 (dd, J = 9.9, 1.3 Hz, 1H)

HPLCMS (Method A): *[m/z]*: 192.9 $[M+H]^+$

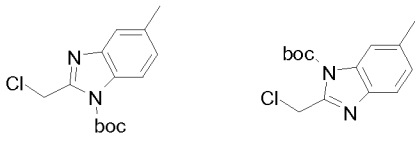
2-(Chloromethyl)-5-(trifluoromethyl)-1H-1,3-benzodiazole (E)



12 M HCl (1 ml, 12 mmol) was added to a mixture of 4-(trifluoromethyl)benzene-1,2-diamine (1 g, 5.68 mmol) and chloroacetic acid (0.590 g, 6.25 mmol) in water (20 ml) and the mixture was heated at 100°C for 2 h. Further 12 M HCl (4 ml, 48 mmol) was added and the reaction mixture heated at 120°C for 3 h. The mixture was then cooled to room temperature and quenched by addition of 7 M ammonia in MeOH until basic, extracted with EtOAc (3 x 20 ml) and the combined organic layers were washed withbrine (20 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo*. Flash column chromatography (eluting with a gradient 5-50% EtOAc / heptane) afforded the crude title compound as a purple solid (0.571 g, 24%, 56% purity) which was used without further purification.

HPLCMS (Method E): [*m/z*]: 234.85 $[M+H]^+$

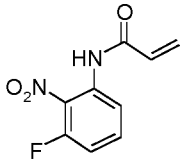
Tert-Butyl 2-(chloromethyl) methyl-1H-1,3-benzodiazole-1-carboxylate (F)



To the solution 2-(chloromethyl)-6-methyl-1H-1,3-benzodiazole (1g, 6 mmol) in DMF (20 ml) was added DIPEA (1.4 g, 11 mmol) followed by addition of Boc anhydride (1.8 g, 8 mmol). The reaction was stirred for 18 h. Water was added to the reaction and extracted with ethyl acetate. The organic phase was dried, Na_2SO_4, concentrated *in vacuo* to the crude product which was purified by flash column chromatography using n-hexane to ethyl acetate / n-hexane (5 : 95) to hexane to give the required product as a yellow oil (0.7 g, 22 %). The required product was obtained as a mixture which was not separable and used in the next step.

1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 7.84 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.2 Hz, 1H), 7.53 (s, 1H), 7.20 (dd, J = 13.0, 4.6 Hz, 2H), 5.05 (s, 2H), 5.04 (s, 2H), 2.50 (s, 3H), 2.47 (s, 3H), 1.74 (s, 9H), 1.73 (s, 9H),

N-(3-fluoro-2-nitrophenyl)prop-2-enamide (G)

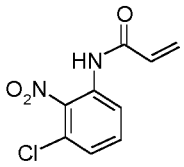


To an N_2 purged suspension of 3-fluoro-2-nitroaniline (500 mg, 3.20 mmol) and K_2CO_3 (1.33 g, 9.61 mmol) in acetone (10 ml) was added prop-2-enoyl chloride dropwise (1.0 ml, 12.8 mmol). The reaction mixture was left stirring at room temperature for 16 h. The reaction was filtered, concentrated *in vacuo* and purified by flash column chromatography (eluting with a gradient of 0-70% EtOAc / heptane) to afford the title compound (604 mg, 87%) as a yellow solid.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 10.58 (s, 1H), 7.69 (m, 1H), 7.46– 7.33 (m, 2H), 6.43 (dd, *J* = 17.0, 9.8 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.85 (dd, *J* = 9.8, 2.1Hz, 1H)

HPLCMS (Method A): [*m/z*]: 210.95 $[M+H]^+$

N-(3-chloro-2-nitrophenyl)prop-2-enamide (H)

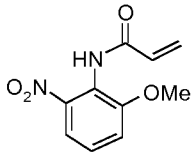


Acryloyl chloride (1.03 ml, 12.67 mmol) was slowly added to a suspension of 3-chloro-2-nitroaniline (0.729 g, 4.22 mmol) and K_2CO_3 (2.34 g, 16.9 mmol) in acetone (20 ml). The recation mixture was stirred at room temperature for 4 h, filtered and the residue was rinsed with acetone. The combined filtrates were evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-60% EtOAc / heptane) afforded the title compound (0.52 g, 47%) as a yellow solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.36 (dd, J = 8.3, 1.1 Hz, 1H), 8.28 (s, 1H), 7.49 (dd, J = 8.3, 8.3 Hz, 1H), 7.32 (dd, J = 8.3, 1.1 Hz, 1H), 6.47 (dd, J = 16.9, 0.8 Hz, 1H), 6.25 (dd, J = 16.9, 10.3 Hz, 1H), 5.90 (dd, J = 10.3, 0.8 Hz, 1H)

HPLCMS (Method M): [*m/z*]: 227.00 $[M+H]^+$

N-(2-methoxy-6-nitrophenyl)prop-2-enamide (I)

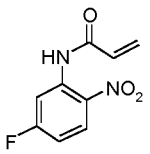


To an N_2 purged stirring suspension of 2-methoxy-6-nitroaniline (0.52 g, 3.09 mmol) and K_2CO_3 (1.71 g, 12.4 mmol) in acetone (30 ml) was added acryloyl chloride (0.754 ml, 9.28 mmol) dropwise. The reaction mixture was left stirring at room temperature for 16 h. The mixture was filtered, concentrated, diluted with EtOAc, washed with water, dried ($MgSO_4$), filtered and concentrated to give the crude product. Purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane followed by 0-2% MeOH / EtOAc) afforded the title compound (0.674 g, 96%) as an orange solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.82 (s, 1H), 7.57 (dd, J = 8.2, 1.3 Hz, 1H), 7.31 (t, J = 8.3 Hz, 1H) 7.19 (dd, J = 8.3, 1.3 Hz, 1H), 6.47 (dd, J = 17.0, 1.7 Hz, 1H), 6.33 (dd, J = 17.0, 9.8 Hz, 1H), 5.85 (dd, J = 9.8, 1.7 Hz, 1H), 3.97 (s, 3H)

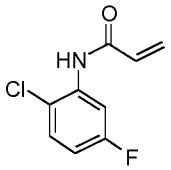
HPLCMS (Method M): [*m/z*]: 223.05 $[M+H]^+$

N-(5-fluoro-2-nitrophenyl)prop-2-enamide (J)



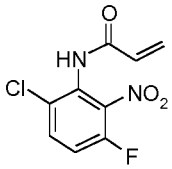
Acryloyl chloride (3.8 ml, 46.5 mmol) was added slowly to a suspension of 5-fluoro-2-nitroaniline (2.4 g, 15.5 mmol) and K_2CO_3 (8.57 g, 62 mmol) in acetone (100 ml) and the mixture was stirred at room temperature for 3 d and at reflux for 6 h. Further acryloyl chloride (3.8 ml, 46.5 mmol) and DMAP (0.95 g, 7.75 mmol) were added and the mixture heated at reflux for a further 2 h. The reaction mixture was cooled to room temperature and filtered. The residue was rinsed with acetone and the combined filtrates evaporated under vacuum. The resultant residue was re-dissolved in Et_2O (350 ml) and saturated $NaHCO_3$ (aq) (200 ml). The mixture was stirred vigourously for 15 min. The phases were separated and the organic phase washed with a further portion of saturated $NaHCO_3$ (aq) (100 ml) and brine (100 ml), dried (sodium sulphate) and evaporated under vacuum. Purification by flushing through a plug of silica (eluting with a gradient of 0-4% Et_2O / heptane) afforded the title compound (1.04 g, 32%) as a pale yellow solid.
1H-NMR ($CDCl_3$, 250MHz): d[ppm]= 10.83 (s, 1H), 8.79 (dd, J = 11.2, 2.5 Hz, 1H), 8.34 (dd, J = 9.2, 5.7 Hz, 1H), 6.99 - 6.82 (m, 1H), 6.53 (d, J = 16.9 Hz, 1H), 6.35 (dd, J = 17.1, 9.9 Hz, 1H), 5.95 (d, J = 10.1 Hz, 1H)
HPLCMS (Method M): [*m/z*]: 211.15 $[M+H]^+$

General Scheme K-I above:
N-(2-chloro-5-fluorophenyl)prop-2-enamide (K1)



To an N_2 purged suspension of 2-chloro-5-fluoroaniline (3.0 g, 20.6 mmol) and K_2CO_3 (11.4 g, 82.4 mmol) in acetone (80 ml) at room temperature was added dropwise prop-2-enoyl chloride (5.0 ml, 61.8 mmol) and stirred for 16 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (eluting with a gradient of 0-35% EtOAc / heptane) to afford the title compound (3.99 g, 84%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.40 (dd, J = 10.9, 3.0 Hz, 1H), 7.79 (s, 1H), 7.35 (dd, J = 8.9, 5.6 Hz, 1H), 6.81 (ddd, J = 8.9, 7.6, 3.0 Hz, 1H), 6.50 (dd, J = 16.9, 1.2 Hz, 1H), 6.32 (dd, J = 16.9, 10.0 Hz, 1H), 5.88 (dd, J = 10.0, 1.2 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 200.10 $[M+H]^+$

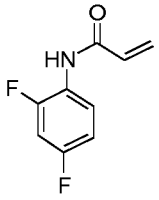
N-(6-chloro-3-fluoro-2-nitrophenyl)prop-2-enamide (K2)



To an N_2 purged solution of N-(2-chloro-5-fluorophenyl)prop-2-enamide **(K1)** (3.99 g, 17.4 mmol), concentrated H_2SO_4 (15 ml) and AcOH (6 ml) at 0°C was added red fuming HNO_3 (1.8 ml, 38.3 mmol) dropwise and the reaction was left stirring for 2 h. The reaction mixture was poured onto ice water and extracted using DCM (4 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography (eluting with a gradient of 0-70% EtOAc / heptane) to give the title compound (1.08 g, 20%) as a white solid.

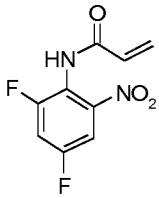
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.64 (dd, J = 9.1, 5.0 Hz, 1H), 7.51 (s, 1H), 7.19 (m, 1H), 6.52 (dd, J = 16.9, 1.1 Hz, 1H), 6.32 (dd, J = 16.9, 10.2 Hz, 1H), 5.94 (dd, J = 10.1, 1.1 Hz, 1H)
HPLCMS (Method A): [m/z]: 244.95 [M+H]+

N-(2,4-difluorophenyl)prop-2-enamide (K3)



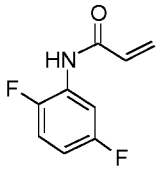
To an N_2 purged suspension of 2,4-difluoroaniline (2 g, 1.49 mmol) and K_2CO_3 (8.56 g, 61.7 mmol) in acetone (60 ml) at room temperature was added prop-2-enoyl chloride (3.7 ml, 46.5 mmol) dropwise. The reaction mixture was left stirring for 16 h. The reaction was filtered, concentrated, purified by flash column chromatography (eluting with a gradient of 0-30% EtOAc / heptane) and triturated with heptane to give the title compound (2.9 g, 100%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.49 - 8.29 (m, 1H), 7.33 (s, 1H), 6.99 - 6.84 (m, 2H), 6.48 (dd, J = 16.9, 1.4 Hz, 1H), 6.29 (dd, J = 16.8, 10.1 Hz, 1H), 5.85 (dd, J = 10.1, 1.4 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 183.95 $[M+H]^+$

N-(2,4-difluoro-6-nitrophenyl)prop-2-enamide (K4)



To an N_2 purged solution of N-(2,4-difluorophenyl)prop-2-enamide **(K3)** (2.9 g, 15.4 mmol), AcOH (5 ml) and concentrated H_2SO_4 (13 ml) at 0°C was added red fuming nitric acid (1.6 ml) dropwise. The reaction mixture was left stirring for 2 h. The reaction was poured onto ice water and the resulting solution extracted using DCM (4 x 40 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and triturated with heptane to give the crude product as a beige solid (3.23 g). Purification by flash column chromatography (eluting with a gradient of 0-40% EtOAc / heptane) gave the title compound (1.25 g, 35.5%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.17 (s, 1H), 7.67 (dt, J = 7.9, 2.4 Hz, 1H), 7.34 - 7.28 (m, 1H), 6.51 (dd, J = 17.0, 1.4 Hz, 1H), 6.35 (dd, J = 17.0, 9.9 Hz, 1H), 5.92 (dd, J = 9.9, 1.3 Hz, 1H)
HPLCMS (Method A): [m/z]: 229.05 [M+H]+

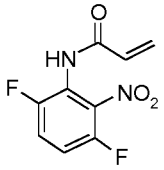
N-(2,5-difluorophenyl)prop-2-enamide (K5)



To an N_2 purged stirring solution of 2,5-difluoroaniline (1.5 ml, 15.5 mmol) and K_2CO_3 (6.42 g, 46.5 mmol) in acetone (60 ml) at room temperature was added prop-2-enoyl chloride (5.0 ml, 61.96 mmol) dropwise. The reaction mixture was left stirring at room temperature for 2 h. The reaction was filtered and the filtrate concentrated to give a white solid, which was triturated with heptane to give the title compound (2.91 g, quantitative) as a white solid.

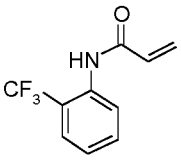
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.30 (m, 1H), 7.50 (s, 1H), 7.07 (m, 1H), 6.85- 6.70 (m, 1H), 6.50 (dd, J = 16.8, 1.2 Hz, 1H), 6.30 (dd, J = 16.9, 10.1 Hz, 1H), 5.87 (dd, J = 10.1, 1.2 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 183.95 $[M+H]^+$

N-(3,6-difluoro-2-nitrophenyl)prop-2-enamide (K6)



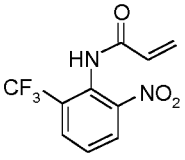
To an N_2 purged stirring solution of N-(2,5-difluorophenyl)prop-2-enamide **(K5)** (2.91 g, 15.9 mmol), AcOH (5 ml) and conconcentrated H_2SO_4 (13 ml) at 0°C was added red fuming HNO_3 (1.6 ml, 34.0 mmol) dropwise. The reaction mixture was left stirring for 2 h. The reaction was poured onto ice water and the resulting solution was extracted using DCM (4 x 40 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-60% EtOAc / heptane), followed by flash column chromatography (eluting with a gradient of 20% EtOAc / heptane) gave the title compound (0.316 g, 8%) as awhite solid.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.64 (s, 1H), 7.39 (m, 1H), 7.19 (m, 1H), 6.51 (dd, J = 17.0, 0.7 Hz, 1H), 6.32 (dd, J = 17.0, 10.4 Hz, 1H), 5.93 (dd, J = 10.4, 0.7 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 228.95 $[M+H]^+$

N-[2-(trifluoromethyl)phenyl]prop-2-enamide (K7)



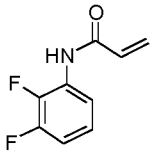
To an N_2 purged suspension solution of 2-(trifluoromethyl)aniline (3.1 ml, 24.83 mmol) and K_2CO_3 (10.3 g, 74.48 mmol) in acetone (90 ml) was added prop-2-enoyl chloride (8.0 ml, 99.30 mmol) dropwise. The reaction mixture was left stirring at room temperature for 3 h. The reaction was filtered, concentrated *in vacuo* and triturated with heptane to afford the title compound (4.74 g, 86%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.34 (d, J = 8.2 Hz, 1H), 7.70 - 7.45 (m, 3H), 7.28 - 7.22 (m, 1H), 6.46 (dd, J = 16.9, 1.3 Hz, 1H), 6.29 (dd, J = 16.9, 10.0 Hz, 1H), 5.86 (dd, J = 10.0, 1.3 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 215.90 $[M+H]^+$

N-[2-nitro-6-(trifluoromethyl)phenyl]prop-2-enamide (K8)



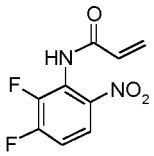
To an N_2 purged solution of N-[2-(trifluoromethyl)phenyl]prop-2-enamide **(K7)** (4.64 g, 20.91 mmol), AcOH (5 ml) and concentrated H_2SO_4 (13 ml) at 0°C was added red fuming HNO_3 (1.6 ml, 34.05 mmol) dropwise. The reaction mixture was left stirring at room temperature for 16 h. The reaction was poured onto ice water and then extracted using DCM (4 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-20% EtOAc / heptane) gave the title compound (0.829 g, 12%) as a beige solid.
HPLCMS (Method A): [*m/z*]: 260.95 $[M+H]^+$

N-(2,3-Difluorophenyl)prop-2-enamide (K9)



To an N_2 purged solution of 2,3-difluoroaniline (3 ml, 31 mmol) and K_2CO_3 (12.9 g, 92.9 mmol) in acetone (120 ml) at room temperature was added dropwise prop-2-enoyl chloride (10 ml, 124 mmol). The reaction mixture was left stirring for 16 h. The reaction was filtered and the filtrate concentrated to give a white solid which was triturated from heptane to give the title compound (4.97 g, 87%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.29 - 8.12 (m, 1H), 7.46 (s, 1H), 7.18 - 7.04 (m, 1H), 7.02 - 6.85 (m, 1H), 6.50 (dd, J = 16.8, 1.3 Hz, 1H), 6.31 (dd, J = 16.9, 10.1 Hz, 1H), 5.87 (dd, J = 10.1, 1.3 Hz, 1H)
HPLCMS (Method A): [*m/z*]: 184.2 $[M+H]^+$

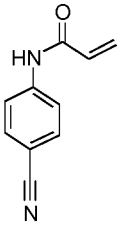
N-(2,3-Difluoro-6-nitrophenyl)prop-2-enamide (K10)



To an N_2 purged solution of N-(2,3-difluorophenyl)prop-2-enamide **(K9)** (4.9 g, 26.8 mmol), AcOH (5 ml) and concentrated H_2SO_4 (13 ml) at 0°C was added nitric acid (1.6 ml) dropwise. The reaction mixture was left stirring for 2 h. The reaction was poured onto ice / water and the solution extracted using DCM (5 x 30 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated to give the crude product. This was triturated with heptane (100 ml). The suspension was filtered and the residue collected to give a mixture of both para / ortho nitrated regioisomers as a beige solid (6 g). Purification by acidic prep-HPLC gave the title compound (4.2 g) as a white solid.
HPLCMS (Method A): [*m/z*]: 228.95 $[M+H]^+$

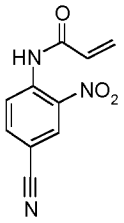
General Scheme K-II above:

N-(4-Cyanophenyl)prop-2-enamide (K11)



Acryloyl chloride (0.69 ml, 8.46 mmol) was added to an ice-cold suspension of 4-aminobenzonitrile (250 mg, 2.12 mmol) and K_2CO_3 (880 mg, 6.35 mmol) in acetone (5 ml). The mixture was stirred for 18h whilst warming to room temperature. The reaction mixture was filtered and the residue rinsed with acetone (5 ml). The combined filtrates were evaporated *in vacuo* and the crude purification by flash column chromatography using an elution gradient 0-80% EtOAc / heptane to afford the title compound (353 mg, 96%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.73 (d, J = 8.8 Hz, 2H), 7.68 - 7.58 (m, 2H), 7.37 (s, 1H), 6.49 (dd, J = 16.8, 1.0 Hz, 1H), 6.25 (dd, J = 16.8, 10.2 Hz, 1H), 5.86 (dd, J = 10.2, 1.0 Hz, 1H)
HPLCMS (Method M): [*m/z*]: 173.45 $[M+H]^+$

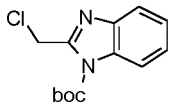
N-(4-Cyano-2-nitrophenyl)prop-2-enamide (K12)



Nitric acid (0.6 ml) was added dropwise to an ice-cold solution of N-(4-cyanophenyl)prop-2-enamide **(K11)** (1.03 g, 5.75 mmol) in acetic acid (2 ml) and sulfuric acid (4.75 ml). The reaction mixture was stirred for 3h, then poured into ice-cold water and the mixture extracted with DCM (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash column chromatography using an elution gradient 0-90% EtOAc / heptane afforded the title compound (1.2 g, 93%) as a yellow solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 10.77 (s, 1H), 9.14 (d, *J* = 8.9 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 8.9, 1.7 Hz, 1H), 6.54 (dd, *J* = 17.0, 0.9 Hz, 1H), 6.35 (dd, *J* = 17.0, 10.1 Hz, 1H), 5.98 (dd, *J* = 10.1, 0.9 Hz, 1H)

Tert-butyl 2-(chloromethyl)-1H-1,3-benzodiazole-1-carboxylate (L)

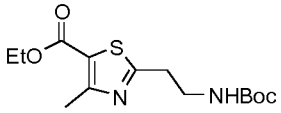


A mixture of 2-(chloromethyl)-1H-1,3-benzodiazole (10 g, 0.06 mol), BOC_2O (18 ml, 0.06 mol) and TEA (6.07 g, 0.06 mol) in DCM (304 ml) was cooled to 0°C. A catalytic amount of DMAP (0.73 g, 0.006 mol) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (150 ml), washed with saturated $NaHCO_3$ (150 ml), brine (150 ml), dried (Na_2SO_4), filtered and concentrated to give the crude product. Purification by flash column chromatography(eluting with a gradient of 5-10% EtOAc / heptane) gave the title compound (7 g, 44%) as an off white oil.

HPLCMS (Method H): [*m/z*]: 167.2 $[M\text{-Boc}+H]^+$

General Scheme I-1 above:

Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4-methyl-1,3-thiazole-5-carboxylate (208)

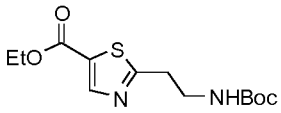


In a similar fashion to general procedure 1, a suspension of tert-butyl (3-amino-3-thioxopropyl)carbamate (1.0 g, 5.34 mmol), $CaCO_3$ (0.29 g, 2.93 mmol) and ethyl 2-chloro-3-oxobutanoate (0.81 ml, 5.86 mmol) in EtOH (15 ml) was heated at 60°C for 18 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between EtOAc and water and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 80 ml) and the combined organic extracts were washed with brine (80 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 5-50% EtOAc / heptane) afforded the title compound (1.57 g, 94%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 5.01 (br s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.57 (dt, J = 5.5, 5.5 Hz, 2H), 3.15 (t, J = 6.3 Hz, 2H), 2.73 (s, 3H), 1.47 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 315.10 $[M+H]^+$

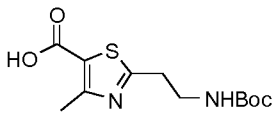
Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-5-carboxylate (209)



In a similar fashion to general procedure 1, Tert-butyl N-(2-carbamothioylethyl)carbamate (1 g, 4.89 mmol), calcium carbonate (0.27 g, 3 mmol) and ethyl 2-chloro-3-oxopropanoate (0.81 g, 5 mmol) were combined in EtOH (15ml) and the mixture heated at 60°C for 18 h. Further 2-chloro-3-oxopropanoate (0.81 g, 5 mmol) was added and the mixture further heated at 80°C for 5 h. The reaction mixture was cooled toroom temperature and concentrated *in vacuo*. The residue was partitioned between water and EtOAc and the mixture extracted with EtOAc (3 x 80 ml). The combined organic extracts were washed with brine (80 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 20-60% EtOAc / heptane) afforded the crude title compound (743 mg) as a brown oil which was used into the next step without further purification.

HPLCMS (Method A): [*m/z*]: 301.05 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-4-methyl-1,3-thiazole-5-carboxylic acid (210)

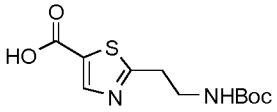


In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4-methyl-1,3-thiazole-5-carboxylate **(208)** (1.57 g, 4.99 mmol) and LiOH (0.72 g, 30 mmol) in THF (30 ml) and water (15 ml) afforded the title compound (1.23 g, 86%) as a white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 6.99 (t, J = 5.3 Hz, 1H), 3.28 (m, 2H), 3.04 (t, J = 6.7 Hz, 2H), 2.58 (s, 3H), 1.37 (s, 9H)

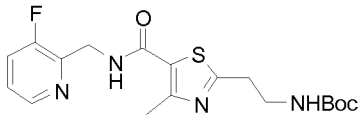
HPLCMS (Method A): [*m/z*]: 287.05 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-5-carboxylic acid (211)



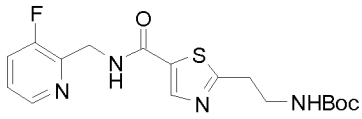
In a similar fashion to general procedure 5, crude ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-5-carboxylate **(209)** (743 mg, 2.47 mmol) and LiOH (300 mg, 12 mmol) in THF (20 ml) and water (10 ml) afforded the crude title compound (500 mg) as a brown oil, which was used into the next step without further purification.
HPLCMS (Method A): [*m/z*]: 273.05 $[M+H]^+$

Tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-4-methyl-1,3-thiazol-2-yl)ethyl]carbamate (212)



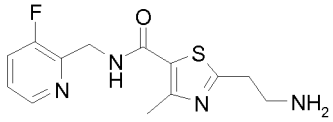
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4-methyl-1,3-thiazole-5-carboxylic acid **(210)** (0.457 g, 1.6 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.349 g, 1.76 mmol), DIPEA (0.92 ml, 5 mmol) and HATU (0.73 g, 2 mmol) in DCM (20 ml) afforded the crude title compound (1.26 g) as a colourless oil.
HPLCMS (Method A): [*m/z*]: 395.1 $[M+H]^+$

Tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (213)



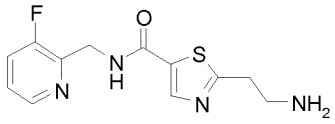
In a similar fashion to general procedure 6, crude 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-5-carboxylic acid **(211)** (500 mg), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (402 mg, 2.02 mmol), DIPEA (1.06 ml, 6 mmol) and HATU (840 mg, 2 mmol) in DCM (30 ml) afforded the crude title compound (953 mg, 87% purity) as a yellow residue after partial purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane followed by 0-10% MeOH / EtOAc).
HPLCMS (Method A): [*m/z*]: 381.05 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-4-methyl-1,3-thiazole-5-carboxamide (214)



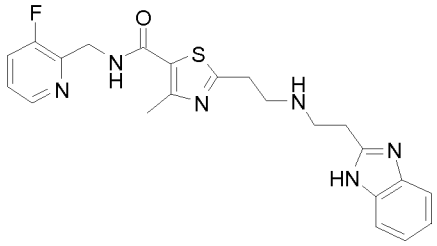
In a similar fashion to general procedure 2, crude tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-4-methyl-1,3-thiazol-2-yl)ethyl]carbamate **(212)** (1.26 g) and 12 M HCl (2 ml) in MeOH (20 ml) afforded the title compound freebase (471 mg) as a white solid after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then eluting with 7 N ammonia in MeOH.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.56 (t, J = 5.5 Hz, 1H), 8.39 (dt, J = 4.6, 1.3 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.43 - 7.38 (m, 1H), 4.61 - 4.56 (m, 2H), 3.03 (t, J = 7.0 Hz, 2H), 2.95 (t, J = 6.5 Hz, 2H), 2.54 (s, 3H)
HPLCMS (Method A): [*m/z*]: 295.05 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-5-carboxamide (215)



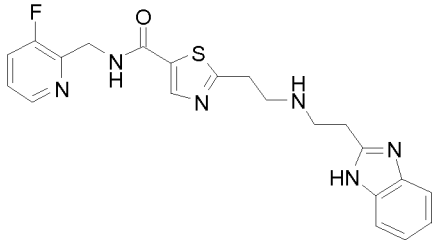
In a similar fashion to general procedure 2, crude tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(213)** (87%, 923 mg, 2.11 mmol) and 12 M HCl (2 ml) in MeOH (20 ml) afforded the title compound freebase (389 mg) as a yellow residue after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then eluting with 7 N ammonia in MeOH.
HPLCMS (Method A): [*m/z*]: 280.95 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-4-methyl-1,3-thiazole-5-carboxamide (Example Compound No. 7)



In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-4-methyl-1,3-thiazole-5-carboxamide **(214)** (471 mg, 1.6 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (295 mg, 1.54 mmol) and DBU (0.26 ml, 2 mmol) gave the crude intermediate which was further reacted with iron powder (280 mg, 5 mmol) in AcOH (5 ml) to give the title compound (115 mg, 20%) as a white solidafter purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM).
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.38 (d, J = 4.7 Hz, 1H), 7.61 (t, J = 9.2 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.43 - 7.38 (m, 1H), 7.22 - 7.15 (m, 2H), 4.73 (s, 2H), 3.22 - 3.14 (m, 4H), 3.14 - 3.05 (m, 4H), 2.51 (s, 3H)
HPLCMS (Method C): [*m/z*]: 439.1 $[M+H]^+$

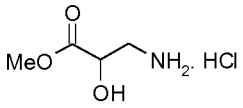
2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-5-carboxamide (Example Compound No. 8)



In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-5-carboxamide **(215)** (389 mg, 1.39 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (267 mg, 1.39 mmol) and DBU (0.25 ml, 2 mmol) in MeCN (15 ml) afforded a crude intermediate which was further reacted with iron powder (230 mg, 4 mmol) in AcOH (5 ml) to afford the title compound (49 mg, 11%) as a white solid after three purifications by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.38 (dt, J = 4.9, 1.3 Hz, 1H), 8.14 (s, 1H), 7.65 - 7.59 (m, 1H), 7.52 - 7.47 (m, 2H), 7.44 - 7.39 (m, 1H), 7.21 - 7.17 (m, 2H), 4.75 (d, J = 1.6 Hz, 2H), 3.23 (t, J = 6.8 Hz, 2H), 3.15 - 3.07 (m, 6H)
HPLCMS (Method C): [*m/z*]: 425.1 $[M+H]^+$

General Scheme 24 above:

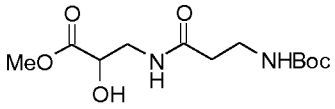
Methyl 3-amino-2-hydroxypropanoate hydrochloride (332)



Thionyl chloride (1.8 ml, 20 mmol) was added dropwise to ice-cold MeOH (60 ml) and stirred for 5 min. 3-Amino-2-hydroxypropanoic acid (1.04 g, 9.9 mmol) was added and the reaction mixture stirred at room temperature for 18 h. The reaction mixture was rigourously evaporated in vacuo to afford the title compound (1.54 g, quant.) as a yellow oil.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.12 (s, 3H), 6.36 (s, 1H), 4.39 (dt, J = 8.8, 4.6 Hz, 1H), 3.69 (s, 3H), 3.24 - 3.05 (m, 1H), 3.00 - 2.84 (m, 1H)

Methyl 3-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-2-hydroxypropanoate (333)

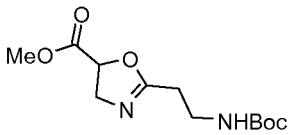


In a similar fashion to general procedure 13, methyl 3-amino-2-hydroxypropanoate hydrochloride **(332)** (4.35 g, 27.96 mmol), 3-{[(tert-butoxy)carbonyl]amino}propanoic acid (5.82 g, 30.76 mmol), TEA (4.68 ml, 34 mmol) and DCC (5.77 g, 28 mmol) in DCM (80 ml) afforded the title compound (5.12 g, 63%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient 0-100% EtOAc / heptane).

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 6.06 (s, 1H), 5.18 (s, 1H), 4.32 (q, J = 4.9 Hz, 1H), 3.83 (s, 3H), 3.72 - 3.60 (m, 2H), 3.46 (d, J = 5.4 Hz, 1H), 3.45 - 3.38 (m, 2H), 2.47 - 2.36 (m, 2H), 1.46 (s, 9H)

HPLCMS (Method A): [*m/z*]: 313.00 $[M+Na]^+$

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4,5-dihydro-1,3-oxazole-5-carboxylate (334)

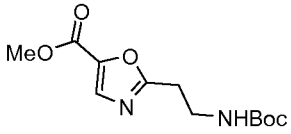


In a similar fashion to general procedure 14, methyl 3-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-2-hydroxypropanoate **(333)** (3.63 g, 12.5 mmol), DAST (1.98 ml, 15 mmol) and K_2CO_3 (3.46 g, 25 mmol) in DCM (100 ml) afforded the title compound (3.4 g, 99%) as a colourless oil after purification by flash column chromatography (eluting with a gradient 40-100% EtOAc / heptane).

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 4.96 (dd, J = 10.8, 6.5 Hz, 1H), 4.24 - 4.09 (m, 1H), 4.04 - 3.88 (m, 1H), 3.83 (s, 3H), 3.58 - 3.38 (m, 2H), 2.57 (d, J = 4.8 Hz, 2H), 1.47 (s, 9H)

HPLCMS (Method M): [*m/z*]: 272.95 $[M+H]^+$

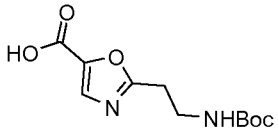
General procedure 16: Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-5-carboxylate (335)



A solution of methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4,5-dihydro-1,3-oxazole-5-carboxylate **(334)** (3.2 g, 11.75 mmol), NBS (2.3 g, 12.93 mmol) and AIBN (0.19 g, 1.18 mmol) in DCE (30 ml) was heated at 80° for 1.5 h. The reaction mixture was cooled to room temperature,quenched with saturated $NaHCO_3$(aq) and extracted with DCM (3 x 80 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-80% EtOAc

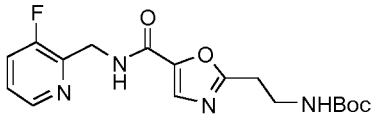
/ heptane) afforded the crude title compound (1.25 g, 29%, 75% purity) as an orange residue. Compound was used in the next step witout further purification.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.69 (s, 1H), 5.17 - 4.98 (m, 1H), 3.94 (s, 3H), 3.62 (q, J = 6.2 Hz, 2H), 3.05 (t, J = 6.2 Hz, 2H), 1.46 (s, 9H)
HPLCMS (Method M): [*m/z*]: 271.00 $[M+H]^+$

2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-5-carboxylic acid (336)



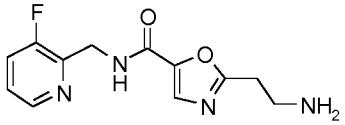
In a similar fashion to general procedure 5, crude methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-5-carboxylate **(335)** (1.24 g, 3.44 mmol, 75% purity) and LiOH (0.329 mg, 13.76 mmol) in THF (20 ml) and water (20 ml) afforded the title compound (0.51 g, 44%) as a pale orange residue. Compound was used in the next step without further purification.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.76 (s, 1H), 5.14 (s, 1H), 3.71 - 3.56 (m, 2H), 3.09 (t, J = 6.2 Hz, 2H), 1.46 (s, 9H)
HPLCMS (Method M): [*m/z*]: 256.95 $[M+H]^+$

Tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate (337)



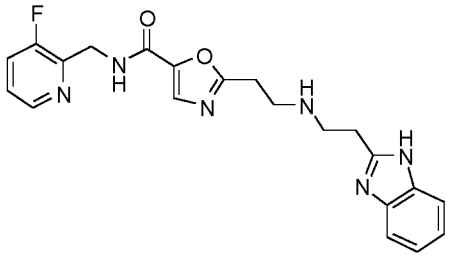
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-5-carboxylic acid **(336)** (513 mg, 2 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (479 mg, 2.4 mmol), DIPEA (1.15 ml, 6.61 mmol) and HATU (837 mg, 2.2 mmol) in DCM (20 ml) afforded the crude title compound (1.08 g, 74%, 50% purity) as a yellow residue. Compound was used in the next step without purification.
HPLCMS (Method M): [*m/z*]: 365.05 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide (338)



In a similar fashion to general procedure 2, crude tert-butyl N-[2-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate **(337)** (1.08 g, 1.48 mmol) and 12M HCl (1 ml) in MeOH (10 ml) afforded the title compound freebase (444 mg, 57%) as a pale yellow solidafter freebasing using an SCX-2 cartridge (10 g), rinsing with DCM and MeOH, then elution with 7N ammonia in MeOH.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.99 (t, J = 5.7 Hz, 1H), 8.39 (dt, J = 4.6, 1.5 Hz, 1H), 7.78 - 7.64 (m, 2H), 7.48 - 7.36 (m, 1H), 4.61 (dd, J = 5.8, 1.6 Hz, 2H), 3.07 - 2.86 (m, 4H)
HPLCMS (Method M): [*m/z*]: 264.95 $[M+H]^+$

2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide Example Compound No. 1)

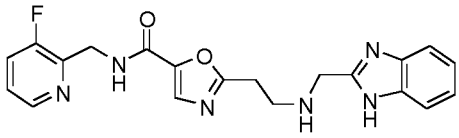


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide **(338)** (444 mg, 1.68 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (323 mg, 1.68 mmol) and DBU (301 µl, 2.02 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (343 mg, 6.13 mmol) and AcOH (10 ml) to give the title compound as a pale yellow solid (166 mg, 25%) after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.12 (s, 1H), 8.96 (t, J = 5.8 Hz, 1H), 8.38 (dt, J = 4.6, 1.4 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.53 - 7.37 (m, 3H), 7.11 (dt, J = 6.0, 3.5 Hz, 2H), 4.61 (dd, J = 5.7, 1.4 Hz, 2H), 3.04 - 2.89 (m, 8H)

HPLCMS (Method B): [*m/z*]: 409.1 $[M+H]^+$

2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide (Example Compound No. 4)



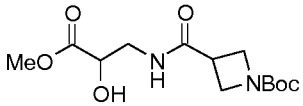
In a similar fashion to general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide **(338)** (250 mg, 0.83 mmol, 88% purity), 1H-benzimidazole-2-carbaldehyde (170 mg, 1.17 mmol), DIPEA (0.44 ml, 2.5 mmol) and $MgSO_4$ (150 mg, 1.25 mmol) in MeOH (10 ml) at room temperature for 16 h gave an intermediate which was further reacted with $NaBH_4$ (47 mg, 1.25 mmol) to give the title compound (156 mg, 48%) as a white solid after purification by flash column chromatography [eluting with a gradient of 0-5% (7N NH_3 in MeOH) / DCM] followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (br s, 1H), 8.95 (t, J = 5.8 Hz, 1H), 8.39 – 8.34 (m, 1H), 7.72 – 7.65 (m, 2H), 7.54 – 7.46 (m, 1H), 7.46 – 7.36 (m, 2H), 7.17 – 7.06 (m, 2H), 4.63 – 4.56 (m, 2H), 3.93 (s, 2H), 3.02 – 2.94 (m, 4H), 2.57 (br s, 1H)

HPLCMS (Method D): [*m/z*]: 395.2 $[M+H]^+$

General Scheme 27 above:

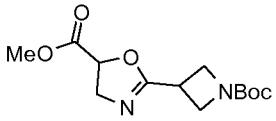
Tert-butyl 3-[(2-hydroxy-3-methoxy-3-oxopropyl)carbamoyl]azetidine-1-carboxylate (354)



In a similar fashion to general procedure 13, methyl 3-amino-2-hydroxypropanoate hydrochloride (2.9 g, 18.64 mmol), 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (4.13 g, 20.5 mmol), TEA (5.45 ml, 39.14 mmol) and DCC (4.04 g, 19.57 mmol) in DCM (80 ml) afforded the title compound (4.47 g, 79%) as a viscous pale yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane followed by 0-3% MeOH / EtOAc).

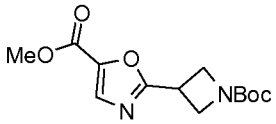
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 5.92 (s, 1H), 4.32 (dd, J = 5.3, 4.3 Hz, 1H), 4.14 - 4.03 (m, 5H), 3.84 (s, 3H), 3.74 - 3.63 (m, 2H), 3.24 - 3.14 (m, 1H), 1.46 (s, 9H)
HPLCMS (Method M): [*m/z*]: 325.00 $[M+Na]^+$

Methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-4,5-dihydro-1,3-oxazole-5-carboxylate (355)



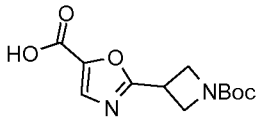
In a similar fashion to general procedure 14, tert-butyl 3-[(2-hydroxy-3-methoxy-3-oxopropyl)carbamoyl]azetidine-1-carboxylate **(354)** (4.47 g, 14.79 mmol) and DAST (2.15 ml, 16.26 mmol) in DCM (100 ml) followed by quenching with K_2CO_3 (4.09 g, 29.57 mmol) afforded the title compound (1.61 g, 38%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane followed by 1% MeOH / EtOAc).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.00 (dd, J = 10.8, 6.7 Hz, 1H), 4.27 - 4.08 (m, 5H), 4.00 (ddd, J = 14.7, 6.7, 1.0 Hz, 1H), 3.83 (s, 3H), 3.55 - 3.39 (m, 1H), 1.46 (s, 9H)

Methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-5-carboxylate (356)



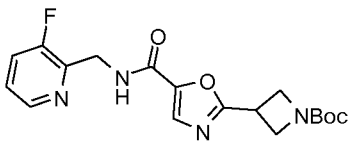
In a similar fashion to general procedure 16, methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-4,5-dihydro-1,3-oxazole-5-carboxylate **(355)** (1.61 g, 5.66 mmol), NBS (1.11 g, 6.23 mmol) and AIBN (0.11 g, 0.57 mmol) in DCE (60 ml) at 80°C for 1.5 h gave the title compound (756 mg, 45%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 0-80% EtOAc / heptane).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.74 (s, 1H), 4.38 - 4.23 (m, 4H), 4.03 - 3.83 (m, 5H), 1.48 (s, 9H)
HPLCMS (Method M): [*m/z*]: 304.95 $[M+Na]^+$

2-{1-[(Tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-5-carboxylic acid (357)



In a similar fashion to general procedure 5, methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-5-carboxylate **(356)** (750 mg, 2.66 mmol) and LiOH (382 mg, 15.94 mmol) in THF / water(20 ml / 20 ml) afforded the title compound (710 mg, 99%) as a pale yellow oil. The title compound was used in the next step without purification.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.83 (s, 1H), 4.40 - 4.25 (m, 4H), 4.04 - 3.94 (m, 1H), 1.48 (s, 9H)
HPLCMS (Method M): [*m/z*]: 290.90 $[M+Na]^+$

Tert-butyl 3-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)azetidine-1-carboxylate (358)



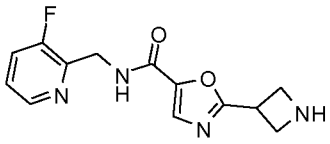
In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-5-carboxylic acid **(357)** (0.74 g, 2.77 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.61 g, 3.04 mmol), DIPEA (1.59 ml, 9.13 mmol) and HATU (1.16 g, 3.04 mmol) in DCM (30 ml) afforded the title

compound (2.26 g, 45% purity) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane followed by 2-10% MeOH / EtOAc). The material was used in the next step without further purification.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.44 (dt, J = 4.8, 1.3 Hz, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7.53- 7.42 (m, 1H), 7.38 - 7.31 (m, 1H), 4.84 (dd, J = 4.8, 1.5 Hz, 2H), 4.42 - 4.24 (m, 4H), 4.06 - 3.91 (m, 1H), 1.49 (s, 9H)

HPLCMS (Method M): [*m/z*]: 377.05 $[M+H]^+$

2-(Azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide (359)

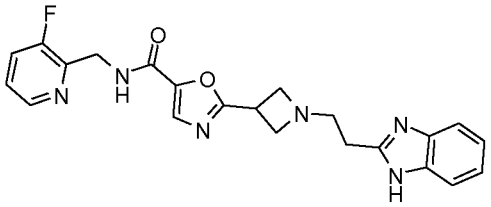


In a similar fashion to general procedure 2, tert-butyl 3-(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)azetidine-1-carboxylate **(358)** (45%, 2.26 g, 2.7 mmol) and 12M HCl (2 ml) in MeOH (20 ml) afforded the title compound (644 mg, 86%) as a white solid afterfreebasing using an SCX-2 cartridge (10 g), rinsing with DCM and MeOH, then elution with 7N ammonia in MeOH.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 9.03 (t, J = 5.6 Hz, 1H), 8.39 (dt, J = 4.5, 1.3 Hz, 1H), 7.74 (s, 1H), 7.70 (ddd, J = 10.0, 8.4, 1.2 Hz, 1H), 7.41 (dt, J = 8.6, 4.4 Hz, 1H), 4.63- 4.60 (m, 2H), 4.11 - 4.02 (m, 1H), 3.85 (t, J = 7.6 Hz, 2H), 3.78 (t, J = 8.2 Hz, 2H)

HPLCMS (Method M): [*m/z*]: 276.95 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide (Example Compound No. 2)

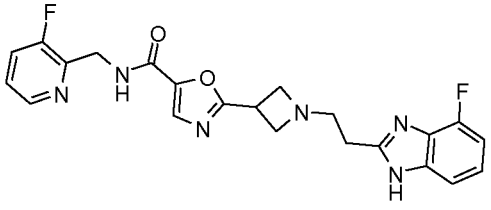


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide **(359)** (255 mg, 0.92 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (186 mg, 0.97 mmol) and DBU (145 µl, 0.97 mmol) in MeCN (10 ml) afforded a crude intermediate which was further reacted with iron powder (167 mg, 3 mmol) in AcOH (4 ml) to afford the title compound (140 mg, 44%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM).

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.36 (dt, J = 4.7, 1.2 Hz, 1H), 7.69 (s, 1H), 7.62 (ddd, J = 9.8, 8.4, 1.2 Hz, 1H), 7.52 (s, 2H), 7.41 (dt, J = 8.6, 4.4 Hz, 1H), 7.24- 7.17 (m, 2H), 4.77 (d, J = 1.6 Hz, 2H), 3.96 - 3.87 (m, 1H), 3.76 (t, J = 7.9 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 3.08 - 3.02 (m, 2H), 3.01 - 2.95 (m, 2H)

HPLCMS (Method B): [*m/z*]: 421.1 $[M+H]^+$

2-{1-[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide Example Compound No. 3)

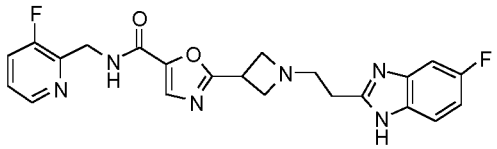


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide **(359)** (400 mg, 1.45 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (335 mg, 1.59 mmol) and DBU (238 µl, 1.59 mmol) in MeCN (10 ml) gave a crude intermediate which was partially purified by flash chromatography (eluting with gradient of 0-20% MeOH / DCM). The intermediate was further reacted with iron powder (76 mg) in AcOH (3 ml) to afford the title compound (52 mg,34%) as a beige solid after purification by flash column chromatography (eluting with a gradient of 0-35% MeOH / DCM).

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.38 - 8.34 (m, 1H), 7.69 (s, 1H), 7.65 - 7.60 (m, 1H), 7.44 - 7.39 (m, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.21 - 7.15 (m, 1H), 6.98 - 6.92 (m, 1H), 4.77 (d, J = 1.6 Hz, 2H), 3.92 (p, J = 7.1 Hz, 1H), 3.77 (t, J = 8.0 Hz, 2H), 3.58 (t, J = 7.4 Hz, 2H), 3.08 - 3.02 (m, 2H), 3.02 - 2.96 (m, 2H)

HPLCMS (Method G): [*m/z*]: 439.2 $[M+H]^+$

2-{1-[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide (Example Compound No. 5)



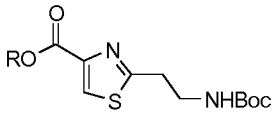
In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide **(359)** (581 mg, 2.1 mmol), N-(5-fluoro-2-nitrophenyl)prop-2-enamide **(J)** (371 mg, 1.77 mmol) and DBU (346 µl, 2.31 mmol) in MeCN (30 ml) gave a crude intermediate which was further reacted with iron powder (186 mg, 3.34 mmol) in AcOH (20 ml) to afford the title compound (205 mg, 56%) as a white solid after purification by basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.37 (dt, J = 4.6, 1.2 Hz, 1H), 7.69 (s, 1H), 7.62 (ddd, J = 9.8, 8.4, 1.2 Hz, 1H), 7.51 - 7.45 (m, 1H), 7.41 (dt, J = 8.7, 4.4 Hz, 1H), 7.22 (dd, J = 9.1, 2.1 Hz, 1H), 7.03 - 6.96 (m, 1H), 4.77 (d, J = 1.6 Hz, 2H), 3.95 - 3.86 (m, 1H), 3.76 (t, J = 8.0 Hz, 2H), 3.57 (t, J = 7.4 Hz, 2H), 3.06 - 3.01 (m, 2H), 3.00 - 2.94 (m, 2H)

HPLCMS (Method B): [*m/z*]: 439.2 $[M+H]^+$

General Scheme 1 above:

General procedure 1: ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate (1)

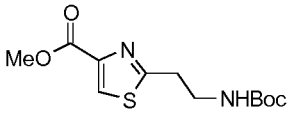


To a suspension of ethyl 3-bromo-2-oxopropanoate (12.35 ml, 107.69 mmol) and tert-butyl (3-amino-3-thioxopropyl) carbamate (20 g, 97.9 mmol) in EtOH (200 ml) was added $CaCO_3$ (5.3 g, 52.87 mmol) portion wise and the reaction mixture stirred at room temperature for 12 h. The mixture was concentrated in vacuo and the residue partitioned between EtOAc (200 ml) and sat. $NaHCO_3$ (100 ml). The organic layer was separated and washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the required product. Purification by flash column chromatography (isocratic elution 20% EtOAc / heptane) afforded the title compound (22 g, 69.6%) as a yellow solid.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.29 (s, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 6.5 Hz, 2H), 1.41 (d, J = 6.2 Hz, 14H)

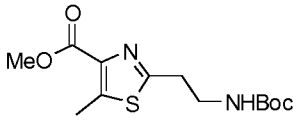
HPLCMS (Method A): [m/z]: 301.0 $[M+H]^+$

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate (2)



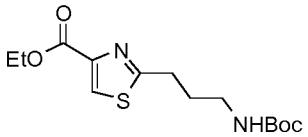
In a similar fashion to general procedure 1, tert-Butyl (3-amino-3-thioxopropyl)carbamate (10 g, 48.95 mmol), methyl 3-bromo-2-oxopropanoate (5.73 ml, 53.85 mmol) and $CaCO_3$ (0.9 ml, 26.43 mmol) in EtOH (120 ml) afforded the title compound (10.2 g, 60%, 83% purity) as a yellow solid after purification by flash chromatography (eluting with a gradient of 20-80% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 286.9 $[M+H]^+$

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-thiazole-4-carboxylate (3)



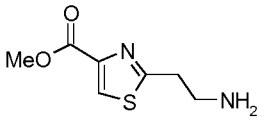
In a similar fashion to general procedure 1, tert-butyl N-(2-carbamothioylethyl)carbamate (0.89 g, 4.35 mmol), methyl 3-bromo-2-oxobutanoate (0.93 g, 4.78 mmol) and $CaCO_3$ (0.23 g, 2 mmol) in EtOH (15 ml) afforded the title compound (0.769 g, 58%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 10-60% EtOAc / heptane).
1H-NMR (CDCl3, 250 MHz): d[ppm]= 4.88 (s, 1H), 3.95 (s, 3H), 3.55 (q, J = 6.5 Hz, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.76 (s, 3H), 1.46 (s, 9H)
HPLCMS (Method A): [*m/z*]: 301.05 $[M+H]^+$

Ethyl 2-(3-{[(tert-butoxy)carbonyl]amino}propyl)-1,3-thiazole-4-carboxylate (4)



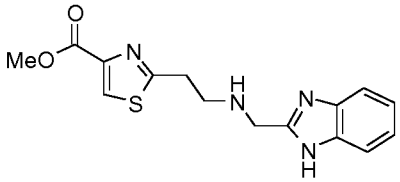
In a similar fashion to general procedure 1, tert-butyl N-(3-carbamothioylpropyl)carbamate (535 mg, 2.45 mmol), ethyl 3-bromo-2-oxopropanoate (0.31 ml, 2.7 mmol) and $CaCO_3$ (132 mg, 1.32 mmol) in EtOH (10 ml) afforded the title compound (726 mg, 93%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-50% EtOAc / heptane).
1H-NMR (DMSO-d6, 500MHz): d[ppm]= 8.38 (s, 1H), 6.90 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.15- 2.90 (m, 4H), 1.83 (m, 2H), 1.38 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 315 $[M+H]^+$

General procedure 2: Methyl 2-(2-aminoethyl)-1,3-thiazole-4-carboxylate (5)



4M HCl in dioxane (44 ml, 176 mmol) was added to a solution of methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(2)** (10.2 g, 35.62 mmol) in dioxane and the mixture was stirred at room temperature for 12 h, then at 40°C for 24 h. The mixture was cooled to room temperature and evaporated *in vacuo*. The residue was dissolved in DCM (20 ml) and washed with saturated $NaHCO_3$ (3 x 10 ml). The combined aqueous phases were re-extracted with diethyl ether (3 x 100 ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford the title compound (1.96 g, 30%) as a brown solid.
HPLCMS (Method A): [*m/z*]: 186.9 $[M+H]^+$

General procedure 3: Methyl 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylate (6)

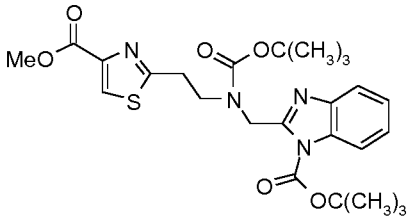


A suspension of methyl 2-(2-aminoethyl)-1,3-thiazole-4-carboxylate **(5)** (1.96 g, 10.52 mmol), 1H-benzimidazole-2-carbaldehyde (2.31 g, 15.79 mmol) and DIPEA (1.83 ml, 10.52 mmol) in MeOH (100 ml) was stirred at room temperature for 12 h. The reaction mixture was cooled to 0°C, $NaBH_4$ (0.597 g, 15.79 mmol) was added and the mixture stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100 ml) and washed with saturated Na_2CO_3 (2 x 50 ml). The combined aqueous layers were extracted with EtOAc (3 x 50 ml) and the combined organic layers dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash column chromatography (KP-NH, eluting with a gradient of 0-10% MeOH / DCM) afforded the title compound (1.4 g, 38%, 90% purity) as a tan solid.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.27 (s, 1H), 7.60 – 7.49 (m, 2H), 7.29 – 7.17 (m, 2H), 4.09 (s, 2H), 3.92 (s, 3H), 3.26 (t, *J* = 6.3 Hz, 2H), 3.10 (t, *J* = 6.8 Hz, 2H)

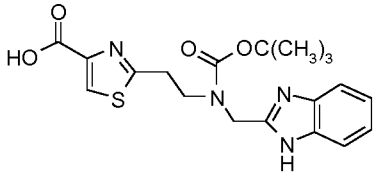
HPLCMS (Method A): [*m/z*]: 317 $[M+H]^+$

General procedure 4:
Tert-butyl 2-({[(tert-butoxy)carbonyl]({2-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]ethyl})amino} methyl)-1H-1,3-benzodiazole-1-carboxylate (7)



To a solution of methyl 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylate **(6)** (74%, 2.94 g, 6.88 mmol), Boc_2O (3.75 g, 17.19 mmol) and TEA (2.38 ml, 17.19 mmol) in THF (60 ml) was added DMAP (168 mg, 1.38 mmol) and the reaction was stirred at room temperature for 16 h. The reaction was evaporated to dryness, diluted with EtOAc (100 ml) and washed with water (3x 50 ml). The organic was dried over $MgSO_4$, filtered and evaporated to dryness. The crude residue was purified by FCC eluting with 0-100% EtOAc in heptane to give 3.8 g of desired product.

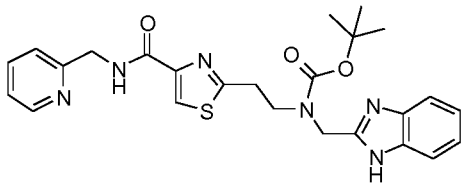
General procedure 5: 2-(2-{[(Tert-butoxy)carbonyl]({1-[(tert-butoxy)carbonyl]-1H-1,3-benzodiazol-2-yl}methyl)amino}ethyl)-1,3-thiazole-4-carboxylic acid (8)



Lithium hydroxide (0.48 mg, 20.08 mmol) was added to a solution of tert-butyl 2-({[(tert-butoxy)carbonyl]({2-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]ethyl})amino}methyl)-1H-1,3-benzodiazole-1-carboxylate **(7)** (3.8 g, 6.69 mmol) in THF / water (40 ml / 10 ml) at 0°C. The reaction mixture was stirred at room temperature for 48 h. The mixture was concentrated *in vacuo* and acidified to pH ~3-4 using AcOH. The reaction mixture was extracted with THF / EtOAc (3:1, 3 x 50 ml). The combined organic extracts were

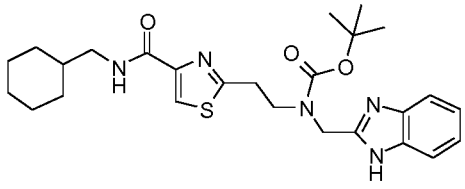
washed with brine (100 ml), dried ($MgSO_4$), filtered, reduced *in vacuo* and azeotroped with heptane (3 x 50 ml) to give the title compound (2.4 g, 84.6%) as a yellow foam.
1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.15 (d, J = 17.0 Hz, 1H), 7.69 (s, 2H), 7.27 (dd, J = 6.1, 3.2 Hz, 2H), 4.79 (s, 2H), 3.87 - 3.74 (m, 2H), 3.40 - 3.33 (m, 3H), 1.38 - 1.01 (m, 10H)
HPLCMS (Method A): [m/z]: 403 $[M+H]^+$

General procedure 6: Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (9)



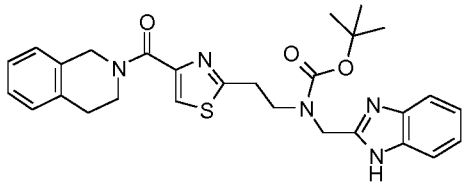
To a stirring solution of 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (3 g, 7.08 mmol), 1-(pyridin-2-yl)methanamine (1.1 ml, 10.62 mmol), DIPEA (3.7 ml, 21.24 mmol) and DMF (50 ml) at room temperature was added HATU (5.39 g, 14.16 mmol). The reaction mixture was allowed to stir at room temperature for 16 h.
The reaction was diluted with EtOAc (100 ml) and washed with sat. $NaHCO_3$ (3 x 50 ml) and brine (3 x 50 ml). The organic layer was separated, dried (MgSO4), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography (kp-NH, eluting with a gradient of 20-100% EtOAc in heptane) and then azeotroped with heptane to give the title compound (2.2 g, 62%) as a yellow foam.
1H-NMR (MeOD, 500 MHz): d[ppm]= 8.49 (d, J = 4.4 Hz, 1H), 8.10 (s, 1H), 7.80 (td, J = 7.8, 1.7 Hz, 1H), 7.54 (s, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.31 (dd, J = 7.1, 5.2 Hz, 1H), 7.26- 7.20 (m, 2H), 4.75 (d, J = 12.3 Hz, 2H), 4.70 (s, 2H), 3.92 - 3.79 (m, 2H), 3.36 (d, J = 8.1 Hz, 1H), 1.43 - 1.25 (m, 10H)
HPLCMS (Method D): [*m/z*]: 493.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(cyclohexylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (10)



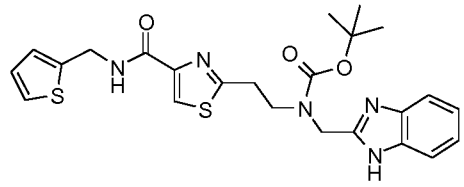
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), cyclohexylmethanamine (33.69 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (116 mg, 47% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step withoutfurther purification.
HPLCMS (Method H): [*m/z*]: 498.7 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1,3-thiazol-2-yl]ethyl}carbamate (11)



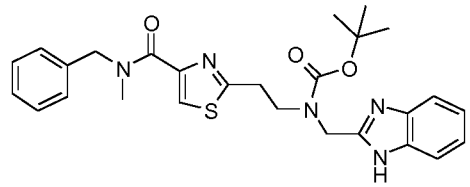
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), 1,2,3,4-tetrahydroisoquinoline (39.64 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (124 mg, 59% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purification.
HPLCMS (Method H): [*m/z*]: 518.7 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(thiophen-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (12)



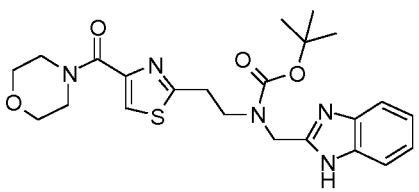
To a solution of 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.373 mmol) in DMF (10 ml) was added 1H-1,2,3-benzotriazol-1-ol (50 mg, 0.373 mmol) and EDC:HCl (71 mg, 0.373 mmol) at 0°C. The reaction mixture was allowed to stir for 15 min before TEA (38 mg, 0.373 mmol) was added followed by thiophen-2-ylmethanamine (42 mg, 0.373 mmol). The reaction mixture was allowed to warm up to room temperature and stir overnight. The title compound (185 mg, 16% purity) was obtained after work up following general procedure 6. Thiswas used in the next step without purification.
HPLCMS (Method H): [*m/z*]: 498.6 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[benzyl(methyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (13)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), benzyl(methyl)amine (36.06 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (118 mg, 55% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purificaton.
HPLCMS (Method H): [*m/z*]: 506.7 $[M+H]^+$

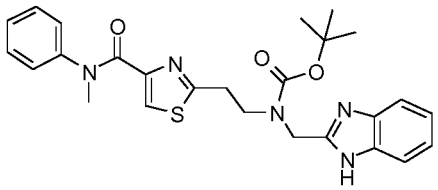
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(morpholine-4-carbonyl)-1,3-thiazol-2-yl]ethyl}carbamate (14)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), morpholine (25.93

mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (110 mg) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purification.

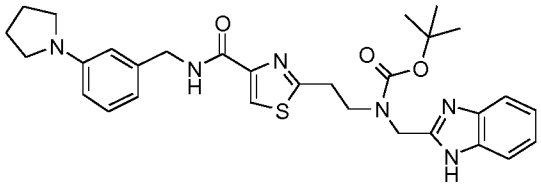
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[methyl(phenyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (15)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), N-methylaniline (31.89 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (118 mg, 59% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purification.

HPLCMS (Method H): [*m/z*]: 492.7 $[M+H]^+$

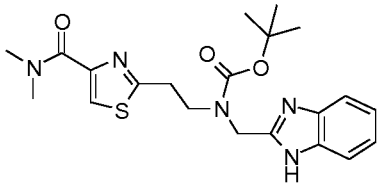
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(pyrrolidin-1-yl)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (16)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (200 mg, 0.497 mmol), [3-(pyrrolidin-1-yl)phenyl]methanamine (105 mg, 0.596 mmol), DIPEA (193 mg, 1.491 mmol) and HATU (227 mg, 0.596 mmol) in DMF (5 ml) at room temperature for 1 h afforded the title compound (100 mg, 30%, 84% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

HPLCMS (Method H): [*m/z*]: 561.7 $[M+H]^+$

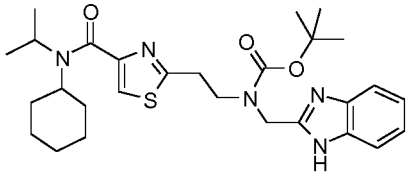
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(dimethylcarbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (17)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.248 mmol), dimethylamine (2 M solution in THF) (13 mg, 0.298 mmol), DIPEA (96 mg, 0.745 mmol) and HATU (113 mg, 0.298 mmol) in DMF (10 ml) at room temperature for 1 h afforded the title compound (90 mg, 67%, 80% purity) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

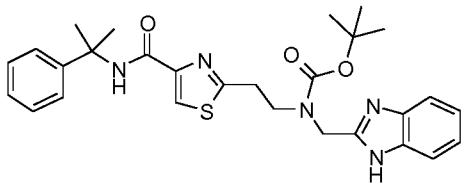
HPLCMS (Method H): [*m/z*]: 430.6 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[cyclohexyl(propan-2-yl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (18)



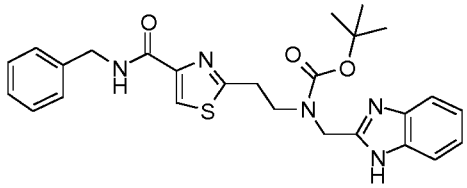
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), N-(propan-2-yl)cyclohexanamine (42.04 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (124 mg, 17% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purification.
HPLCMS (Method H): [*m/z*]: 526.8 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(2-phenylpropan-2-yl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (19)



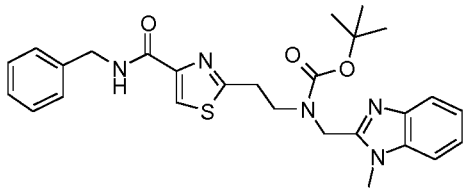
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), 2-phenylpropan-2-amine (40.24 mg, 0.298 mmol), DIPEA (96.16 mg, 0.744 mmol) and HATU (113.16 mg, 0.298 mmol) in DMF (4 ml) at room temperature for 1 h afforded the title compound (120 mg, 51% purity) as an off white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM). The title compound was used in the next step without further purification.
HPLCMS (Method H): [*m/z*]: 520.7 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (20)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (350 mg, 0.87 mmol), phenylmethanamine (103 mg, 0.957 mmol), DIPEA (337 mg, 2.61 mmol) and HATU (397 mg, 1.04 mmol) in DMF (10 ml) afforded the title compound (390 mg, 89% purity) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).
HPLCMS (Method H): [*m/z*]: 492.6 $[M+H]^+$

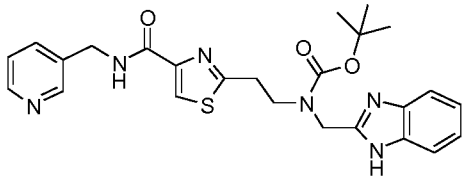
Tert-butyl N-{2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}-N-[(1-methyl-1H-1,3-benzodiazol-2-yl)methyl]carbamate (21)



To a stirred solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl] ethyl} carbamate **(20)** (380 mg, 0.773 mmol) and TEA (78 mg, 0.773 mmol) in DCM (15 ml) was added MeI (165 mg, 1.159 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated under vacuum to dryness to afford the title compound (280 mg, 72% purity) as an off white solid. The crude product was used in the next step without purification.

HPLCMS (Method H): [*m/z*]: 506.6 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (22)

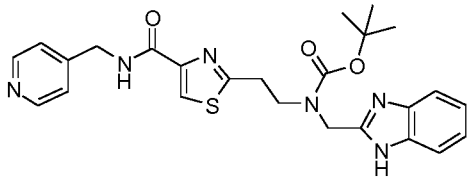


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (199.6 mg, 0.496 mmol), pyridin-3-ylmethanamine (59 mg, 0.546 mmol), DIPEA (192.3 mg, 1.488 mmol) and HATU (226 mg, 0.595 mmol) in DMF (8 ml) afforded the title compound (184 mg, 75%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 8.61 (d, J = 1.6 Hz, 1H), 8.52 (d, J = 3.6 Hz, 1H), 7.96 (s, 1H), 7.81 (s, 1H), 7.73 – 7.67 (m, 1H), 7.55 (dd, J = 6.0, 3.2 Hz, 2H), 7.28 (s, 1H), 7.25 (dd, J = 6.1, 3.2 Hz, 2H), 4.63 (d, J= 6.6 Hz, 4H), 3.77 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 6.3 Hz, 2H), 1.37 (s, 9H)

HPLCMS (Method H): [*m/z*]: 493.4 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-4-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (23)

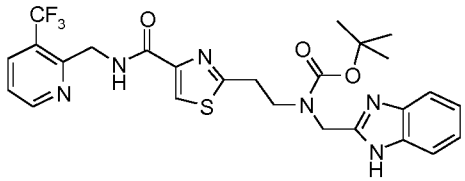


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (199.6 mg, 0.496 mmol), pyridin-4-ylmethanamine (59 mg, 0.546 mmol), DIPEA (192.3 mg, 1.488 mmol) and HATU (226 mg, 0.595 mmol) in DMF (8 ml) afforded the title compound (140 mg, 57%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 8.56 (d, J = 5.9 Hz, 2H), 7.98 (s, 1H), 7.82 (s, 1H), 7.59 – 7.48 (m, 2H), 7.24 (dd, J = 6.0, 3.2 Hz, 4H), 4.62 (d, J = 6.6 Hz, 4H), 3.78 (t, J = 6.5 Hz, 2H), 3.25 (t, J = 6.4 Hz, 2H), 1.41(d, J = 13.9 Hz, 9H)

HPLCMS (Method H): [*m/z*]: 493.4 $[M+H]^+$

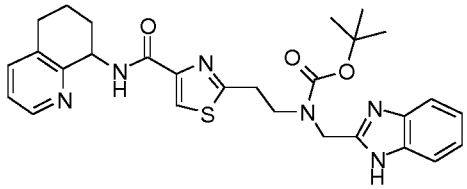
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[3-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (24)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (80.09 mg, 0.199 mmol), [3-(trifluoromethyl)pyridin-2-yl]methanamine hydrochloride (46.54 mg, 0.219 mmol), DIPEA (102.9mg, 0.796 mmol) and HATU (90.8 mg, 0.239 mmol) in DMF (2.5 ml) afforded the title compound (85 mg, 76%, 98% purity) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

HPLCMS (Method H): [*m/z*]: 561.5 $[M+H]^+$

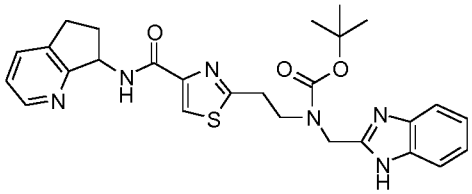
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(5,6,7,8-tetrahydroquinolin-8-yl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (25)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (80.09 mg, 0.199 mmol), N-methyl-5,6,7,8-tetrahydroquinolin-8-amine dihydrochloride (48.4 mg, 0.219 mmol), DIPEA (102.9 mg, 0.796 mmol) and HATU (90.8 mg, 0.239 mmol) in DMF (2.5 ml) afforded the title compound (92 mg, 87%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

HPLCMS (Method H): [*m/z*]: 533.5 $[M+H]^+$

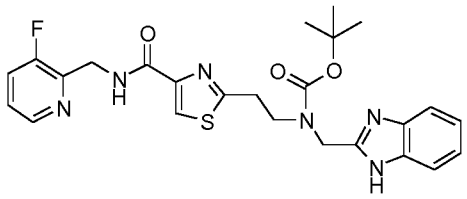
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (26)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (80.9 mg, 0.199 mmol), N-methyl-5H,6H,7H-cyclopenta[b]pyridin-7-amine hydrochloride (37.35 mg, 0.219 mmol), DIPEA (102.9 mg, 0.796 mmol) and HATU (90.8 mg, 0.239 mmol) in DMF (2.5 ml) afforded the title compound (90 mg, 87%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

HPLCMS (Method H): [*m/z*]: 519.5 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4-methylmorpholin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (27)

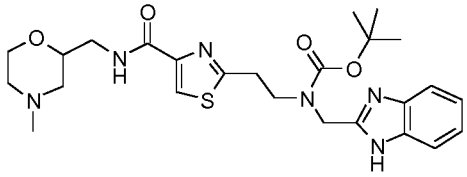


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (3 g, 7.545 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (2.26 g, 11.18 mmol), DIPEA (12.98 ml, 74.54 mmol) and HATU (4.251 g, 11.18 mmol) in DMF (60 ml) afforded the title compound (4.13 mg, 89%) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 20-100% EtOAc / heptane followed by 0-20% MeOH / EtOAc).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.29 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 8.17 (s, 1H), 7.70 (t, J = 9.5 Hz, 1H), 7.48 (s, 2H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.14 (s, 2H), 4.66 (d, J = 8.8 Hz, 4H), 3.73 (s, 2H), 2.52 (s, 2H), 1.99 (s, 4H), 1.26 (d, J = 44.9 Hz, 9H)

HPLCMS (Method A): [*m/z*]: 511.15 $[M+H]^+$

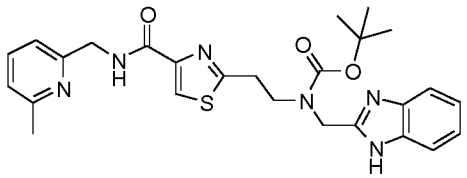
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4-methylmorpholin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (28)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), (4-methylmorpholin-3-yl)methanamine (35.5 mg, 0.273 mmol), DIPEA (96.16 mg, 0.744 mmol) and T3P (189.4 mg, 0.298 mmol) in DMF (4 ml) afforded the title compound (90 mg, 70%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 7.90 (s, 1H), 7.59 (s, 3H), 7.28 (t, *J* = 3.6 Hz, 1H), 4.64 (s, 2H), 3.79 (td, *J* = 12.0, 4.7 Hz, 5H), 3.70 - 3.59 (m, 2H), 3.47 (ddd, *J* = 14.7, 10.3, 6.6 Hz, 4H), 3.22 (t, *J* = 6.4 Hz, 2H), 2.74 (d, *J* = 11.4 Hz, 1H), 2.49 - 2.32 (m, 6H), 1.40 (s, 9H)

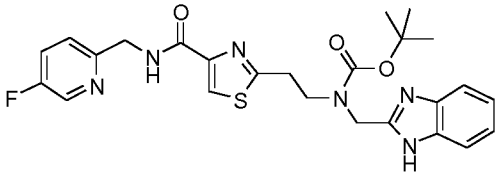
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (29)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **6** (99.8 mg, 0.248 mmol), (6-methylpyridin-2-yl)methanamine (33.33 mg, 0.273 mmol), DIPEA (96.16 mg, 0.744 mmol) and T3P (189.4 mg, 0.298 mmol) in DMF (4 ml) afforded the title compound (95 mg, 75%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

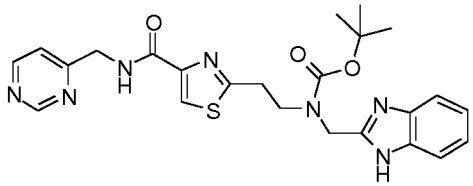
1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 8.14 (s, 1H), 7.90 (s, 1H), 7.55 (dd, *J* = 14.1, 6.6 Hz, 3H), 7.23 (dd, *J* = 6.0, 3.2 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 4.71 (d, *J* = 5.5 Hz, 2H), 4.66 (s, 2H), 3.80(t, *J* = 6.3 Hz, 2H), 3.22 (t, *J* = 6.4 Hz, 2H), 2.55 (s, 3H), 1.34 (s, 9H)

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (30)



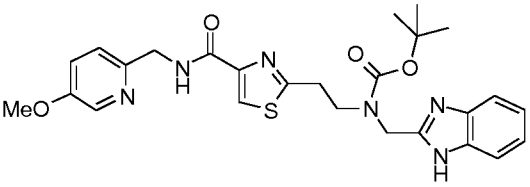
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (99.8 mg, 0.248 mmol), (5-fluoropyridin-2-yl)methanamine (34.41 mg, 0.273 mmol), DIPEA (96.16 mg, 0.744 mmol) and T3P (189.4 mg, 0.298 mmol) in DMF (4 ml) afforded the title compound (89 mg, 70%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).
1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 8.44 (s, 1H), 8.12 (s, 1H), 7.92 (s, 1H), 7.56 (s, 2H), 7.44- 7.30 (m, 2H), 7.25 (dd, *J* = 6.1, 3.2 Hz, 2H), 4.73 (d, *J* = 5.6 Hz, 2H), 4.66 (s, 2H), 3.79 (t, *J* = 6.3 Hz, 2H), 3.23 (t, *J* = 6.3Hz, 2H), 3.04 (s, 1H), 1.34 (s, 9H)

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyrimidin-4-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (31)



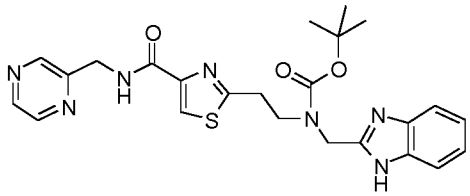
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.373mmo), pyrimidin-4-ylmethanamine (48.8 mg , 0.447 mmol), DIPEA (48.1 mg, 0.373 mmol) and HATU (141.7 mg, 0.373 mmol) in DMF (2 ml) at room temperature overnight gave the title compound (80 mg, 60% purity) as an yellow oil after purification by flash column chromatography (eluting with a gradient of 10% MeOH in DCM).
HPLCMS (Method H): [*m/z*]: 494.6 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-methoxypyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (32)



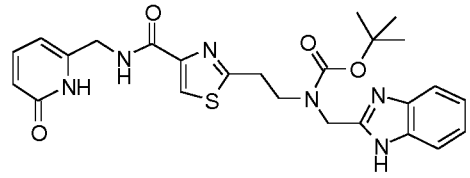
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.373mmo), (5-methoxypyridin-2-yl)methanamine (48.17 mg , 0.447 mmol), DIPEA (48.1 mg, 0.373 mmol)and HATU (141.7 mg, 0.373 mmol) in DMF (2 ml) at room temperature overnight gave the title compound (80 mg, 41%) as brown solid after purification by flash column chromatography (eluting with a gradient of 10% MeOH in DCM).
HPLCMS (Method H): [*m/z*]: 523.6 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyrazin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (33)



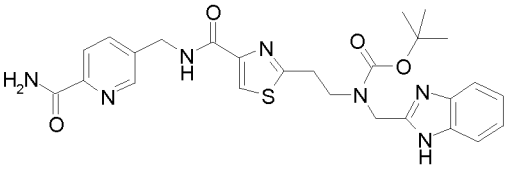
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.373 mmol), pyrazin-2-ylmethanamine (48.8 mg , 0.447 mmol), DIPEA (192.68 mg, 1.491 mmol) and HATU (141.7 mg, 0.373 mmol) in DMF (2 ml) at room temperature overnight gave the title compound (95 mg , 52%) as yellow solid after purification by flash column chromatography (eluting with a gradient of10% MeOH in DCM).
HPLCMS (Method H): [*m/z*]: 394.5 $[M+H\text{-}Boc]^+$

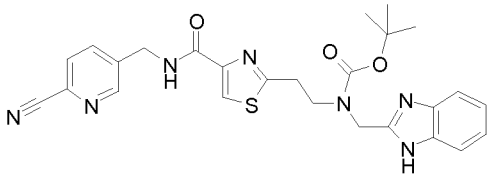
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-oxo-1,6-dihydropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (34)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.373 mmol), 6-(aminomethyl)-1,2-dihydropyridin-2-one (55.52 mg , 0.447 mmol), DIPEA (48.17 mg, 0.373 mmol) and HATU (141.7 mg, 0.373 mmol) in DMF (2 ml) at room temperature overnight gave the title compound (90 mg , 47%) as yellow solid after purification by flash column chromatography (eluting with a gradient of 10% MeOH / DCM).
HPLCMS (Method H): [*m/z*]: 509.6 $[M+H]^+$

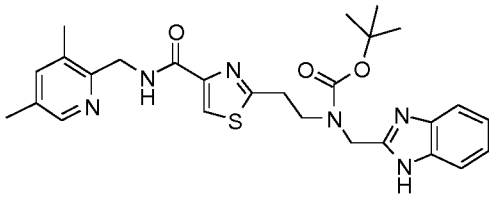
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-carbamoylpyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (35) and
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-cyanopyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (36)





In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.248 mmol), 5-(aminomethyl)pyridine-2-carbonitrile (33 mg, 0.248 mmol), HATU (189 mg, 0.497 mmol) and DIPEA (96 mg, 0.745 mmol) in DMF (1 ml) at room temperature for 18 h, gave a 2:1 ratio of boc amide and boc nitrile (80 mg) after purification by flash column chromatography (DCM : MeOH, 9:1). The mixture was used in the next step without separation.
HPLCMS (Method H): [m/z]: 418.5 $[M+H\text{-}boc]^+$ and 436.3 $[M+H\text{-}boc]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3,5-dimethylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (37)

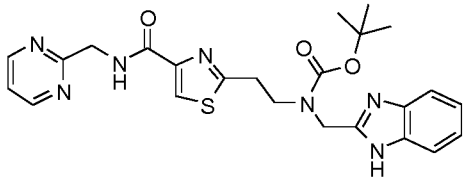


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (0.3 g, 0.708 mmol), (3,5-dimethylpyridin-2-yl)methanamine hydrochloride (0.183 g, 1.062 mmol), DIPEA (0.555 ml, 3.187 mmol) and HATU (0.404 g, 1.062 mmol) in DMF (6 ml) at room temperature for 4 h, gave the title compound (0.198 g, 51%) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of EtOAc (30%) / heptane (70%) followed by 100% EtOAc).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.29 (s, 1H), 8.75 (s, 1H), 8.19 (s, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.14 (p, J = 7.0 Hz, 2H), 4.66 (s, 2H), 4.53 (d, J = 4.8 Hz, 2H), 3.73 (s, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.31 (s, 9H)

HPLCMS (Method A): [m/z]: 521.15 $[M+H]^+$

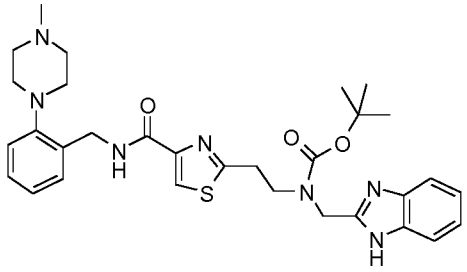
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (38)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.20 mmol), 1-(pyrimidin-2-yl)methanamine (22 mg, 0.20 mmol), DIPEA (0.1 ml, 0.60 mmol) and HATU (113 mg, 0.30 mmol) in DCM (5 ml) afforded the title compound (86 mg, 73%) as a brown residue after purificaton by flash column chromatography (eluting with a gradient of 0-20% MeOH / EtOAc).

HPLCMS (Method A): [*m/z*]: 494.1 $[M+H]^+$

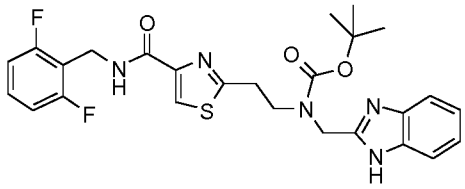
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(4-methylpiperazin-1-yl)phenyl] methyl} carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (39)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (130mg, 0.24mmol, 75% purity), 1-[2-(4-methylpiperazin-1-yl)phenyl]methanamine (75 mg, 0.36 mmol), DIPEA (127 µl, 0.73 mmol) and HATU (138 mg, 0.36 mmol) in DMF (2 ml) afforded the title compound (13 mg, 9%) as a white solid following purification by basic prep-HPLC.

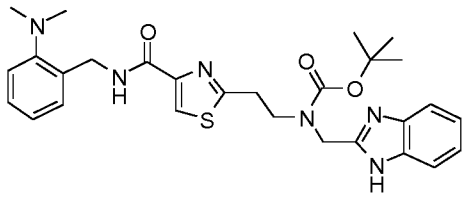
HPLCMS (Method D): [*m/z*]: 590.3 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2,6-difluorophenyl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (40)



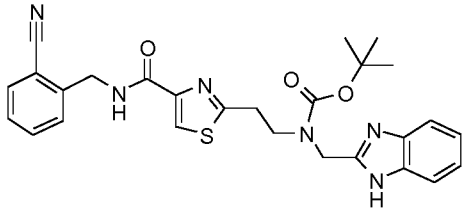
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (110 mg, 0.25 mmol, 90% purity), 1-(2,6-difluorophenyl)methanamine (53 mg, 0.37 mmol), DIPEA (0.13 ml, 0.74 mmol) and HATU (140 mg, 0.37 mmol) in DMF (2 ml) afforded the title compound (90 mg, 68%) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 2-100% EtOAc / heptane).
HPLCMS (Method E): [*m/z*]: 528.3 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(dimethylamino)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (41)



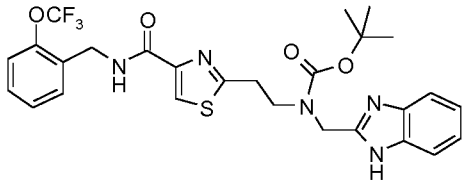
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (109 mg, 0.22 mmol, 80% purity), 2-(aminomethyl)-N,N-dimethylaniline (66 mg, 0.44 mmol), DIPEA (226 µl, 1.30 mmol) and HATU (240 mg, 0.64 mmol) in DMF (2 ml) at 50°C afforded the title compound (73 mg, 61%) as an orange oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 5-100% EtOAc / heptane).
HPLCMS (Method D): [*m/z*]: 535.2 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-cyanophenyl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (42)



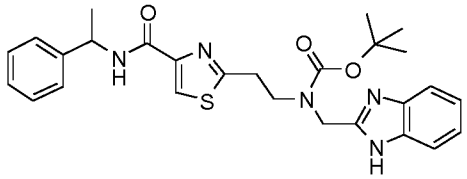
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (109 mg, 0.22 mmol, 80% purity), 2-(aminomethyl)benzonitrile hydrochloride (74 mg, 0.44 mmol), DIPEA (226 µl, 1.30 mmol) and HATU (240 mg, 0.64 mmol) in DMF (2 ml) at 50°C afforded the crude title compound (54 mg, 30%, 63% purity) as an orange oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 5-100% EtOAc / heptane).
HPLCMS (Method D): [*m/z*]: 517.2 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(trifluoromethoxy)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (43)



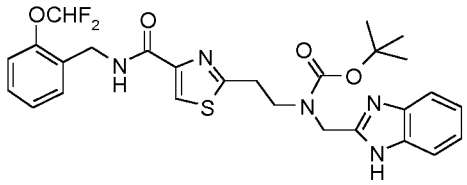
In a similar fashion to general procedure 6, 2 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (109 mg, 0.22 mmol, 80% purity), 1-[2-(trifluoromethoxy)phenyl]methanamine (103 mg, 0.54 mmol), DIPEA (283 µl, 1.63 mmol) and HATU (248 mg, 0.65 mmol) in DMF (2 ml) at 50°C afforded the crude title compound (110 mg, 78%, 88% purity) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 8-100% EtOAc / heptane).
HPLCMS (Method E): [*m/z*]: 576.2 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(1-phenylethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (44)



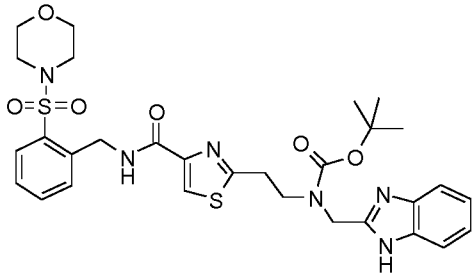
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (0.11 g, 0.22 mmol, 80% purity), 1-phenylethanamine (0.07 ml, 0.54 mmol), DIPEA (0.303 ml, 1.63 mmol) and HATU (0.25 g, 0.64 mmol) in DMF (2 ml) afforded the crude title compound (110 mg, 77%, 77% purity) as a yellow oil after purification by flash column chromatography (KP-NH, eluting with a gradient of 8-100% EtOAc / heptane).
HPLCMS (Method E): [*m/z*]: 506.2 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(difluoromethoxy)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (45)



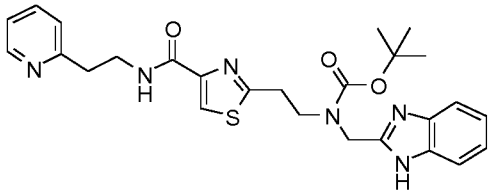
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (109 mg, 0.22 mmol, 80% purity), 1-[2-(difluoromethoxy)phenyl]methanamine (83 mg, 0.48 mmol), DIPEA (0.23 ml, 1.3 mmol) and HATU (250 mg, 0.65 mmol) in DMF (2 ml) afforded the crude title compound (470 mg) as an orange oil which was used in the next step without purification.
HPLCMS (Method A): [*m/z*]: 558.25 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(morpholine-4-sulfonyl)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (46)



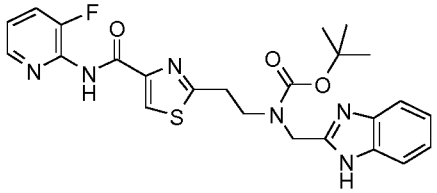
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (109 mg, 0.217 mmol, 80% purity), 1-[2-(morpholin-4-ylsulfonyl)phenyl]methanamine hydrochloride (140 mg, 0.48 mmol), DIPEA (0.23 ml, 1.3 mmol) and HATU (247 mg, 0.65 mmol) in DMF (2 ml) afforded the crude title compound (440 mg) as an orange oil after direct evaporation of the reaction mixture *in vacuo*. The material was used without purification.
HPLCMS (Method A): [*m/z*]: 641.35 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[2-(pyridin-2-yl)ethyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (47)



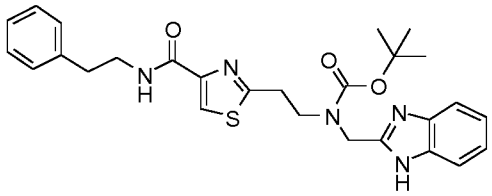
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.2 mmol, 80% purity), 2-(pyridin-2-yl)ethanamine (49 mg, 0.4 mmol), DIPEA (104 µl, 0.6 mmol) and HATU (151 mg, 0.4 mmol) in DMF (2 ml) afforded the title compound (52 mg, 52%) as a cream solid after purification by flash column chromatography KP-NH, eluting with a gradient of 5-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 507.15 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(3-fluoropyridin-2-yl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (48)



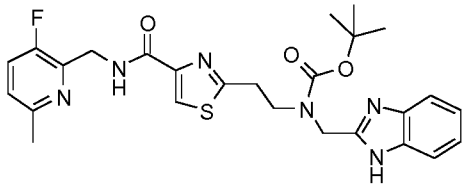
In a similar fashion to general procedure 6, a solution of 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (80%, 150 mg, 0.3 mmol), 3-fluoropyridin-2-amine (100 mg, 0.89 mmol), DIPEA (312 µl, 1.78 mmol) and HATU (340 mg, 0.87 mmol) in DMF (2 ml) was heated at 100°C for 16 h. The reaction mixture was concentrated *in vacuo* to give the crude title compound (705 mg) as a brown oil which was used in the next step without purification.
HPLCMS (Method A): [*m/z*]: 497.10 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(2-phenylethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (49)



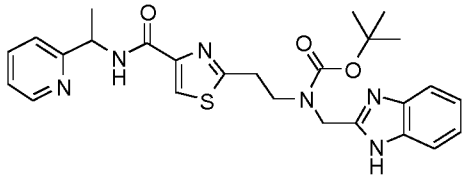
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (0.1 g, 0.25 mmol), 2-phenylethanamine (0.03 ml, 0.25 mmol), DIPEA (0.13 ml, 0.75 mmol) and HATU (0.14 g, 0.37 mmol) in DMF (2 ml) afforded the title compound (71 mg, 56%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 2-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 506.2 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-fluoro-6-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (50)



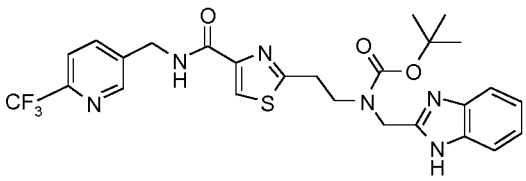
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.298 mmol, 80% purity), (3-fluoro-6-methylpyridin-2-yl)methanamine hydrochloride (79 mg, 0.447 mmol), DIPEA (156 µl, 0.894 mmol) and HATU (230 mg, 0.596 mmol) in DMF (3 ml) afforded the title compound (76 mg, 48%) as a pale yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 525.40 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[1-(pyridin-2-yl)ethyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (51)



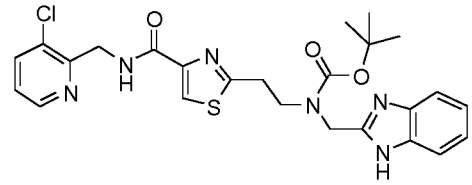
In a similar manner to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.298 mmol, 80% purity), 1-(pyridin-2-yl)ethanamine (55 mg, 0.447 mmol), DIPEA (156 µl, 0.894 mmol) and HATU (227 mg, 0.596 mmol) in DMF (3 ml) afforded the title compound (78 mg, 50%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 507.20 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[6-(trifluoromethyl)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (52)



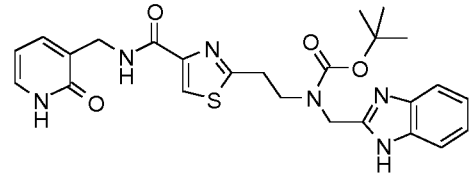
In a similar manner to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.298 mmol, 80% purity), 1-[6-(trifluoromethyl)pyridin-3-yl]methanamine (79 mg, 0.447 mmol), DIPEA (156 µl, 0.894 mmol) and HATU (227 mg, 0.596 mmol) in DMF (3 ml) afforded the title compound (92 mg, 46%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 561.35 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (53)



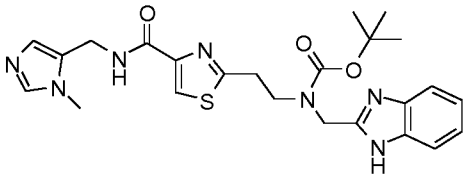
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.34 mmol, 92% purity), 1-(3-chloropyridin-2-yl)methanamine dihydrochloride (111 mg, 0.51 mmol), DIPEA (299 µl, 1.71 mmol) and HATU (196 mg, 0.51 mmol) in DMF (2 ml) afforded the title compound (161 mg, 73% purity, 63%) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 20-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.47 (s, 1H), 8.59 (s, 1H), 8.52 - 8.42 (m, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.32 (s, 1H), 7.25 - 7.16 (m, 3H), 4.85 (d, J = 4.8 Hz, 2H), 4.69 (s, 2H), 3.81 (s, 2H), 3.23 (t, J = 6.5 Hz, 2H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 527.35 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(tert-butoxy)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (54)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.34 mmol, 92% purity), 1-(2-tert-butoxypyridin-3-yl)methanamine (93 mg, 0.514 mmol), DIPEA (179 µl, 1.03 mmol) and HATU (196 mg, 0.51 mmol) in DMF (2 ml) afforded the title compound (205 mg, 61%, 58% purity) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 20-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.09 (s, 1H), 7.89 (d, J = 15.7 Hz, 2H), 7.71 (s, 1H), 7.54 - 7.45 (m, 2H), 7.40 (d, J = 4.9 Hz, 1H), 7.24 (s, 1H), 6.77 (td, J = 7.3, 5.0 Hz, 2H), 4.60 (s, 2H), 4.49 (d, J = 6.5 Hz, 2H), 3.77 (t, J = 6.5 Hz, 2H), 3.22 (s, 2H), 1.63 (s, 9H), 1.33 (s, 9H)
HPLCMS (Method A): [*m/z*]: 565.15 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-imidazol-5-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (55)

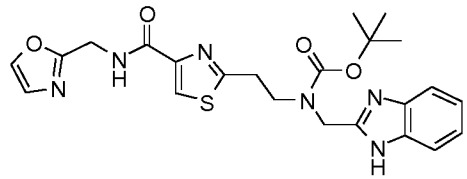


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.37 mmol), (1-methyl-1H-imidazol-5-yl)methanamine (62 mg, 0.56 mmol), DIPEA (185 µl, 1.12 mmol) and HATU (213 mg, 0.56 mmol) in DMF (2 ml) afforded the title compound (175 mg, 95%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-3% MeOH / DCM).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.08 (s, 1H), 7.58 - 7.52 (m, 3H), 7.26 - 7.20 (m, 2H), 6.96 (s, 1H), 4.69 (d, J = 12.4 Hz, 2H), 4.60 (s, 2H), 3.95 - 3.75 (m, 2H), 3.70 (s, 3H), 3.39 - 3.24 (m, 2H), 1.44 - 1.26 (m, 9H)

HPLCMS (Method A): [*m/z*]: 496.05 $[M+H]^+$

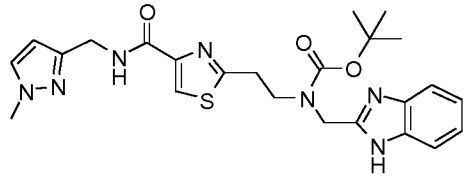
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(1,3-oxazol-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (56)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.298 mmol, 80% purity), 1,3-oxazol-2-ylmethanamine dihydrochloride (102 mg, 0.596 mmol), DIPEA (312 µl, 1.79 mmol) and HATU (227 mg, 0.596 mmol) in DMF (3 ml) afforded the title compound (94 mg, 63%) as a tan oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 483.05 $[M+H]^+$

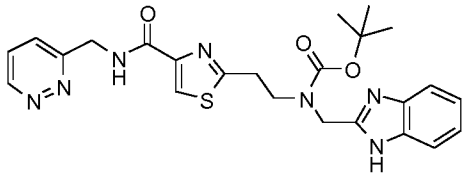
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (57)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (150 mg, 0.298 mmol, 80% purity), 1-(1-methyl-1H-pyrazol-3-yl)methanamine (50 mg, 0.45 mmol), DIPEA (156 µl, 0.894 mmol) and HATU (227 mg, 0.596 mmol) in DMF (3 ml) afforded the title compound (53 mg, 34%) as a tan oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).

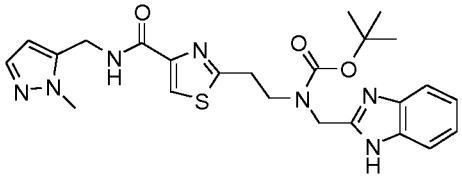
HPLCMS (Method A): [*m/z*]: 496.45 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (58)



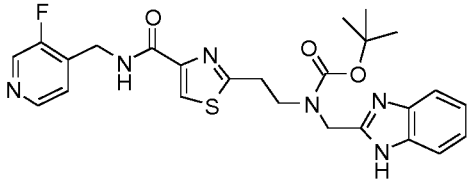
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.23 mmol, 92% purity), 1-(pyridazin-3-yl)methanamine (37 mg, 0.34 mmol), DIPEA (119 µl, 0.69 mmol) and HATU (130 mg, 0.34 mmol) in DMF (2 ml) afforded the title compound (101 mg, 88%) as a pale yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 50-100% EtOAc / heptane followed by 0-15% MeOH / EtOAc).
HPLCMS (Method A): [*m/z*]: 494.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-5-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (59)



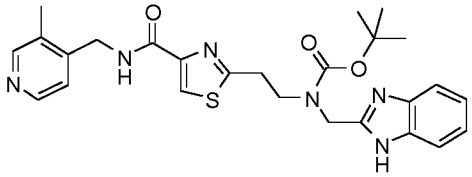
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.23 mmol, 92% purity), 1-(1-methyl-1H-pyrazol-5-yl)methanamine (38 mg, 0.34 mmol), DIPEA (119 µl, 0.69 mmol) and HATU (130 mg, 0.34 mmol) in DMF (2 ml) afforded the title compound (51 mg, 45%) as a pale yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 50-100% EtOAc / heptane followed by 0-20% MeOH / EtOAc).
HPLCMS (Method A): [*m/z*]: 496.3 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-fluoropyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (60)



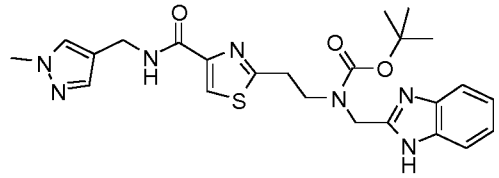
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.23 mmol, 92% purity), 1-(3-fluoropyridin-4-yl)methanamine (43 mg, 0.34 mmol), DIPEA (119 µl, 0.69 mmol) and HATU (130 mg, 0.34 mmol) in DMF (3 ml) afforded the title compound (137 mg, 83%, 71% purity) as a yellow oil after flash column chromatography (kp-NH, eluting with a gradient of 50-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.10 (s, 1H), 8.43 (d, J = 6.0 Hz, 1H), 8.37 (dd, J = 9.8, 4.9 Hz, 2H), 7.96 (s, 1H), 7.81 - 7.68 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.35 - 7.27 (m, 1H), 7.25 - 7.22 (m, 1H), 4.68 (d, J = 6.0 Hz, 2H), 4.62 (s, 2H), 3.78 (t, J = 6.5 Hz, 2H), 3.27 - 3.23 (m, 2H), 1.37 (s, 9H)
HPLCMS (Method A): [*m/z*]: 511.15 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-methylpyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (61)



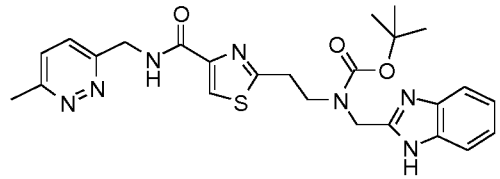
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (700 mg, 1.65 mmol, 95% purity), (3-methylpyridin-4-yl)methanamine dihydrochloride (387 mg, 1.98 mmol), DIPEA (863 µl, 4.9 mmol) and HATU (1260 mg, 3.3 mmol) in DMF (10 ml) afforded the title compound (363 mg, 43%) as a yellow oil after purification by flash chromatography (kp-NH, using an elution gradient 20-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 507.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (62)



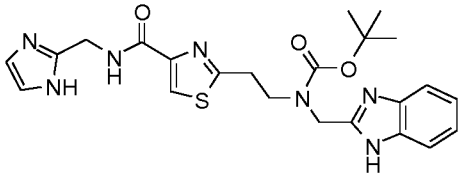
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.25 mmol), (1-methyl-1H-pyrazol-4-yl)methanamine (41 mg, 0.37 mmol), DIPEA (130 µl, 0.75 mmol) and HATU (142 mg, 0.37 mmol) in DMF (2 ml) afforded the title compound (125 mg, quant.) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / EtOAc).
HPLCMS (Method A): [*m/z*]: 496.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-methylpyridazin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (63)



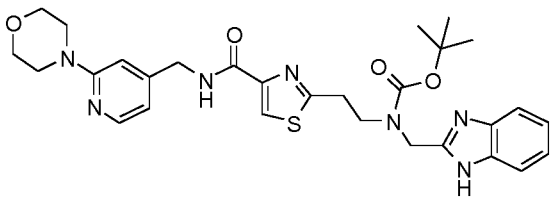
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.23 mmol, 92% purity), (6-methylpyridazin-3-yl)methanamine (42 mg, 0.34 mmol), DIPEA (119 µl, 0.69 mmol) and HATU (130 mg, 0.34 mmol) in DMF (3 ml) afforded the crude title compound (99 mg, 67%, 79% purity) after flash column chromatography (kp-NH, eluting with a gradient of 70-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.50 (s, 1H), 8.28 (s, 1H), 7.92 (s, 1H), 7.72 (s, 1H), 7.40- 7.29 (m, 3H), 7.23 (dd, J = 6.4, 2.8 Hz, 2H), 4.68 (s, 2H), 3.82 (s, 2H), 3.24 (s, 2H), 2.73 (s, 2H), 2.71 (s, 3H), 1.36 (s, 9H)
HPLCMS (Method A): [*m/z*]: 508.10 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(1H-imidazol-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (64)



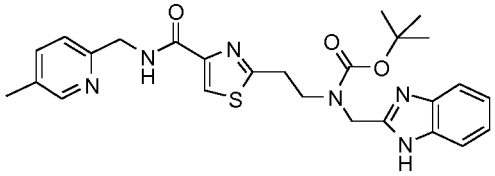
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.25 mmol), 1-(1H-imidazol-2-yl)methanamine (42 mg, 0.25 mmol), DIPEA (164 µl, 0.99 mmol) and HATU (188 mg, 0.50 mmol) in DMF (2 ml) afforded the title compound (65 mg, 54%) as a yellow oil after purification by flash column chromatography (kp-NH, eluting with a gradient 0-5% MeOH / DCM).
HPLCMS (Method A): [*m/z*]: 482.25 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(morpholin-4-yl)pyridin-4-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (65)



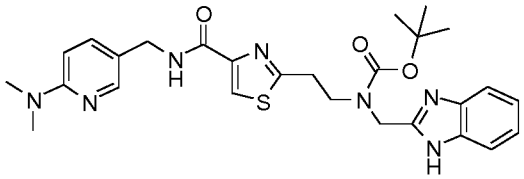
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.25 mmol), [3-(morpholin-4-yl)pyridin-4-yl]methanamine (48 mg, 0.25 mmol), DIPEA (164 µl, 0.99 mmol) and HATU (189 mg, 0.50 mmol) in DMF (2 ml) afforded the title compound (112 mg, 78%) as a yellow solid afterpurification by flash column chromatography (kp-NH, eluting with a gradient of 50-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 578.10 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (66)



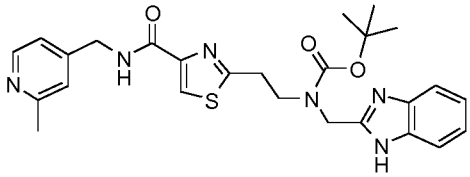
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.20 mmol, 80% purity), 1-(5-methylpyridin-2-yl)methanamine (29 mg, 0.24 mmol), DIPEA (104 µl, 0.60 mmol) and HATU (15 1mg, 0.40 mmol) in DMF (2 ml) afforded the title compound (48 mg, 47%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 507.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[6-(dimethylamino)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (67)



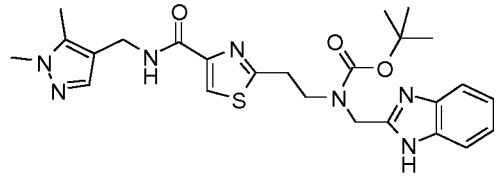
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.20 mmol, 80% purity), 5-(aminomethyl)-N,N-dimethylpyridin-2-amine (30 mg, 0.20 mmol), DIPEA (104 µl, 0.60 mmol) and HATU (151 mg, 0.40 mmol) in DMF (2 ml) afforded the title compound (36 mg, 34%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 536.35 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-methylpyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (68)



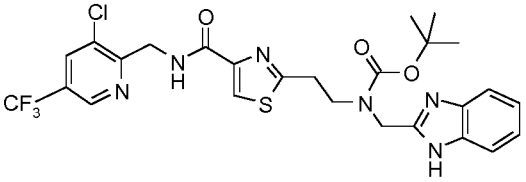
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.20 mmol, 80% purity), 1-(2-methylpyridin-4-yl)methanamine (36 mg, 0.30 mmol), DIPEA (104 µl, 0.60 mmol) and HATU (151 mg, 0.40 mmol) in DMF (2 ml) afforded the title compound (36 mg, 36%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 507.3 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (69)



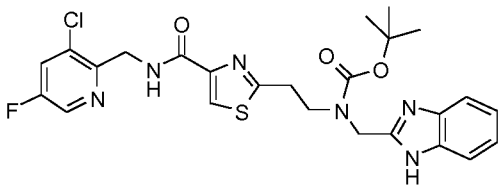
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.20 mmol, 80% purity), 1-(1,5-dimethyl-1H-pyrazol-4-yl)methanamine (37 mg, 0.30 mmol), DIPEA (104 µl, 0.60 mmol) and HATU (151 mg, 0.40 mmol) in DMF (2 ml) afforded the title compound (74 mg, 73%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 510.15 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (70)



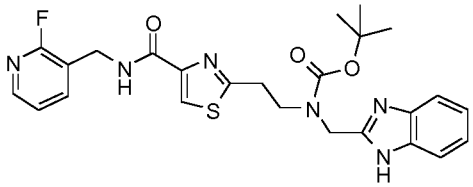
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol), 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methanamine hydrochloride (87 mg, 0.354 mmol), DIPEA (0.21 ml, 1.18 mmol), and HATU (135 mg, 0.354 mmol) in DMF (3 ml) afforded the title compound (216 mg, 69%, 45% purity) as a yellow oil after flash column chromatography (KP-NH, eluting with a gradient of 20-100% EtOAc / heptane). The title compound was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 595.1 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-chloro-5-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (71)



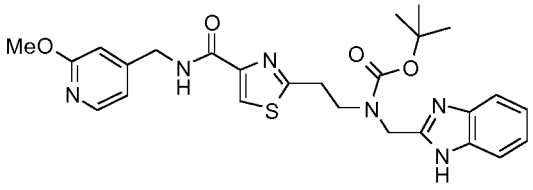
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol), (3-chloro-5-fluoropyridin-2-yl)methanamine hydrochloride (70 mg, 0.354 mmol), DIPEA (0.21 ml, 1.18 mmol), and HATU (135 mg, 0.354 mmol) in DMF (3 ml) afforded the title compound (157 mg, 76%, 62% purity) as a yellow oil after flash column chromatography (KP-NH, eluting with a gradient of 20-100% EtOAc / heptane). The title compound was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 545.15 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-fluoropyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (72)



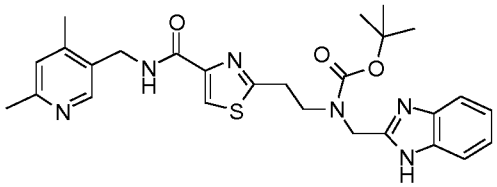
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), 1-(2-fluoropyridin-3-yl)methanamine (47.01 mg, 0.373 mmol), DIPEA (0.13 ml, 0.745 mmol) and HATU (141.7 mg, 0.373 mmol) in DMF (2 ml) afforded the title compound (0.359 g, quant.) as a brown solid after evaporation of the solvent. The title compound was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 511.10 $[M+H]^+$

Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-methoxypyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (73)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), 1-(2-methoxypyridin-4-yl)methanamine (49 mg, 0.354 mmol), DIPEA (0.12 ml, 0.708 mmol) and HATU (135 mg, 0.354 mmol) in DMF (3 ml) afforded the title compound (104 mg, 81%, 96% purity) as a white solid after purification by flash column chromatography (eluting with a gradient of 30-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.07 (s, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.96 (s, 1H), 7.73 - 7.66 (m, 2H), 7.41 - 7.37 (m, 1H), 7.25 - 7.22 (m, 2H), 6.85 - 6.82 (m, 1H), 6.69 (s, 1H), 4.62 (s, 2H), 4.56 (d, J = 6.3 Hz, 2H), 3.91 (s, 3H), 3.78 (t, J = 6.6 Hz, 2H), 3.24 (t, J = 6.2 Hz, 2H), 1.39 (s, 9H)
HPLCMS (Method A): [*m/z*]: 523.3 $[M+H]^+$

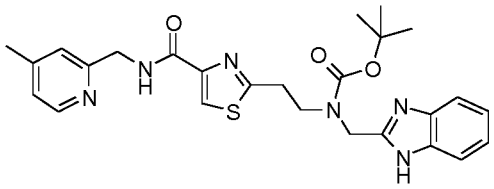
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4,6-dimethylpyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (74)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), (4,6-dimethylpyridin-3-yl)methanamine dihydrochloride **(B1)** (93 mg, 0.354 mmol, 80% purity), DIPEA (0.206 ml, 1.18 mmol) and HATU (135 mg, 0.354 mmol) in DMF (3 ml) afforded the title compound (77 mg, 63 %) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-15% MeOH / EtOAc).

HPLCMS (Method A): [*m/z*]: 521.05 $[M+H]^+$

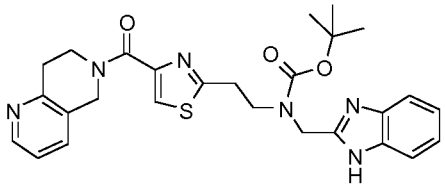
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4-methylpyridin-2-yl)methyl]carbamoyl}1,3-thiazol-2-yl)ethyl]carbamate (75)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), (4,6-dimethylpyridin-3-yl)methanamine dihydrochloride (93 mg, 0.354 mmol), DIPEA (0.123 ml, 0.708 mmol) and HATU (135 mg, 0.354 mmol) in DMF (2 ml) afforded the title compound (90 mg, 72%) as a yellow oil after purification by flash column chromatography (KP-NH, eluting with a gradient of 20-100% EtOAc / heptane followed by 0-20% MeOH / EtOAc).

HPLCMS (Method A): [*m/z*]: 507.10 $[M+H]^+$

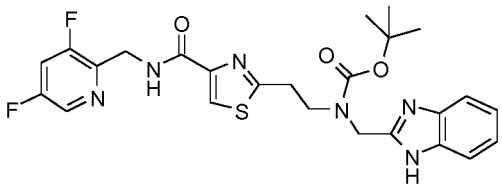
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-(5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1,3-thiazol-2-yl]ethyl}carbamate (76)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), 5,6,7,8-tetrahydro-1,6-naphthyridine dihydrochloride (62 mg, 0.298 mmol), DIPEA (0.173ml, 0.994 mmol) and HATU (151 mg, 0.398 mmol) in DMF (2 ml) afforded the title compound (90 mg, 72%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 519.15 $[M+H]^+$

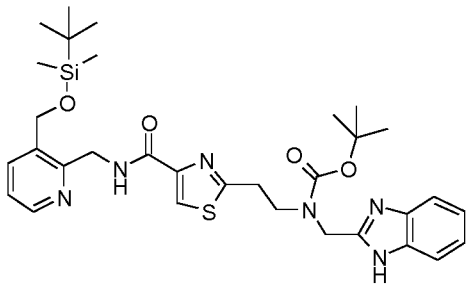
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl] carbamoyl} -1,3-thiazol-2-yl)ethyl]carbamate (77)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (100 mg, 0.236 mmol, 95% purity), (3,5-difluoropyridin-2-yl)methanamine dihydrochloride (65 mg, 0.298 mmol), DIPEA (0.173 ml, 0.994 mmol) and HATU (151 mg, 0.398 mmol) in DMF (3 ml) afforded the title compound (112 mg, quant.) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-100% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 529.10 $[M+H]^+$

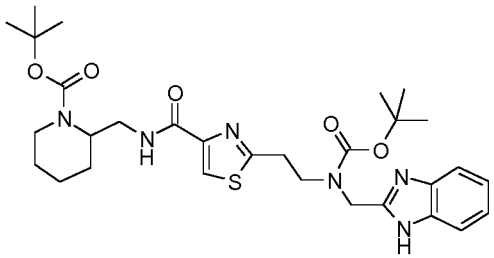
Tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-{[(tert-butyldimethylsilyl)oxy]methyl} pyridin-2-yl) methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (78)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (15.94 mg, 0.04 mmol), (3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)methanamine **(C3)** (10 mg, 0.04 mmol), DIPEA (0.03 ml, 0.16 mmol) and HATU (30.13 mg, 0.08 mmol) in DMF (2 ml) afforded the title compound (17.5 mg, 34%, 30% purity) as an orange oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 637.15 $[M+H]^+$

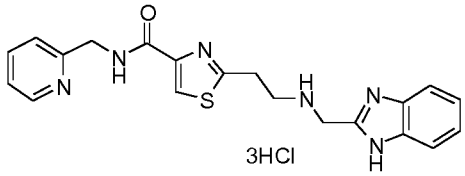
Tert-butyl 2-{[(2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazol-4-yl)formamido]methyl}piperidine-1-carboxylate (79)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (200 mg, 0.5 mmol), tert-butyl 2-(aminomethyl)piperidine-1-carboxylate (149 mg, 0.7 mmol), TEA (66.16 µl, 0.5 mmol) and HATU (280 mg, 0.75 mmol) in DMF (5 ml) at room temperature for 2 h, afforded the title compound (50 mg, 17%) as an orange oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) followed by basic prep-HPLC.

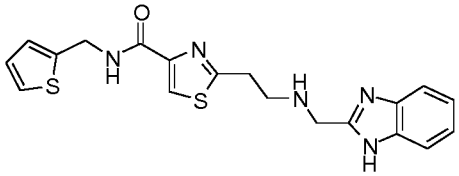
HPLCMS (Method A): [*m/z*]: 599.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 12)



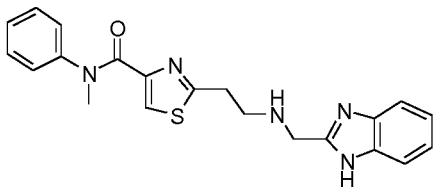
In a similar fashion to general procedure 2, 4M HCl in dioxane (11 ml) and tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(9)** (2.2 g, 4.47 mmol) in dioxane (30ml) at room temperature for 16 h, gave the title compound (HCl salt) (1.7 g, 76%) as a yellow solid after trituration from Et_2O (2 x 30 ml) followed by DCM (2 x 20 ml) and Et_2O (2 x 30 ml).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.39 (s, 1H), 9.68 (t, J = 6.0 Hz, 1H), 8.86 - 8.75 (m, 1H), 8.44 (td, J = 7.9, 1.5 Hz, 1H), 8.30 (s, 1H), 7.96 - 7.84 (m, 2H), 7.76 (dt, J = 6.5, 3.3 Hz, 2H), 7.44 (dq, J = 6.5, 3.4 Hz, 2H), 4.86 (d, J = 6.0 Hz, 2H), 4.76 (s, 2H), 3.66 (dt, J = 38.8, 7.1 Hz, 4H)
HPLCMS (Method C): [*m/z*]: 493.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(thiophen-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 16)



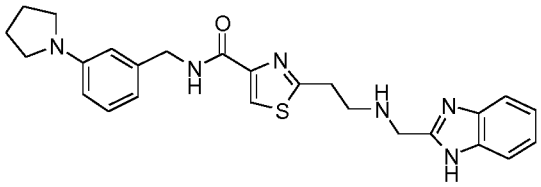
In a similar fashion to general procedure 7, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(thiophen-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(12)** (180 mg, 0.362 mmol) and 50% TFA in DCM (10 ml) at room temperature overnight gave the title compound (51 mg, 34%, 98% purity) as a white oil after purification by prep-HPLC.
1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 8.05 (s, 1H), 7.59 (m, 3H), 7.24 (m, 2H), 7.21 - 7.19 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.01 (m, 1H), 6.94 (m, 1H), 4.78 (d, *J* = 6.0, 2H), 4.15 (s, 2H), 3.27 – 3.07 (m, 4H)
HPLCMS (Method J): [*m/z*]: 398.5 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-methyl-N-phenyl-1,3-thiazole-4-carboxamide (Example Compound No. 19)



In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[methyl(phenyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(15)** (110.12 mg, 0.224 mmol) and 50% TFA in DCM (10 ml) at room temperature overnight gave the title compound (40 mg, 45%, 85% purity) as a white oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH in DCM).
1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 7.69 (bs, 2H), 7.29 - 7.21 (m, 5H), 7.10 (s, 2H), 4.28 (s, 2H), 3.60 - 3.43 (m, 3H), 3.18 (bs, 2H), 3.05 (bs, 2H)
HPLCMS (Method J): [*m/z*]: 392.5 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(pyrrolidin-1-yl)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 21)

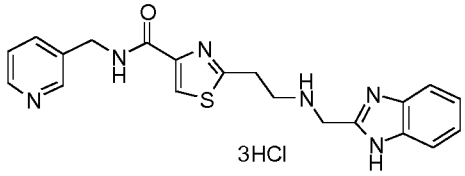


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(pyrrolidin-1-yl)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(16)** (100 mg, 0.178 mmol) and 50% TFA in DCM (8 ml) at room temperature overnight gave the title compound (70 mg, 69%, 82% purity) as a white oil after purification by flash column chromatography (eluting with a gradient of 5-7% MeOH in DCM).

1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 7.94 (s, 1H), 7.85 (t, J = 5.6 Hz, 1H), 7.53 - 7.47 (m, 2H), 7.24 - 7.16 (m, 2H), 7.12 (t, J =7.8 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.48 (s, 1H), 6.43 (d, J = 8.1 Hz, 1H), 4.53 (d, J = 5.9 Hz, 2H), 4.14 (s, 2H), 3.21 (m, 4H), 3.12 - 3.05 (m, 4H), 2.00 – 1.90 (m, 4H)

HPLCMS (Method J): [*m/z*]: 461.6 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridin-3-ylmethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 35)

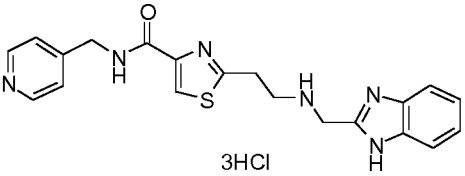


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(22)** (184 mg, 0.374 mmol) and 4M HCl in dioxane (15 ml) at room temperature for 18 h gave the title compound (80 mg, 53%) as the tri HCl salt as a white solid after precipitation with Et_2O.

1H-NMR (DMSO-d6, 400 MHz): d[ppm]= 10.28 (bs, 3H), 9.64 (t, J = 6.2 Hz, 1H), 8.90 (s, 1H), 8.81 (d, J = 5.4 Hz, 1H), 8.55 (d, J = 8.1Hz, 1H), 8.25 (s, 1H), 8.00 (dd, J = 8.0, 5.7 Hz, 1H), 7.73 (m, 2H), 7.48– 7.34 (m, 2H), 4.71 (s, 2H), 4.65 (d, J = 6.2 Hz, 2H), 3.66 (t, J = 6.6 Hz, 2H), 3.57 (t, J = 6.3 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 493.3 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridin-4-ylmethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 36)

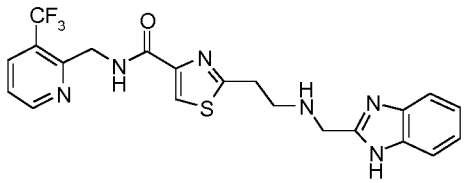


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridin-4-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(23)** (145.8 mg, 0.296 mmol) and 4M HCl in dioxane (15 ml) at room temperature for 18 h gave the title compound (70 mg, 47%) as the tri HCl salt as a white solid after precipitation with Et_2O.

1H-NMR (DMSO, 400 MHz): d[ppm]= 10.40 (bs, 3H), 9.69 (t, J = 6.2 Hz, 1H), 8.83 (d, J = 6.7 Hz, 2H), 8.28 (s, 1H), 7.98 (d, J = 6.6 Hz, 2H), 7.81 – 7.69 (m, 2H), 7.49 – 7.37 (m, 2H), 4.73 (d, J = 5.1 Hz, 4H), 3.68 (t, J = 6.5 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 493.3 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[3-(trifluoromethyl)pyridin-2-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 37)

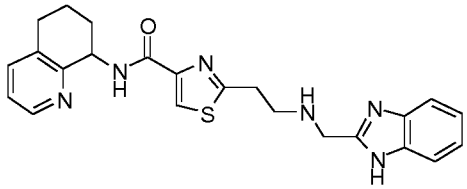


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[3-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(24)** (86.33 mg, 0.154 mmol) and 4M HCl in dioxane (10 ml) at room temperature for 18 h gave the title compound (25 mg, 35%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 10-15% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.62 (d, J = 4.8 Hz, 1H), 8.13 - 8.09 (m, 1H), 8.08 (s, 1H), 7.52 - 7.47 (m, 2H), 7.47 - 7.41 (m, 1H), 7.22 - 7.14 (m, 2H), 4.86 (s, 2H), 4.09 (s, 2H), 3.27 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 461.6 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(5,6,7,8-tetrahydroquinolin-8-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 38)

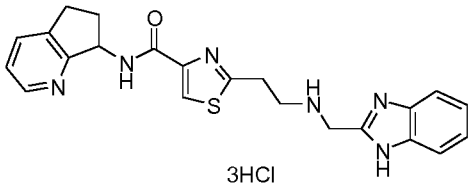


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(5,6,7,8-tetrahydroquinolin-8-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(25)** (82.03 mg, 0.154 mmol) and 4M HCl in dioxane (10 ml) at room temperature for 18 h gave the title compound (35 mg, 52%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 10-15% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.27 (d, J = 3.6 Hz, 1H), 8.08 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.49 (m, 2H), 7.27 - 7.15 (m, 3H), 5.22 - 5.12 (m, 1H), 4.05 (s, 2H), 3.21 (t, J = 6.7 Hz, 2H), 3.05 (t, J = 6.4 Hz, 2H), 2.96 - 2.77 (m, 2H), 2.34 - 2.20 (m, 1H), 2.05 - 1.79 (m, 3H)

HPLCMS (Method J): [*m/z*]: 433.6 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 39)

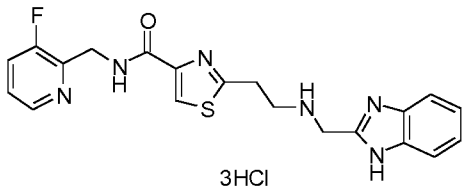


In a similar fashion to general procedure 2, 4M HCl in dioxane (6.36 ml) was added to tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1,3-thiazol 2-yl]ethyl}carbamate **(26)** (1.32 g, 2.55 mmol) in dioxane (30 ml) and stirred at room temperature for 48 h to give the title compound (1.03 g, 76%) after crystalisation from DCM / MeOH.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.56 (d, J = 5.8 Hz, 1H), 8.52 - 8.48 (m, 1H), 8.31 (s, 1H), 7.92 (dd, J = 7.7, 6.0 Hz, 1H), 7.86 (dt, J = 6.7, 3.3 Hz, 2H), 7.66 (dt, J = 6.3, 3.3 Hz, 2H), 5.95 (t, J = 8.8 Hz, 1H), 5.01 (s, 2H), 3.87 (t, J = 6.2 Hz, 2H), 3.71 - 3.63 (m, 2H), 3.42 - 3.35 (m, 1H), 3.21 (dt, J = 17.1, 8.7 Hz, 1H), 2.86 - 2.77 (m, 1H), 2.51 (dq, J = 12.9, 9.2 Hz, 1H)

HPLCMS (Method C): [*m/z*]: 419.05 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 40)

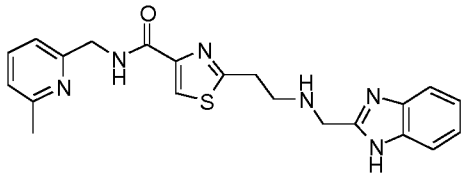


In a similar fashion to general procedure 2, 4M HCl in dioxane (16.57 ml, 66.26 mmol) was added to tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(27)** (4.13 g, 6.63 mmol) in dioxane (40 ml) and stirred at room temperature for 16 h to give the title compound (3.04 g, 88%) as a white solid after precipitation from Et_2O (100 ml).

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.47 (d, J = 5.1 Hz, 1H), 8.28 (s, 1H), 8.11 (s, 1H), 7.84 (dd, J = 6.1, 3.1 Hz, 2H), 7.76 (s, 1H), 7.62 (dd, J = 6.1, 3.0 Hz, 2H), 4.99 (s, 2H), 4.95 (s, 2H), 3.84 (t, J = 6.2 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 411.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(6-methylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 42)

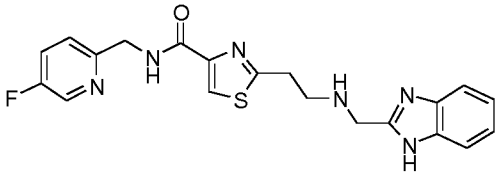


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(29)** (79.5 mg, 0.157 mmol) and 4M HCl in dioxane (15 ml) at room temperature overnight gave the title compound (25.5 mg, 36%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 10-15% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.09 (s, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.50 (m, 2H), 7.23 - 7.17 (m, 3H), 7.15 (m, 2H), 4.63 (s, 2H), 4.08 (s, 2H), 3.26 (t, *J* = 6.7 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 2.50 (s, 3H)

HPLCMS (Method J): [*m/z*]: 405.5 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(5-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 43)

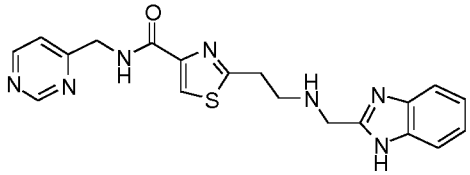


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(30)** (80.2 mg, 0.157 mmol) and 4M HCl in dioxane (15 ml) at room temperature overnight gave the title compound (12.5 mg, 17%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 10-15% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.36 (d, *J* = 2.6 Hz, 1H), 8.08 (s, 1H), 7.59 – 7.46 (m, 3H), 7.42 (m, 1H), 7.20 (m, 2H), 4.66 (s, 2H), 4.08 (s, 2H), 3.26 (t, *J* = 6.5 Hz, 2H), 3.11 (t, *J* = 6.5 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 411.5 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyrimidin-4-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 44)

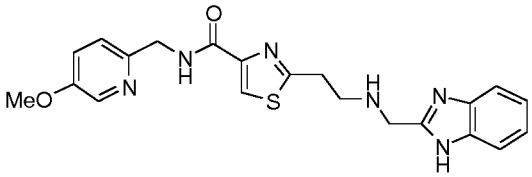


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyrimidin-4-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(31)** (75 mg, 0.152 mmol) and 4M HCl in dioxane (2 ml) at room temperature for 4 h gave the title compound (22 mg, 37%) as a yellow solidafter purification by flash column chromatography (eluting with a gradient of 8% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 9.05 (d, J = 1.1 Hz, 1H), 8.67 (d, J = 5.3 Hz, 1H), 8.12 (s, 1H), 7.51 (dd, J = 6.0, 3.2 Hz, 2H), 7.46 (d, J = 5.3 Hz, 1H), 7.26– 7.18 (m, 2H), 4.68 (s, 2H), 4.10 (s, 2H), 3.28 (t,J = 6.5 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 394.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(5-methoxypyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 45)

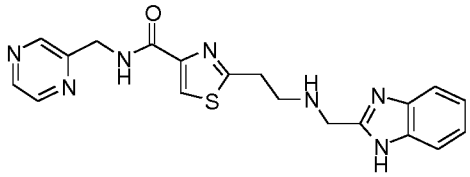


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-methoxypyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(32)** (80 mg, 0.153 mmol) and 4M HCl in dioxane (2 ml) at room temperature for 4 h gave the title compound (53 mg, 82%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 8% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.17 – 8.13 (m, 1H), 8.08 (s, 1H), 7.54 – 7.47 (m, 2H), 7.35 – 7.31 (m, 2H), 7.25 – 7.18 (m, 2H), 4.61 (s, 2H), 4.07 (d, *J* = 8.0 Hz, 2H), 3.84 (s, 3H), 3.26 (t, *J* = 6.6 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 423.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyrazin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 46)

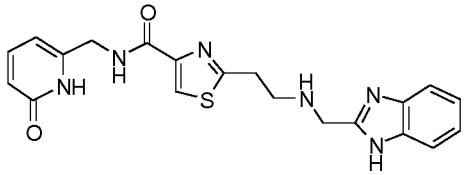


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyrazin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(33)** (70 mg, 0.142 mmol) and 4M HCl in dioxane (2 ml) at room temperature for 4 h gave the title compound (30 mg, 53.7%) as a brown solidafter purification by flash column chromatography (eluting with a gradient of 8% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.63 (s, 1H), 8.56 – 8.51 (m, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.12 (s, 1H), 7.52 (dd, J = 6.0, 3.2 Hz, 2H), 7.22 (dd, J = 6.1, 3.1 Hz, 2H), 4.74 (s, 2H), 4.13 (s, 2H), 3.28 (t, J = 6.5Hz, 2H), 3.17 (t, J = 6.5 Hz, 2H)

HPLCMS (Method I): [*m/z*]: 394.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(6-oxo-1,6-dihydropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 47)

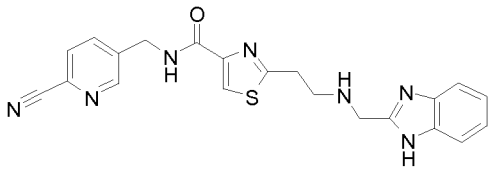


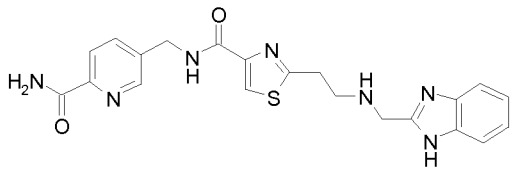
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-oxo-1,6-dihydropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(34)** (70 mg, 0.138 mmol) and 4M HCl in dioxane HCl (2 ml) at room temperature for4 h gave the title compound (30 mg, 53%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 8% MeOH in DCM).

1H-NMR (MeOD, 400 MHz): d[ppm]= 8.12 (s, 1H), 7.51 (m, 3H), 7.22 (dd, J = 6.0, 3.2 Hz, 2H), 6.42 (d,J = 9.1 Hz, 1H), 6.30 (d, J = 6.9 Hz, 1H), 4.44 (s, 2H), 4.09 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 3.12 (t, J = 6.7 Hz, 2H)

HPLCMS (Method J): [*m/z*]: 409.4 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(6-cyanopyridin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 56) and 5-{[(2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazol-4-yl)formamido]methyl}pyridine-2-carboxamide (Example Compound No. 54)





In a similar fashion to general procedure 2, a mixture of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-carbamoylpyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(35)** and tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-cyanopyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(36)** (80 mg, 0.155 mmol) and 4 M HCl in dioxane (3 ml) at room temperature for 18 h gave two products. Formamide **(Example Compound No. 54)** (16 mg, 23%) was isolated following flash column chromatography (eluting with a gradient of DCM / MeOH, 9:1). Crudenitrile **(Example Compound No. 56)** was also isolated and was further purified by basic prep-HPLC to give the required product as a brown solid (24 mg, 37%).

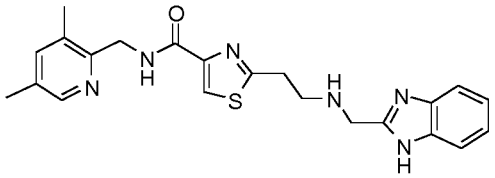
Formamide: 1H-NMR (Methanol-d4, 400 MHz): d[ppm]= 8.49 (t, J = 10.2 Hz, 1H), 7.99 (s, 1H), 7.94 (t, J = 10.0 Hz, 1H), 7.78 (dt, J = 8.1, 4.0 Hz, 1H), 7.46 –7.34 (m, 2H), 7.11 (dd, J = 6.0, 3.1 Hz, 2H), 4.56 (d, J = 14.2 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 3.19 (m, 4H), 3.06 (t, J = 6.5 Hz, 2H)

HPLCMS (Method I): [*m/z*]: 436.5 $[M+H]^+$

Nitrile: 1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 9.08 (t, J = 6.2 Hz, 1H), 8.70 (s, 1H), 8.14 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 8.1, 2.0 Hz, 1H), 7.48 (d, J = 29.4 Hz, 2H), 7.12 (d, J = 4.7 Hz, 2H), 4.54 (d, J = 6.2 Hz, 2H), 4.10 (d, J = 5.2 Hz, 1H), 3.96 (s, 2H), 3.18 - 3.15 (m, 2H), 2.98 (d, J = 6.6 Hz, 2H)

HPLCMS (Method I): [*m/z*]: 418.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3,5-dimethylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 57)

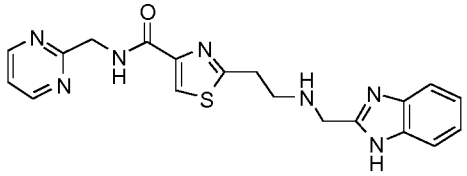


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3,5-dimethylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(37)** (198 mg, 0.36 mmol) and 12 M HCl (0.307 ml, 8.42 mmol) in MeOH (10 ml) at 40°C for 21 h gave the title compound (90 mg, 59%) as a yellow solid after purification by neutral prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.71 (t, J = 4.8 Hz, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.51 (s, 1H), 7.42 (s, 2H), 7.12 (d, J = 4.9 Hz, 2H), 4.52 (d, J = 4.9 Hz, 2H), 3.97 (s, 2H), 3.17 (d, J = 4.9 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H)

HPLCMS (Method B): [m/z]: 421.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 61)

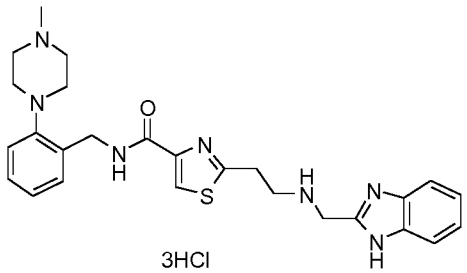


In a similar fashion to general procedure 2, tert-butyl 2-({[(tert-butoxy)carbonyl](2-{4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)amino}methyl)-1H-1,3-benzodiazole-1-carboxylate **(38)** (86 mg, 0.145 mmol) and 12 M HCl (0.282 ml, 3.378 mmol) in MeOH (2 ml) at 40°C for 24 h gave the title compound (24 mg, 42%) as a brown solid after purification by flash column chromatography (eluting with a gradient 100% DCM, 90% DCM: 10% MeOH and 90% DCM : 10% methanolic ammonia)followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 8.75 (dd, J = 10.2, 5.4 Hz, 3H), 8.13 (s, 1H), 7.48 (d, J = 36.0 Hz, 2H), 7.39 (t, J = 4.9 Hz, 1H), 7.19 - 7.03 (m, 2H), 4.66 (d, J = 5.8 Hz, 2H), 3.97 (s, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H), 2.66 (s, 1H)

HPLCMS (Method B): [*m/z*]: 394.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(4-methylpiperazin-1-yl)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 68)

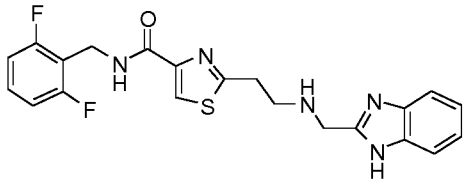


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(4-methylpiperazin-1-yl)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(39)** (13.4 mg, 0.02 mmol) in dioxane (0.5 ml) and 4M HCl in dioxane (55.1 µl) at 50°C for 16 h gave the title compound (11.5 mg, 85%) as a white solid after trituration with DCM.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.28 (s, 1H), 7.88 (dt, J = 6.6, 3.3 Hz, 2H), 7.69 (dt, J = 6.3, 3.3 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 6.7 Hz, 2H), 7.20 - 7.14 (m, 1H), 5.06 (s, 2H), 4.78 (s, 2H), 3.87 (t, J = 6.2 Hz, 2H), 3.72 - 3.59 (m, 4H), 3.49 (t, J = 10.5 Hz, 2H), 3.37 (s, 2H), 3.27 (d, J = 11.0 Hz, 2H), 3.02 (s, 3H)

HPLCMS (Method D): [*m/z*]: 490.3 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2,6-difluorophenyl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 69)

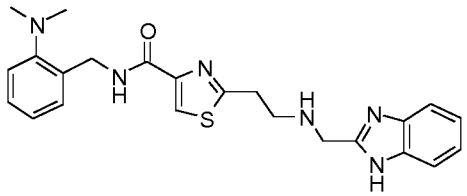


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2,6-difluorophenyl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(40)** (90 mg, 0.17 mmol) in dioxane (2 ml) and 4M HCl in dioxane (427 µl) at room temperature for 16 h gave the title compound (15 mg, 20.6%) as a off white solid after purification by prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.06 (s, 1H), 7.53 (dd, J = 5.8, 3.2 Hz, 2H), 7.34 (tt, J = 8.4, 6.5 Hz, 1H), 7.29 - 7.16 (m, 2H), 7.03 - 6.88 (m, 2H), 4.68 (s, 2H), 4.07 (s, 2H), 3.23 (t, J = 6.6 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 428.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(dimethylamino)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 70)

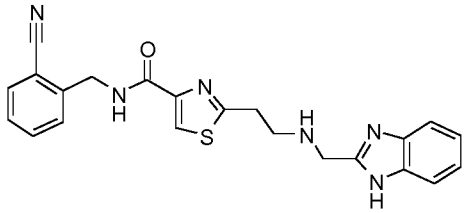


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(dimethylamino)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(41)** (73 mg, 0.14 mmol) in dioxane (2 ml) and 4M HCl in dioxane (341 µl) at 50°C for 16 h gave title compound (8.7 mg, 14%) following purification by prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.08 (s, 1H), 7.53 (dd, J = 5.9, 3.2 Hz, 2H), 7.29 - 7.14 (m, 5H), 7.02 (td, J = 7.4, 1.1 Hz, 1H), 4.68 (s, 2H), 4.08 (s, 2H), 3.25 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.8 Hz, 2H), 2.67 (s, 6H)

HPLCMS (Method D): [*m/z*]: 435.3 $[M+H]^+$

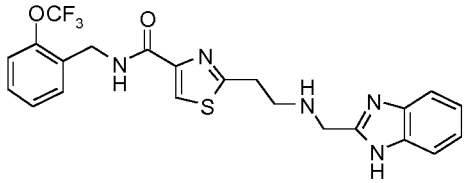
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-cyanophenyl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 71)



In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-cyanophenyl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(42)** (54 mg, 0.1 mmol) in dioxane (2 ml) and 4M HCl in dioxane (261 µl) at 50°C for 12 h gave the title compound (8 mg, 18%) as a yellow solid after purification by prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.11 (s, 1H), 7.74 - 7.69 (m, 1H), 7.60 (td, J = 7.8, 1.2 Hz, 1H), 7.56 - 7.50 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.25 - 7.19 (m, 2H), 4.78 (s, 2H), 4.09 (s, 2H), 3.27 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H)

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(trifluoromethoxy)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 72)

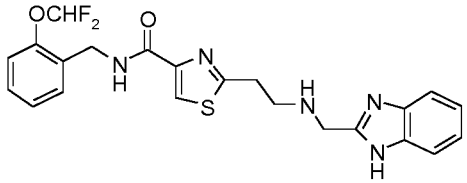


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(trifluoromethoxy)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(43)** (110 mg, 0.191 mmol), 12M HCl (0.317 ml, 4.458 mmol) in MeOH (2 ml) at room temperature for 16 h, gave the title compound (41 mg, 45%) as a white solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 8.88 (t, J = 6.2 Hz, 1H), 8.15 (s, 1H), 7.48 (d, J = 31.2 Hz, 2H), 7.42 - 7.30 (m, 4H), 7.13 (d, J = 4.9 Hz, 2H), 4.53 (d, J = 6.3 Hz, 2H), 3.97 (s, 2H), 3.19 (t, J = 6.8 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 476.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(difluoromethoxy)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 74)

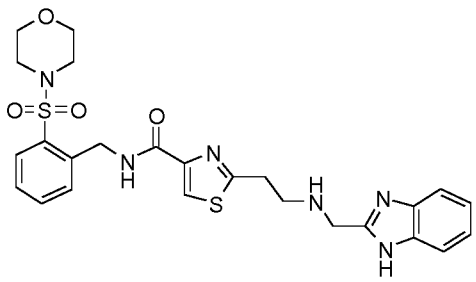


In a similar fashion to general procedure 2, crude tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(difluoromethoxy)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(45)** (470 mg), 12 M HCl (5ml) in MeOH (5ml) at 50°C for 2 h, afforded the title compound (56 mg, 35%) as a pale yellow solid after purification by flash column chromatography (KP-NH, eluting with a gradient of 0-15% MeOH / DCM) followed by prep-HPLC.

1H-NMR (DMSO-d6, 500MHz): d[ppm]= 12.18 (s, 1H), 8.79 (t, J = 6.2 Hz, 1H), 8.13 (s, 1H), 7.47 (s, 2H), 7.35 - 7.28 (m, 2H), 7.25 - 7.06 (m, 5H), 4.48 (d, J = 6.2 Hz, 2H), 3.96 (s, 2H), 3.22 - 3.17 (m, 2H), 2.98 (t, J = 6.8 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 458.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(morpholine-4-sulfonyl)phenyl] methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 75)

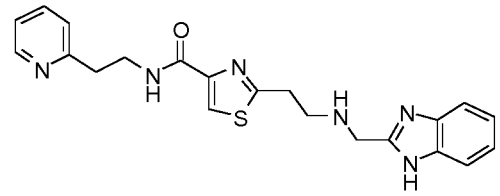


In a similar fashion to general procedure 2, crude tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(morpholine-4-sulfonyl)phenyl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(46)** (440 mg), 12M HCl (5 ml) in MeOH (5 ml) at 50°C for 2 h, afforded the title compound (67 mg, 42%) as a pale yellow solid after purification by flash column chromatography (KP-NH, eluting with a gradient of 0-15% MeOH / DCM) followed by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 8.88 (t, J = 6.3 Hz, 1H), 8.17 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.50 (dd, J = 11.8, 7.7 Hz, 4H), 7.17 - 7.06 (m, 2H), 4.81 (d, J = 6.2 Hz, 2H), 3.97 (s, 2H), 3.70 - 3.61 (m, 4H), 3.20 (t, J = 6.8 Hz, 2H), 3.10 - 3.04 (m, 4H), 2.99 (t, J = 6.7 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 541.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[2-(pyridin-2-yl)ethyl]-1,3-thiazole-4-carboxamide (Example Compound No. 76)

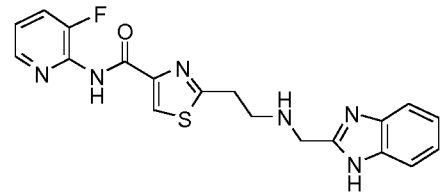


In a similar fashion to general procedure 2, dioxane (2 ml) was added to tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[2-(pyridin-2-yl)ethyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(47)** (52 mg, 0.103 mmol) and 4 M HCl in dioxane (257 µl, 1.03mmol). The reaction mixture was stirred at room temperature for 16 h to afford the title compound (11 mg, 26%) as a tan solid after purification by neutral prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.44 (ddd, J = 5.0, 1.7, 0.8 Hz, 1H), 8.03 (s, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.55 (dd, J = 5.8, 3.2 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.29- 7.19 (m, 3H), 4.09 (s, 2H), 3.74 (t, J = 7.1 Hz, 2H), 3.25 (t, J = 6.7 Hz, 2H), 3.13 - 3.05 (m, 4H)

HPLCMS (Method B): [*m/z*]: 407.1 $[M+H]^+$

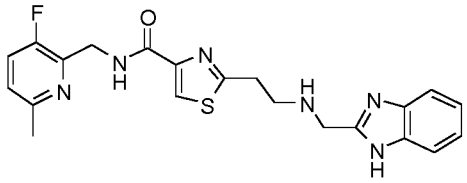
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(3-fluoropyridin-2-yl)-1,3-thiazole-4-carboxamide (Example Compound No. 77)



In a similar fashion to general procedure 2, dioxane (4 ml) was added to crude tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(3-fluoropyridin-2-yl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(48)** (705 mg) and 4M HCl in dioxane (1.56 ml, 6.24 mmol). The reaction mixture wasstirred at room temperature for 16 h to afford the title compound (10 mg, 3.9%) as a tan solid after purification by neutral prep-HPLC.

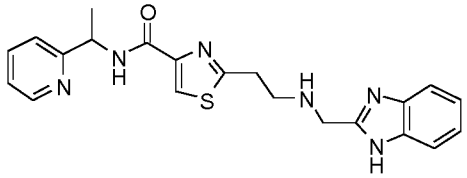
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.37 (s, 1H), 8.29 (dd, J = 4.7, 1.0 Hz, 1H), 7.75 (ddd, J = 9.8, 8.4, 1.4 Hz, 1H), 7.52 (dd, J = 6.1, 3.2 Hz, 2H), 7.41 (ddd, J = 8.4, 4.7, 3.8 Hz, 1H), 7.24 (dd, J = 6.1, 3.2 Hz, 2H), 4.44 (s, 2H), 3.56 - 3.46 (m, 4H)
HPLCMS (Method D): [*m/z*]: 397.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoro-6-methylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 79)



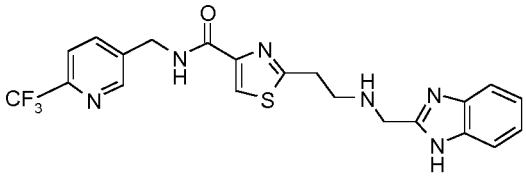
In a similar fashion to general procedure 2, 4M HCl in dioxane (0.36 ml) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-fluoro-6-methylpyridin-2-yl)methyl] carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(50)** (76 mg, 0.14 mmol) in dioxane (2 ml) and the mixture was stirred at room temperature for 16 h, to give the title compound (24 mg, 39%) as a colourless oil after purification by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.09 (s, 1H), 7.55 - 7.42 (m, 3H), 7.29 - 7.14 (m, 3H), 4.71 (d, J = 1.7 Hz, 2H), 4.09 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 3.14 (t, J = 6.7 Hz, 2H), 2.45 (s, 3H)
HPLCMS (Method D): [*m/z*]: 425.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[1-(pyridin-2-yl)ethyl]-1,3-thiazole-4-carboxamide (Example Compound No. 80)



In a similar fashion to general procedure 2, 4M HCl in dioxane (0.39 ml, 1.56 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[1-(pyridin-2-yl)ethyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(51)** (78 mg, 0.15 mmol) in dioxane (2 ml) and the mixture was stirred at room temperature for 16 h, to give the title compound (15 mg, 23%) as a colourless oil after purification by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.48 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 8.08 (s, 1H), 7.79 (td, J = 7.8, 1.7 Hz, 1H), 7.54 (dd, J = 5.7, 3.2 Hz, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.29 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 7.26 - 7.18 (m, 2H), 5.25 (d, J = 7.0 Hz, 1H), 4.11 (s, 2H), 3.29 (t, J = 6.7 Hz, 2H), 3.16- 3.12 (m, 2H), 1.57 (d, J = 7.0 Hz, 3H)
HPLCMS (Method D): [*m/z*]: 407.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 81)



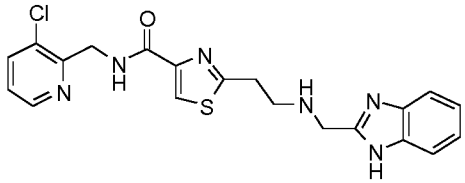
In a similar fashion to general procedure 2, 4M HCl in dioxane (0.41ml, 1.64mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[6-(trifluoromethyl)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(52)** (92 mg, 0.16 mmol) in dioxane (2 ml) and the mixture was stirred at

room temperature for 16 h, to afford the title compound (21 mg, 27%) as a colourless oil after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.71 (d, J = 1.5 Hz, 1H), 8.11 (s, 1H), 8.00 (dd, J = 8.1, 1.5 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.53 (dd, J = 5.8, 3.2 Hz, 2H), 7.28- 7.14 (m, 2H), 4.68 (s, 2H), 4.09 (s, 2H), 3.27 (t, J = 6.7 Hz, 2H), 3.12 (t, J = 6.7 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 461.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 82)

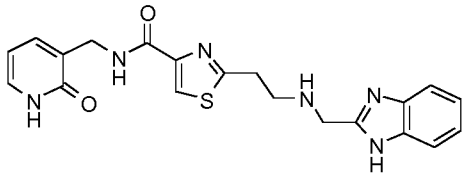


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(53)** (161 mg, 0.363 mmol) and 12M HCl (1.6 ml, 19.2 mmol) in MeOH (1.6 ml) at 50°C for 4 h, afforded the title compound (72 mg, 54%) as a white solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.22 (s, 1H), 8.71 (t, J = 5.5 Hz, 1H), 8.47 (dd, J = 4.7, 1.3 Hz, 1H), 8.15 (s, 1H), 7.95 (dd, J = 8.1, 1.3 Hz, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.37 (dd, J = 8.1, 4.7 Hz, 1H), 7.12 (d, J = 4.8 Hz, 2H), 4.67 (d, J = 5.5 Hz, 2H), 3.97 (s, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 427.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-oxo-1,2-dihydropyridin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 83)

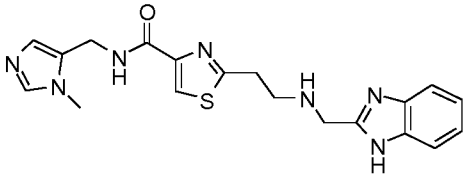


In a similar fashion to general procedure 2, crude tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(tert-butoxy)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(54)** (205 mg, 0.36 mmol) and 12M HCl (2 ml) in MeOH (2 ml) at 50°C for 4 h, afforded the title compound (66 mg, 44%) as a pale yellow solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (br s, 1H), 11.65 (br s, 1H), 8.59 (t, J = 6.0 Hz, 1H), 8.11 (s, 1H), 7.48 (s, 2H), 7.32 – 7.26 (m, 1H), 7.24 (d, J = 6.7 Hz, 1H), 7.12 (dd, J = 6.0, 3.1 Hz, 2H), 6.15 (t, J = 6.6 Hz, 1H), 4.22 (d, J = 6.0 Hz, 2H), 3.96 (s, 2H), 3.21 – 3.14 (m, 2H), 2.97 (t, J = 6.8 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 409.2 $[M+H]^+$

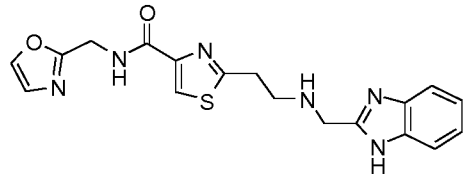
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1-methyl-1H-imidazol-5-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 84)



In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-imidazol-5-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(55)** (148 mg, 0.3 mmol) and

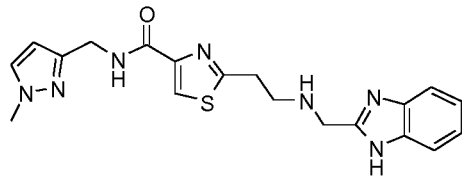
4M HCl in dioxane (7 ml) at room temperature for 2 h, afforded title compound (58 mg, 49%) as a colourless glass after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.66 (t, J = 6.0 Hz, 1H), 8.13 (s, 1H), 7.60 - 7.31 (m, 3H), 7.28 - 6.97 (m, 2H), 6.79 (s, 1H), 4.41 (d, J = 6.0 Hz, 2H), 3.96 (s, 2H), 3.60 (s, 3H), 3.16 (t, J = 6.8 Hz, 2H), 2.97 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 396.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(1,3-oxazol-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 85)



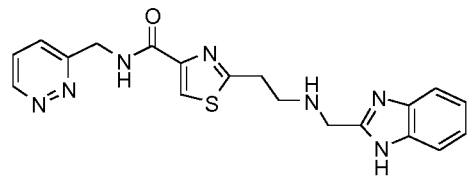
In a similar fashion to general procedure 2, 4M HCl in dioxane (0.49 ml, 1.96 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(1,3-oxazol-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(56)** (95 mg, 0.196 mmol) in dioxane (2 ml) and the mixture was stirred at room temperature for 3 h, to give the title compound (13 mg, 17%) as a pale yellow oil after purification by neutral prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.11 (s, 1H), 7.87 (d, J = 0.8 Hz, 1H), 7.54 (dd, J = 5.9, 3.2 Hz, 2H), 7.27 - 7.18 (m, 2H), 7.13 (d, J = 0.8 Hz, 1H), 4.70 (s, 2H), 4.10 (s, 2H), 3.27 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 383.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1-methyl-1H-pyrazol-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 86)



In a similar fashion to general procedure 2, 4M HCl in dioxane (0.27 ml, 1.08 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(57)** (53 mg, 0.11 mmol) in dioxane (2 ml) at room temperature for 3 h, to give the title compound (16 mg, 38%) as a transparent oil after purification by neutral prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.08 (s, 1H), 7.57 - 7.46 (m, 3H), 7.28 - 7.15 (m, 2H), 6.22 (d, J = 2.2 Hz, 1H), 4.55 (s, 2H), 4.08 (s, 2H), 3.84 (s, 3H), 3.25 (t, J = 6.7 Hz, 2H), 3.10 (t, J = 6.7 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 396.2 $[M+H]^+$

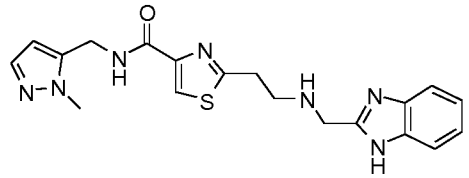
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 87)



In a similar fashion to general procedure 2, 4M HCl in dioxane (0.51 ml, 2.04 mmol) was addedto a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-

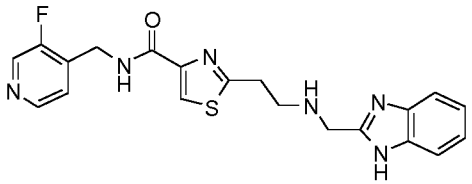
thiazol-2-yl}ethyl)carbamate **(58)** (101 mg, 0.2 mmol) in dioxane (2 ml) at 50°C for 1 h, to give the title compound (15 mg, 19%) as a tan solid after purification by neutral prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 9.10 (dd, J = 4.8, 1.7 Hz, 1H), 8.12 (s, 1H), 7.76 - 7.64 (m, 2H), 7.53 (dd, J = 6.0, 3.2 Hz, 2H), 7.22 (dd, J = 6.0, 3.2 Hz, 2H), 4.89 (s, 2H), 4.10 (s, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 394.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1-methyl-1H-pyrazol-5-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 88)



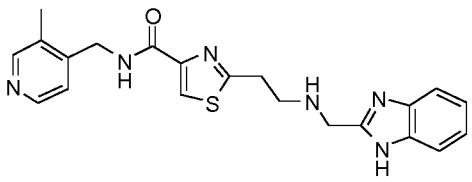
In a similar fashion to general procedure 2, 4M HCl in dioxane (0.26 ml, 1.04 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-5-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(59)** (51 mg, 0.103 mmol) in dioxane (2 ml) at 50°C for 1 h, to give the title compound (12 mg, 30%) as an orange oil after purification by neutral prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.10 (s, 1H), 7.53 (dd, J = 6.0, 3.2 Hz, 2H), 7.36 (d, J = 1.9 Hz, 1H), 7.23 (dd, J = 6.0, 3.2 Hz, 2H), 6.25 (d, J = 1.9 Hz, 1H), 4.63 (s, 2H), 4.08 (s, 2H), 3.89 (s, 3H), 3.26 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.7 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 396.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-4-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 89)



In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-fluoropyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(60)** (137 mg, 0.191 mmol, 71% purity) and 12M HCl (1.4 ml, 16.8 mmol) in MeOH (1.4 ml) at 50°C for 2 h afforded the title compound (46 mg, 59%) as a pale yellow solid after purification by neutral prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 8.99 (t, J = 6.1 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 8.35 (d, J = 4.8 Hz, 1H), 8.15 (s, 1H), 7.48 (br s, 2H), 7.35 - 7.26 (m, 1H), 7.12 (d, J = 3.5 Hz, 2H), 4.52 (d, J = 6.1 Hz, 2H), 3.97 (s, 2H), 3.19 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 411.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-methylpyridin-4-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 90)



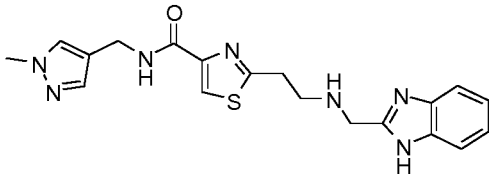
In a similar fashion to general procedure 2, 4M HCl in dioxane (1.8 ml) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-methylpyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(61)** (363 mg, 0.72 mmol) in dioxane (5 ml) at room temperature for 16 h to afford the

title compound (203 mg, 55%) as a white solid. The solid was obtained from precipitation from DCM / MeOH on addition of heptane, followed by a wash with Et_2O.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.69 (s, 1H), 8.60 (d, J = 6.1 Hz, 1H), 8.30 (s, 1H), 8.00 (d, J = 6.1 Hz, 1H), 7.83 (dt, J = 6.5, 3.3 Hz, 2H), 7.61 (dt, J = 6.5, 3.3 Hz, 2H), 5.00 (s, 2H), 3.89 (t, J = 6.3 Hz, 2H), 3.69 (t, J = 6.3 Hz, 2H), 2.63 (s, 3H) (a CH_2 signal obscured by solvent)

HPLCMS (Method B): [*m/z*]: 407.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1-methyl-1H-pyrazol-4-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 91)

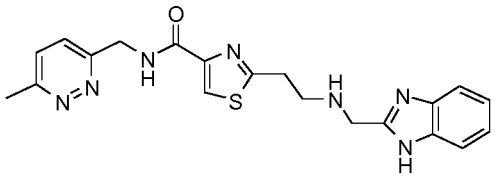


In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1-methyl-1H-pyrazol-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(62)** (125 mg, 0.25 mmol) and 12M HCl (0.49 ml, 5.88 mmol) in MeOH (5 ml) at 50°C for 2 h, gave the title compound (42 mg, 42%) as a yellow/brown solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.16 (s, 1H), 8.55 (t, J = 6.0 Hz, 1H), 8.08 (s, 1H), 7.55 (s, 1H), 7.48 (d, J = 38.4 Hz, 2H), 7.32 (s, 1H), 7.20 - 7.03 (m, 2H), 4.25 (d, J = 6.0 Hz, 2H), 3.95 (s, 2H), 3.76 (s, 3H), 3.15 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 396.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(6-methylpyridazin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 93)

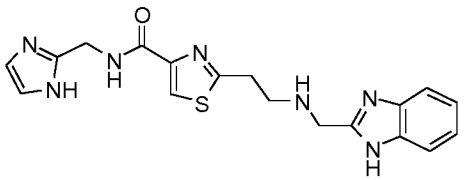


In a similar fashion to general procedure 2, crude tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(6-methylpyridazin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(63)** (99 mg, 0.154 mmol, 79% purity) and 12M HCl (1ml) in MeOH (1 ml) at 50°C for 2 h gave the title compound (32 mg,51%) as a light-brown solid after purification by neutral prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 9.01 (t, J = 6.1 Hz, 1H), 8.14 (s, 1H), 7.57 - 7.39 (m, 4H), 7.13 (s, 2H), 4.70 (d, J = 6.1 Hz, 2H), 3.96 (s, 2H), 3.19 (t, J = 6.8 Hz,2H), 2.98 (t, J = 6.8 Hz, 2H), 2.58 (s, 3H)

HPLCMS (Method B): [*m/z*]: 408.2 $[M+H]^+$

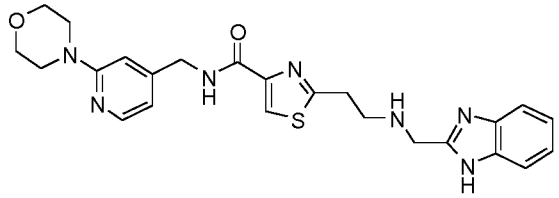
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(1H-imidazol-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 95)



In a similar fashion to general procedure 2, 4M HCl in dioxane (1 ml, 4 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-(2-{4-[(1H-imidazol-2-ylmethyl)carbamoyl]-1,3-thiazol-2-

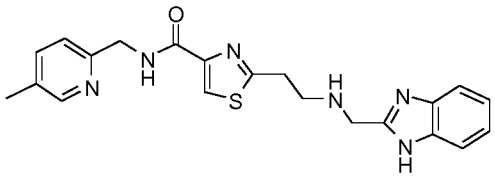
yl}ethyl)carbamate **(64)** (61 mg, 0.13 mmol) in dioxane (4 ml) at room temperature for 18h, to afford the title compound (23 mg, 48%) as a yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 11.77 (s, 1H), 8.61 (t, J = 5.9 Hz, 1H), 8.14 (s, 1H), 7.49 (br s, 2H), 7.13 (dd, J = 5.9, 2.8 Hz, 2H), 7.00 (br s, 1H), 6.81 (br s, 1H), 4.48 (d, J = 5.9 Hz, 2H), 3.97 (s, 2H), 3.17 (d, J = 6.2 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 382.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(morpholin-4-yl)pyridin-4-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 96)



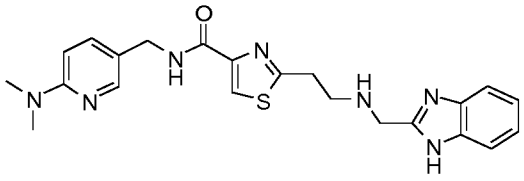
In a similar fashion to general procedure 2, 4M HCl in dioxane (1 ml) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[2-(morpholin-4-yl)pyridin-4-yl]methyl} carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(65)** (108 mg, 0.19 mmol) in dioxane (4 ml) at room temperature for 15 h, to afford the title compound (46 mg, 51%) as an orange solid after purification by neutral prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.90 (t, J = 6.3 Hz, 1H), 8.15 (s, 1H), 8.03 (d, J = 5.1 Hz, 1H), 7.50 (dd, J = 5.7, 3.3 Hz, 2H), 7.14 (dq, J = 7.1, 3.9 Hz, 2H), 6.73 (s, 1H), 6.61 (d, J = 5.1 Hz, 1H), 4.38 (d, J = 6.3 Hz, 2H), 4.15 (d, J = 29.7 Hz, 1H), 4.05 (s, 2H), 3.72 - 3.62 (m, 4H), 3.23 (t, J = 6.8 Hz, 2H), 3.18 (s, 2H) 3.07 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 478.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(5-methylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 97)



In a similar fashion to general procedure 2, 4M HCl in dioxane (0.24 ml, 0.96 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(5-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(66)** (48 mg, 0.095 mmol) in dioxane (2 ml) at room temperature for 12 h to afford the title compound (10 mg, 26%) as a colourless oil after purification by neutral prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.31 (s, 1H), 8.10 (s, 1H), 7.60 (dd, J = 8.0, 1.8 Hz, 1H), 7.52 (dd, J = 6.0, 3.1 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 6.0, 3.1 Hz, 2H), 4.65 (s, 2H), 4.10 (s, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H), 2.33 (s, 3H)
HPLCMS (Method D): [*m/z*]: 407.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[6-(dimethylamino)pyridin-3-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 98)

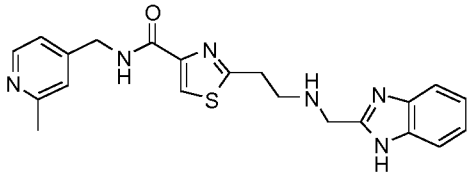


In a similar fashion to general procedure 2, 4M HCl in dioxane (0.17 ml, 0.68 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[6-(dimethylamino)pyridin-3-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(67)** (36 mg, 0.07 mmol) in dioxane (2 ml) at room temperature for 12 h to afford the title compound (8 mg, 27%) as a colourless oil after purification by neutral prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.07 (s, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.26 - 7.20 (m, 2H), 6.61 (d, J = 8.8 Hz, 1H), 4.43 (s, 2H), 4.07 (s, 2H), 3.24 (t, J = 6.6 Hz, 2H), 3.10 (t, J = 6.6 Hz, 2H), 3.06 (s, 6H)

HPLCMS (Method B): [*m/z*]: 436.3 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-methylpyridin-4-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 99)

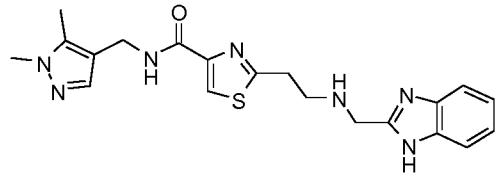


In a similar fashion to general procedure 2, 4M HCl in dioxane (0.18 ml, 0.72 mmol)was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-methylpyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(68)** (36 mg, 0.07 mmol) in dioxane (2 ml) at room temperature for 12 h to afford the title compound (20 mg, 69%) as a colourless oil after purification by neutral prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.31 (d, J = 5.3 Hz, 1H), 8.11 (s, 1H), 7.52 (dd, J = 5.9, 3.2 Hz, 2H), 7.30 - 7.13 (m, 4H), 4.58 (s, 2H), 4.09 (s, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H), 2.49 (s, 3H)

HPLCMS (Method B): [*m/z*]: 407.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 100)

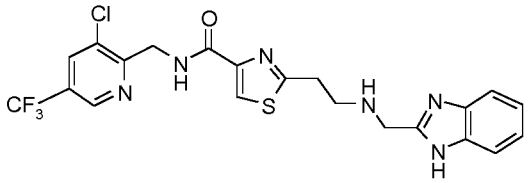


In a similar fashion to general procedure 2, 4M HCl in dioxane (0.36 ml, 1.44 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(1,5-dimethyl-1H-pyrazol-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(69)** (74 mg, 0.15 mmol) in dioxane (2 ml) at room temperature for 12 h, to afford the title compound (19 mg, 33%) as a colourless oil after purification by neutral prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.05 (s, 1H), 7.53 (dd, J = 5.8, 3.2 Hz, 2H), 7.38 (s, 1H), 7.30-7.17 (m, 2H), 4.38 (s, 2H), 4.07 (s, 2H), 3.74 (s, 3H), 3.23 (t, J = 6.7 Hz, 2H), 3.09 (t, J = 6.7 Hz, 2H), 2.29 (s, 3H)

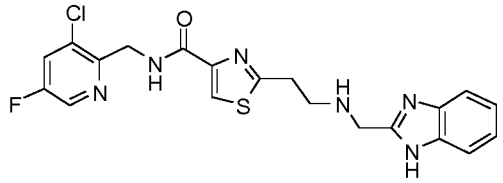
HPLCMS (Method D): [*m/z*]: 410.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 101)



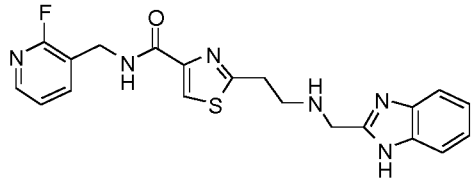
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-{2-[4-({[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(70)** (216 mg, 0.163 mmol, 45% purity) and 12M HCl (2.1 ml) in MeOH (2.1 ml) at 50°C for 2 h gave the title compound (67 mg, 80%) as a white solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 8.91 - 8.86 (m, 1H), 8.77 (t, J = 5.6 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.14 (s, 1H), 7.59 - 7.35 (m, 2H), 7.19 - 7.05 (m, 2H), 4.75 (d, J = 5.6 Hz, 2H), 3.97 (s, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.99 (t, J = 6.8 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 495.0 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-chloro-5-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 102)



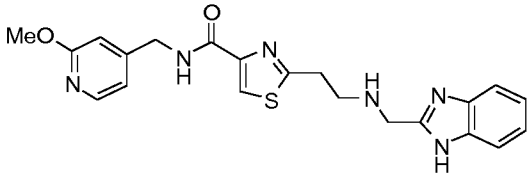
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-chloro-5-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(71)** (157 mg, 76%, 62% purity) and 12 M HCl (1.6 ml) in MeOH (1.6 ml) at 50°C for 2 h gave the title compound (50 mg, 62%) as a white solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.67 (t, J = 5.6 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.14 (s, 1H), 8.11 (dd, J = 8.5, 2.5 Hz, 1H), 7.60 - 7.36 (m, 2H), 7.12 (d, J = 4.7 Hz, 2H), 4.64 (d, J = 5.1 Hz, 2H), 3.97 (s, 2H), 3.19 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 445.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-fluoropyridin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 103)



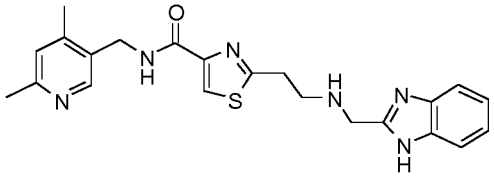
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-fluoropyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(72)** (127 mg, 0.249 mmol) and 4M HCl in dioxane (0.622 ml, 2.487 mmol) in dioxane (4.4 ml) at room temperature for 5 h gave the title compound (26 mg, 25%) as a yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.94 (t, J = 6.2 Hz, 1H), 8.17 (s, 1H), 8.13 - 8.09 (m, 1H), 7.85 - 7.79 (m, 1H), 7.55 - 7.46 (m, 2H), 7.32 - 7.28 (m, 1H), 7.18 - 7.12 (m, 2H), 4.47 (d, J = 6.1 Hz, 2H), 4.11 - 4.08 (m, 2H), 3.27 - 3.23 (m, 2H), 3.15 - 3.08 (br m, 2H)
HPLCMS (Method F): [*m/z*]: 411.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-methoxypyridin-4-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 104)



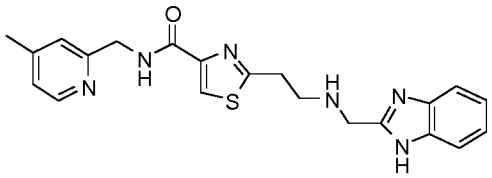
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(2-methoxypyridin-4-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(73)** (104 mg, 0.199 mmol, 96% purity) and 12M HCl (1 ml) in MeOH (1 ml) at 50°C for 2 hgave the title compound (35 mg, 42%) as a pale yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.95 (t, J = 6.3 Hz, 1H), 8.13 (s, 1H), 8.06 (d, J = 5.3 Hz, 1H), 7.58 - 7.38 (m, 2H), 7.17 - 7.07 (m, 2H), 6.89 (dd, J = 5.3, 1.1 Hz, 1H), 6.65 (s, 1H), 4.40 (d, J = 6.3 Hz, 2H), 3.96 (s, 2H), 3.81 (s, 3H), 3.19 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 423.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(4,6-dimethylpyridin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 105)



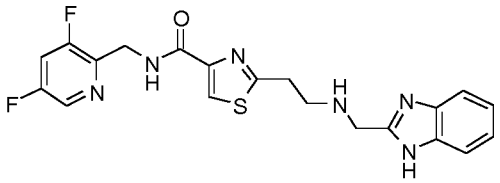
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4,6-dimethylpyridin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(74)** (0.077 g, 0.148 mmol) and 12M HCl (0.287 ml, 3.449 mmol) in MeOH (5 ml) at 45°C for 20 h gave the title compound (25 mg, 40%) as a yellow solid after purification by neutral prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.73 (t, J = 6.1 Hz, 1H), 8.25 (s, 1H), 8.11 (s, 1H), 7.56 - 7.37 (br m, 2H), 7.16 - 7.09 (m, 2H), 7.02 (s, 1H), 4.42 (d, J = 6.0 Hz, 2H), 3.95 (s, 2H), 3.16 (t, J = 6.5 Hz, 5H), 2.96 (t, J = 6.8 Hz, 2H), 2.37 (s, 3H), 2.28 (s, 3H)
HPLCMS (Method G): [*m/z*]: 421.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(4-methylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 106)



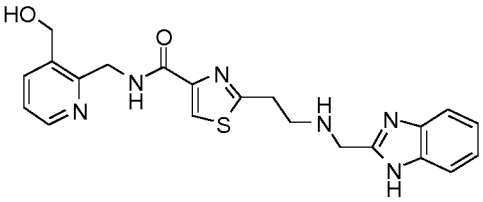
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(4-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(75)** (90 mg, 0.178 mmol) and 12M HCl (0.345 ml, 4.143 mmol) in MeOH (5 ml) at 45°C for 20 h gave the title compound (21 mg, 29%) as a yellow solid after purification by neutral prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.82 (t, J = 6.0 Hz, 1H), 8.34 (d, J = 5.0 Hz, 1H), 8.14 (s, 1H), 7.57 - 7.39 (m, 2H), 7.14 - 7.10 (m, 3H), 7.09 (d, J = 5.1 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.97 (s, 2H), 3.19 (t, J = 6.8 Hz, 3H), 3.01 - 2.96 (m, 2H), 2.27 (s, 3H)
HPLCMS (Method G): [*m/z*]: 407.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3,5-difluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 108)



In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(77)** (112 mg, 0.21 mmol) and 4M HCl in dioxane (0.53 ml, 2.119 mmol) in dioxane (2 ml) at room temperature for 16 h gave the title compound (36.7 mg, 40%) as a colourless oil after purification by neutral prep-HPLC.
1H-NMR (Methanol-d_4, 500 MHz): d[ppm]= 8.27 (d, J = 2.3 Hz, 1H), 8.09 (s, 1H), 7.61 - 7.55 (m, 1H), 7.54 - 7.49 (m, 2H), 7.25 - 7.16 (m, 2H), 4.74 (s, 2H), 4.10 (s, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.14 (t, J = 6.6 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 429.2 $[M+H]^+$

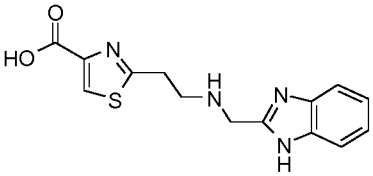
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[3-(hydroxymethyl)pyridin-2-yl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 110)



In a similar fashion to general procedure 2, 4M HCl in dioxane (3.28 ml, 13.13 mmol) was added to a solution of tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-{[(tert-butyldimethylsilyl)oxy]methyl}pyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(78)** (191.5 mg, 0.09 mmol, 30% purity) in dioxane (2 ml) at room temperature for 15 h to give the title compound (8.9 mg, 23.5%) as a yellow oil after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.21 (s, 1H), 8.75 (t, J = 5.0 Hz, 1H), 8.40 (dd, J = 4.8, 1.4 Hz, 1H), 8.14 (s, 1H), 7.81 - 7.77 (m, 1H), 7.57 - 7.40 (br m, 2H), 7.31 (dd, J = 7.6, 4.8 Hz, 1H), 7.14 - 7.10 (m, 2H), 5.41 (br s, 1H), 4.63 - 4.59 (m, 4H), 3.97 (s, 2H), 3.20 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 422.2 $[M+H]^+$

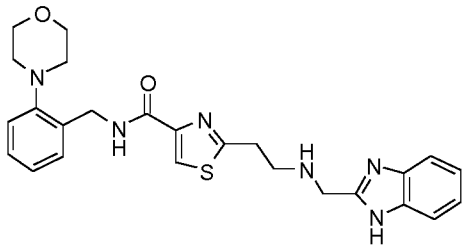
General Scheme 2 above:

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylic acid (80)



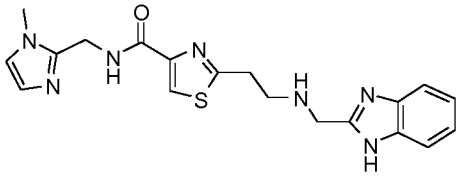
In a similar fashion to general procedure 5, LiOH (0.142 g, 5.92 mmol) andtert-butyl 2-({[(tert-butoxy)carbonyl]({2-[4-(methoxycarbonyl)-1,3-thiazol-2-yl]ethyl})amino}methyl)-1H-1,3-benzodiazole-1-carboxylate **(7)** (1.12 g) in THF / Water (50 ml / 10 ml) was stirred at room temperature for 16 h.The reaction mixture was acidified to pH ~1-2 using saturated $KHSO_4$ solution and then concentrated *in vacuo*. The crude residue was triturated with DCM / IPA followed by MeOH / EtOAc to give the title compound (1.2 g, 50% purity) as a cream solid.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.39 (s, 1H), 7.96 - 7.91 (m, 2H), 7.71 - 7.76 (m, 2H), 5.07 (s, 2H), 3.84 (t, J = 6.3 Hz, 2H), 3.64 (t, J = 6.3 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 303.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{[2-(morpholin-4-yl)phenyl]methyl}-1,3-thiazole-4-carboxamide (Example Compound No. 63)



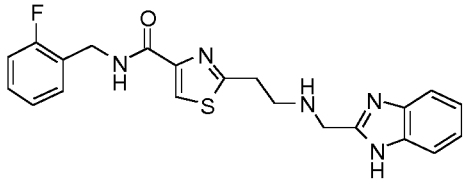
In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylic acid **(80)** (200 mg, 0.66 mmol, 50% purity), 1-[2-(morpholin-4-yl)phenyl]methanamine (127 mg, 0.66 mmol), DIPEA (0.35 ml, 1.98 mmol) and HATU (377 mg, 0.99 mmol) in DMF (5ml) afforded the title compound (37 mg, 12%) as a yellow solid after purification by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.06 (s, 1H), 7.50 (dd, J = 5.9, 3.2 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.24 - 7.18 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 4.67 (s, 2H), 4.05 (s, 2H), 3.88-3.80 (m, 4H), 3.23 (t, J = 6.8 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 2.90 - 2.84 (m, 4H)
HPLCMS (Method B): [*m/z*]: 477.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(1-methyl-1H-imidazol-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 64)



In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylic acid **(80)** (200 mg, 0.33 mmol, 50% purity), 1-(1-methyl-1H-imidazol-2-yl)methanamine (36 mg, 0.33 mmol), DIPEA (230 µl, 1.32 mmol) and HATU (189 mg, 0.496 mmol) in DCM (5 ml) and DMF (1 ml) afforded the title compound (15 mg, 12%) after purification by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.09 (s, 1H), 7.53 (dd, J = 5.9, 3.2 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.03 (d, J = 1.1 Hz, 1H), 6.89 (d, J = 1.2 Hz, 1H), 4.66 (s, 2H), 4.08 (s, 2H), 3.73 (s, 3H), 3.25 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.7 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 396.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(2-fluorophenyl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 65)

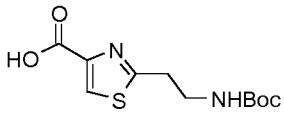


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxylic acid **(80)** (200 mg, 0.53 mmol, 50% purity), 1-(2-fluorophenyl)methanamine (66 mg, 0.53 mmol), DIPEA (369 µl, 2.12 mmol) and HATU (302 mg, 0.79 mmol) in DMF (2 ml) afforded the title compound (13 mg, 6%) as a white solid after purification by basic prep-HPLC.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.09 (s, 1H), 7.53 (dd, J = 5.9, 3.2 Hz, 2H), 7.40 - 7.35 (m, 1H), 7.32 - 7.26 (m, 1H), 7.25 - 7.19 (m, 2H), 7.15 - 7.05 (m, 2H), 4.64 (s, 2H), 4.08 (s, 2H), 3.26 (t, J = 6.7 Hz, 2H), 3.11 (t, J = 6.7 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 410.2 $[M+H]^+$

General Scheme 4 above:

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid (87)



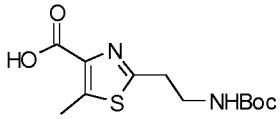
In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(1)** (8 g, 26.63 mmol) and LiOH (1.91 g, 79.90 mmol) in THF / water (200 ml / 70 ml) at room temperature for 20 h, gave the title compound (10.16 g, 99.7%) as a yellow oil.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.32 (s, 1H), 6.99 (s, 1H), 3.28 (t, J = 6.9 Hz, 2H overlapping with solvent), 3.10 (t, J = 6.9 Hz, 2H), 1.36 (s, 9H)

1H-NMR (Methanol-d4, 500MHz): d[ppm]= 8.24 (s, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.19 (t, J = 6.6 Hz, 2H), 1.41 (s, 9H)

HPLCMS (Method A): [*m/z*]: 294.9 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-thiazole-4-carboxylic acid (88)

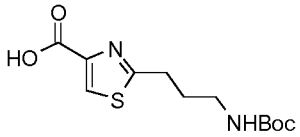


In a similar fashion to general procedure 5, methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-thiazole-4-carboxylate **(3)** (769 mg, 2.56 mmol) and LiOH (310 mg, 13 mmol) in THF / water (20 ml / 20 ml) afforded the title compound (681 mg, 88%) as a yellow oil.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 12.76 (s, 1H), 6.99 (t, J = 5.6 Hz, 1H), 3.30 - 3.19 (m, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.65 (s, 3H), 1.37 (s, 9H)

HPLCMS (Method A): [*m/z*]: 301.05 $[M+H]^+$

2-(3-{[(Tert-butoxy)carbonyl]amino}propyl)-1,3-thiazole-4-carboxylic acid (89)

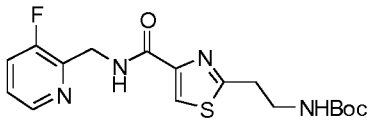


In a similar fashion to general procedure 5, ethyl 2-(3-{[(tert-butoxy)carbonyl]amino}propyl)-1,3-thiazole-4-carboxylate **(4)** (726 mg, 2.31 mmol) and LiOH (166 mg, 6.93 mmol) in THF (12 ml) and water (4 ml) afforded the crude title compound (791 mg) as a yellow oil.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.13 (s, 1H), 6.91 (t, J = 5.0 Hz, 1H), 3.05 – 2.93 (m, 4H), 1.83 (p, J = 7.2 Hz, 2H), 1.38 (s, 9H)

HPLCMS (Method A): [*m/z*]: 285 $[M+H]^+$

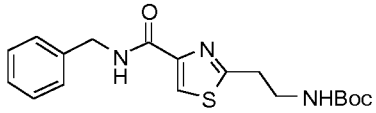
Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (90)



In a similar fashion to general procedure 6, (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (8.03 g, 40.35 mmol), 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (10.2 g, 26.9 mmol), DIPEA (28.1 ml, 161.4 mmol) and HATU (12.3 g, 32.3 mmol) in THF (300 ml) at room temperature for 2 h, gave the title compound (13.27 g) as an orange oil after purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane).

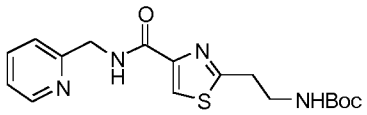
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.70 (t, J = 5.6 Hz, 1H), 8.39 (d, J = 4.6 Hz, 1H), 8.15 (s, 1H), 7.73 - 7.67 (m, 1H), 7.40 (dt, J = 8.5, 4.4 Hz, 1H), 7.04 (s, 1H), 4.65 (d, J = 5.6 Hz, 2H), 3.31 (t, J = 6.8 Hz, 2H, overlapping with NMR solvent), 3.13 (t, J = 6.8 Hz, 2H), 1.36 (s, 9H)
HPLCMS (Method A): [*m/z*]: 381 $[M+H]^+$

Tert-butyl N-{2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (91)



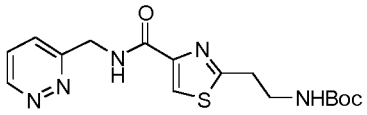
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (4.09 g, 15.0 mmol), benzylamine (1.8 ml, 16.5 mmol), DIPEA (7.9 ml, 45.1 mmol) and HATU (8.570 g, 22.5 mmol) in DCM (205 ml) afforded the title compound (3.38 g, 56%, 90% purity) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.03 (s, 1H), 7.61 (s, 1H), 7.39 - 7.32 (m, 4H), 7.31 - 7.27 (m, 1H), 4.64 (d, J = 6.1 Hz, 2H), 3.54 (d, J = 6.4 Hz, 2H), 3.17 (t, J = 6.4 Hz, 2H), 1.42 (s, 9H)
HPLCMS (Method E): [*m/z*]: 384 $[M+Na]^+$

Tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (92)



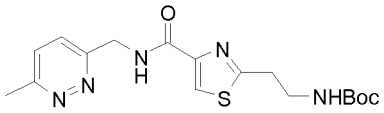
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (0.500 g, 1.836 mmol), 1-(pyridin-2-yl)methanamine (0.199 g, 1.836 mmol), HATU (1.047 g, 2.754 mmol) and DIPEA (0.959 ml, 5.508 mmol) in DCM (25 ml) gave the title compound (0905 g, quant.) as a yellow oil after purification by flash chromatography (using a gradient of 20% heptane :80% ethyl acetate to 100% ethyl acetate).
HPLCMS (Method A): [*m/z*]: 363.05 $[M+H]^+$

Tert-butyl N-(2-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (93)



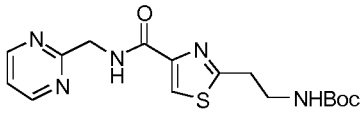
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (0.7 g, 2.57 mmol), pyridazin-3-ylmethanamine (0.42 g, 3.86 mmol), DIPEA (2.24 ml, 12.85 mmol) and HATU (1.47 g, 3.86 mmol) in DMF (15 ml) afforded the title compound (0.919 g, 98%) as a brown oil after purification by flash column chromatography (eluting with a gradient of 0-5% MeOH-DCM).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 9.21 (d, *J* = 4.0 Hz, 1H), 8.41 - 8.32 (br m, 1H), 8.03 (s, 1H), 7.91 - 7.85 (br m, 1H), 7.77 - 7.69 (br m, 1H), 5.01 (d, *J* = 5.7 Hz, 2H), 4.96 (br s, 1H), 3.65 - 3.46 (m, 2H), 3.20 (t, *J* = 6.2 Hz, 2H), 1.42 (s, 9H)
HPLCMS (Method A): [*m/z*]: 364.05 $[M+H]^+$

Tert-butyl N-[2-(4-{[(6-methylpyridazin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (94)



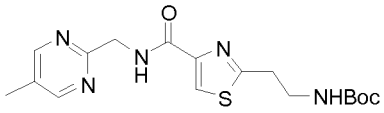
In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (1.3 g, 4.15 mmol), (6-methylpyridazin-3-yl)methanamine hydrochloride (0.8 g, 5.01 mmol), DIPEA (2.89 ml, 16.61 mmol) and HATU (1.90 g, 5.01 mmol) in THF (35 ml) and DMF (5 ml) gave the title compound (0.878 g, 45%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-15 % MeOH / EtOAc) followed by a second flash column chromatography (kp-NH, eluting with a gradient of 70-100 % EtOAc / heptane).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 9.04 (t, J = 6.0 Hz, 1H), 8.17 (s, 1H), 7.50 (q, J = 8.6 Hz, 2H), 7.05 (s, 1H), 4.71 (d, J = 6.1 Hz, 2H), 3.13 (t, J = 6.8 Hz, 2H), 2.59 (s, 3H), 1.36 (s, 9H)
HPLCMS (Method A): [*m/z*]: 378.05 $[M+H]^+$

Tert-butyl N-(2-{4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (95)



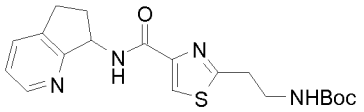
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (0.7 g, 2.57 mmol), pyrimidin-2-ylmethanamine (0.42 g, 3.86 mmol), DIPEA (2.24 ml, 12.85 mmol) and HATU (1.47 g, 3.86 mmol) in DMF (15 ml) afforded the title compound (0.545 g, 58%) as a pale yellow solid after purification by flash column chromatography (eluting with a gradient of 0-5% MeOH / DCM).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.83 (s, 1H), 8.81 (s, 1H), 8.46 (br s, 1H), 8.06 (s, 1H), 7.32 (app t,J = 4.8 Hz, 1H), 5.01 (br s, 1H), 4.97 (d, J = 5.3 Hz, 2H), 3.67 - 3.56 (m, 2H), 3.26 (t, J = 6.4 Hz, 2H), 1.47 (s, 9H)
HPLCMS (Method A): [*m/z*]: 364.05 $[M+H]^+$

Tert-butyl N-[2-(4-{[(5-methylpyrimidin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (96)



In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (500 mg, 1.6 mmol, 87% purity), (5-methylpyrimidin-2-yl)methanamine (295 mg, 2.4 mmol), DIPEA (1.39 ml, 7.99 mmol) and HATU (911 mg, 2.4 mmol) in THF (15ml) and DMF (3 ml) afforded the crude title compound (600 mg, 85%, 85% purity) as a yellow oil after flash chromatography (eluting with a gradient of 0-80% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 378.10 $[M+H]^+$

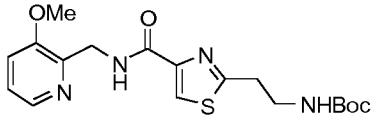
Tert-butyl N-{2-[4-({5H,6H,7H-cyclopenta[b]pyridine-7-yl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate (97)



In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (1.2 g, 4.41 mmol), 5H,6H,7H-cyclopenta[b]pyridin-7-amine hydrochloride (1.13 g, 6.61 mmol), DIPEA (2.3 ml, 13.22 mmol) and HATU (2.51 g, 6.61 mmol) in DMF (24 ml) afforded the title

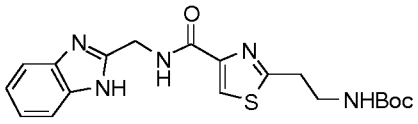
compound (1.53 g, 85%) as a pale pink powder after purification by flash column chromatography (eluting with a gradient of 0-5% MeOH / DCM).
HPLCMS (Method A): [*m/z*]: 389.15 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-methoxypyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (98)



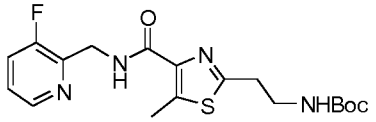
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (250 mg, 0.918 mmol), (3-methoxypyridin-2-yl)methanamine dihydrochloride (213 mg, 1.01 mmol), DIPEA (0.80 ml, 4.59 mmol) and HATU (524 mg, 1.38 mmol) in DCM (15 ml) afforded the crude title compound (417 mg) as a yellow oil after flash column chromatography (eluting with a gradient of 30-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.68 (s, 1H), 8.21 (d, J = 4.7 Hz, 1H), 8.02 (s, 1H), 7.21 (dd, J = 8.2, 4.7 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 5.02 (s, 1H), 4.76 (d, J = 4.7 Hz, 2H), 3.89 (s, 3H), 3.63 (d, J = 6.0 Hz, 2H), 3.23 (t, J = 6.0 Hz, 2H), 1.44 (s, 9H)
HPLCMS (Method A): [*m/z*]: 393.40 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-methoxypyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (99)



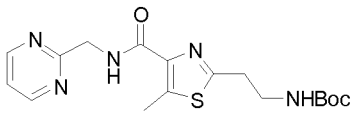
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(87)** (250 mg, 0.918 mmol), 1-(1H-benzimidazol-2-yl)methanamine (149 mg, 1.01 mmol), DIPEA (0.48 ml, 2.75 mmol) and HATU (524 mg, 1.38 mmol) in DCM (15 ml) afforded the crude title compound (0.709 mg, quantitative, 81% purity) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).
HPLCMS (Method A): [*m/z*]: 402 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1,3-thiazol-2-yl)ethyl]carbamate (100)



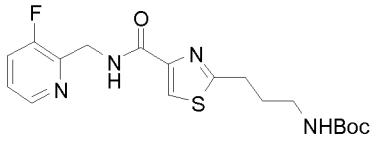
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-thiazole-4-carboxylic acid **(88)** (680 mg, 2.37 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (615 mg, 3.09 mmol), TEA (1.16 ml, 8.0 mmol) and HATU (1350 mg, 3.56 mmol) in DCM (30 ml) afforded the title compound (824 mg, 85%) as a yellow oil.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.45 (m, 2H), 7.42 (ddd, J = 9.4, 8.3, 1.2 Hz, 1H), 7.30 - 7.24 (m, 1H), 4.99 (s, 1H), 4.83 (dd, J = 5.2, 1.5 Hz, 2H), 3.59 (d, J = 6.0 Hz, 2H), 3.13 (t, J = 6.0 Hz, 2H), 2.83 (s, 3H), 1.46 (s, 9H)
HPLCMS (Method A): [*m/z*]: 395.15 $[M+H]^+$

Tert-butyl N-(2-{5-methyl-4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (101)



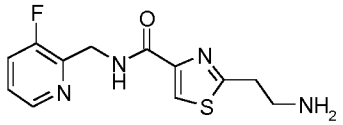
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-thiazole-4-carboxylic acid **(88)** (0.315 g, 0.912 mmol), 1-(pyrimidin-2-yl)methanamine (0.119 g, 1.094 mmol), THF (7 ml), DMF (1 ml), DIPEA (0.318 ml, 1.824 mmol) and HATU (0.416 g, 1.094 mmol) gave the title compound (0.134 g, 27 %) as a colourless oil after purification by flash column chromatography (with a gradient of 30-100 % EtOAc in heptane).
HPLCMS (Method A): [*m/z*]: 378.10 $[M+H]^+$

Tert-butyl N-[3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)propyl]carbamate (102)



In a similar fashion to general procedure 6, 2-(3-{[(tert-butoxy)carbonyl]amino}propyl)-1,3-thiazole-4-carboxylic acid **(89)** (661 mg, 2.31 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (689 mg, 3.46 mmol), DIPEA (2.41 ml, 13.85 mmol) and HATU (1053 mg, 2.77 mmol) in DMF (4 ml) and THF (4 ml) afforded the title compound (914 mg, 93%, 93% purity) as a yellow oil after purification by flash chromatography (eluting with a gradient of 20-100% EtOAc / heptane).
HPLCMS (Method A): [*m/z*]: 395.05 $[M+H]^+$

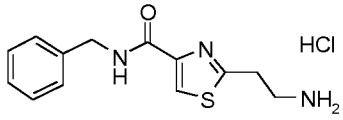
2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (103)



2HCl

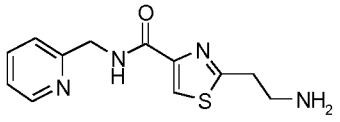
In a similar fashion to general procedure 2, 12M HCl (35.3 ml) and tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(90)** (13.3 g, 28.25 mmol) in MeOH (250 ml) were stirred at 50°C for 3 h. The mixture was concentrated *in vacuo* to give the title compound (12.8 g) as an off-white solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.98 (s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 8.21 (s, 1H), 8.17 (s, 3H), 7.72 (t, J = 9.3 Hz, 1H), 7.42 (dt, J = 8.5, 4.4 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H), 3.38(t, J = 6.5 Hz, 2H), 3.30 - 3.25 (m, 2H)
HPLCMS (Method A): [*m/z*]: 280.9 $[M+H]^+$

2-(2-Aminoethyl)-N-benzyl-1,3-thiazole-4-carboxamide hydrochloride (104)



In a similar fashion to general procedure 2, 12M HCl (2.5 ml) and tert-butyl N-{2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(91)** (456 mg, 1.29 mmol) in MeOH (4.5 ml) at room temperature for 4 h gave the title compound (336 mg, 100%) as a beige solid. The product was used in subsequent reactions without purification.
HPLCMS (Method E): [*m/z*]: 261.95 $[M+H]^+$

2-(2-Aminoethyl)-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (105)

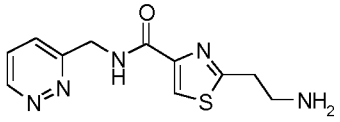


2HCl

In a similar fashion to general procedure 2, tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(92)** (0.905 g, 2.50 mmol), 12M HCl (4.852 ml, 58.23 mmol) in MeOH (9 ml) gave the title compound (0.840 g, quant.) as a white solid.

HPLCMS (Method A): [*m/z*]: 262.95 $[M+H]^+$

2-(2-Aminoethyl)-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (106)



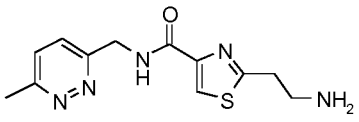
2HCl

In a similar fashion to general procedure 2, tert-butyl N-(2-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(93)** (0.919 g, 2.53 mmol) and 12M HCl (4.22 ml) in MeOH (15 ml) at room temperature for 16 h gave the title compound (0.840 g, 97%)as a brown residue.

1H-NMR (Deuterium Oxide, 500 MHz): d[ppm]= 9.17 (dd, J = 4.9, 1.5 Hz, 1H), 8.12 (s, 1H), 8.03 (dd, J = 8.6, 1.5 Hz, 1H), 7.99 (dd, J = 8.6, 4.9 Hz, 1H), 4.86 (s, 2H), 3.45- 3.39 (m, 2H), 3.48 - 3.43 (m, 2H)

HPLCMS (Method A): [*m/z*]: 263.95 $[M+H]^+$

2-(2-Aminoethyl)-N-[(6-methylpyridazin-3-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (107)



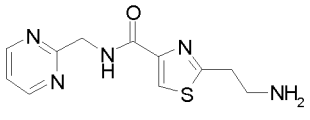
2HCl

In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(6-methylpyridazin-3-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(94)** (878 mg, 1.86 mmol) and 12M HCl (3.10 ml) in MeOH (15 ml) at room temperature for 24 h, gave the title compound (764 mg, quant.) as an off-white solid. The product was used in subsequent reactions without purification.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.49 (d, J = 8.9 Hz, 1H), 8.41 (d, J = 8.9 Hz, 1H), 8.26 (s, 1H), 4.97 (s, 2H), 3.53 - 3.47 (m, 4H), 2.91 (s, 3H)

HPLCMS (Method A): [*m/z*]: 277.95 $[M+H]^+$

2-(2-Aminoethyl)-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (108)



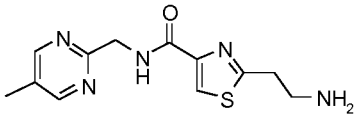
2HCl

In a similar fashion to general procedure 2, tert-butyl N-(2-{4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(95)** (0.545 g, 1.499 mmol) and 12M HCl (4.22 ml) in MeOH (15 ml) at room temperature for 16 h gave the title compound (0.530 g, quart.) as a pale yellow foam.

1H-NMR (Deuterium Oxide, 500 MHz): d[ppm]= 8.73 (d, J = 5.1 Hz, 2H), 8.16 (s, 1H), 7.47 (app t, J = 5.1 Hz, 1H), 4.80 (s, 2H), 3.51 - 3.46 (m, 2H), 3.45 - 3.41 (m, 2H)

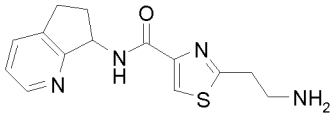
HPLCMS (ESI+): [*m/z*]: 263.95 $[M+H]^+$ as the freebase (METCR1673 Generic 2 min)

2-(2-Aminoethyl)-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide (109)



In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(5-methylpyrimidin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(96)** (600 mg, 1.59 mmol) and 12 M HCl (2.65 ml) in MeOH (10ml) afforded the title compound freebase (283 mg, 44%) as a white solid after purification by flash chromatography (eluting with a gradient of 0-10% 7 M ammonia in MeOH / DCM).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.77 – 8.70 (m, 1H), 8.62 (s, 2H), 8.14 (s, 1H), 4.64 (d, J = 4.0 Hz,, 2H), 3.13 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 2.26 (s, 3H)
HPLCMS (Method A): [*m/z*]: 278.2 $[M+H]^+$

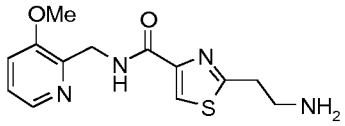
2-(2-Aminoethyl)-N-{5H,6H,7H-cyclopenta[b]pyridine-7-yl}-1,3-thiazole-4-carboxamide dihydrochloride (110)



2HCl

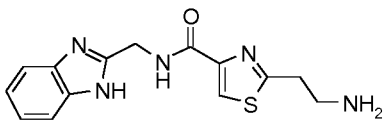
In a similar fashion to general procedure 2, 4M HCl in dioxane (14.45 ml, 57.8 mmol) was added to an ice cold solution of tert-butyl N-{2-[4-({5H, 6H, 7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1,3-thiazol-2-yl]ethyl}carbamate **(97)** (1.53 g, 3.94 mmol) in MeOH (5 ml). The mixture was stirred at room temperature for 2 h. The title compound (1.32 g, 93%) was isolated by filtration after precipitation from Et_2O (5 ml).
HPLCMS (Method A): [*m/z*]: 289.05 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-methoxypyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (111)



In a similar fashion to general procedure 2, 12M HCl (2.5 ml) and crude tert-butyl N-[2-(4-{[(3-methoxypyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(98)** (417 mg) in MeOH (5 ml) at room temperature for 2 h, gave the title compound (125 mg) as a white solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / DCM).
1H-NMR (DMSO-d6, 500MHz): d[ppm]= 8.59 (s, 1H), 8.15 - 8.11 (m, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.33 (dd, J = 8.3, 4.7 Hz, 1H), 4.57 (d, J = 5.2 Hz, 2H), 3.88 (s, 3H), 3.08 (t, J = 6.6 Hz, 2H), 2.94 (t, J = 6.6 Hz, 2H), 2.69 (s, 2H)
HPLCMS (Method A): [*m/z*]: 292.95 $[M+H]^+$

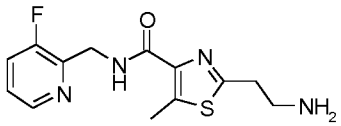
2-(2-Aminoethyl)-N-(1H-1,3-benzodiazol-2-ylmethyl)-1,3-thiazole-4-carboxamide (112)



In a similar fashion to general procedure 2, 12M HCl (2.5 ml) and crude tert-butyl N-(2-{4-[(1H-1,3-benzodiazol-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(99)** (709 mg, 1.43 mmol, 81% purity) in MeOH (5 ml) at room temperature for 2 h, gave the title compound (111 mg, 25%) as a brown solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.88 (s, 1H), 8.17 (s, 1H), 7.49 (s, 2H), 7.13 (dd, J = 6.0, 3.1 Hz, 2H), 4.68 (d, J = 6.0 Hz, 2H), 3.08 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 6.6 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 301.95 $[M+H]^+$

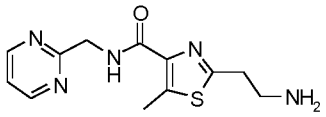
2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-thiazole-4-carboxamide dihydrochloride (113)



2HCl

In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1,3-thiazol-2-yl)ethyl]carbamate **(100)** (823 mg, 2.09 mmol) and 12M HCl (3 ml) in MeOH (30 ml) afforded the title compound (794 mg, quant.) as a tan solid.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.87 (t, J = 5.9 Hz, 1H), 8.40 (dt, J = 4.4, 1.3 Hz, 1H), 8.13 (s, 3H), 7.73 (ddd, J = 9.9, 8.3, 1.2 Hz, 1H), 7.43 (dt, J = 8.5, 4.5 Hz, 1H), 4.69- 4.60 (m, 2H), 3.32 - 3.19 (m, 4H), 2.71 (s, 3H)
HPLCMS (Method A): [*m/z*]: 295.05 $[M+H]^+$

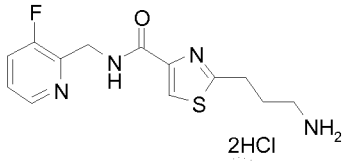
2-(2-Aminoethyl)-5-methyl-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (114)



2HCl

In a similar fashion to general procedure 2, tert-butyl N-(2-{5-methyl-4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(101)** (0.482 g, 0.795 mmol), MeOH (6 ml) and 12M HCl (1.325 ml, 15 .90 mmol) give the title compound (0.420 g, 99 %) as a yellow solid
HPLCMS (Method A): [*m/z*]: 277.95 $[M+H]^+$

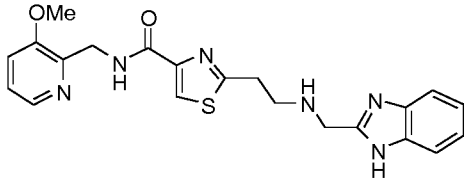
2-(3-Aminopropyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (115)



2HCl

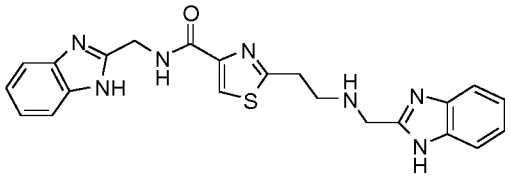
In a similar fashion to general procedure 2, 4M HCl in dioxane (2.89 ml, 11.55 mol) and tert-butyl N-[3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)propyl]carbamate **(102)** (0.91 g, 2.31 mmol) in dioxane (6 ml) and MeOH (2 ml) afforded the title compound (1.13 g, 85%, 64% purity) as a pale orange oil. Compound was used on the next step without purification.
HPLCMS (Method A): [*m/z*]: 295.00 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-methoxypyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 59)



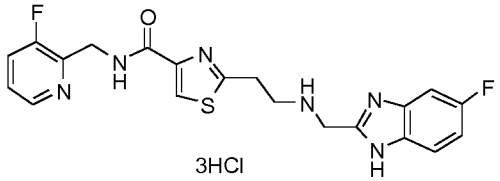
In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-methoxypyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(111)** (90 mg, 0.308 mmol) and 1H-benzimidazole-2-carbaldehyde (49 mg, 0.339 mmol) in DCE (9 ml) at room temperature for 2 h, followed by the addition of $NaBH(OAc)_3$ (91 mg, 0.431 mmol) gave the title compound (50 mg, 38%) as a yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500MHz): d[ppm]= 12.18 (s, 1H), 8.58 (t, J = 5.2 Hz, 1H), 8.14 (s, 1H), 8.09 - 8.06 (m, 1H), 7.59 - 7.40 (m, 3H), 7.31 (dd, J = 8.3, 4.7 Hz, 1H), 7.12 (d, J = 3.5 Hz, 2H), 4.56 (d, J = 5.2 Hz, 2H), 3.97 (s, 2H), 3.87 (s, 3H), 3.20 (t, J = 6.8 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 423.2 $[M+H]^+$

N-(1H-1,3-Benzodiazol-2-ylmethyl)-2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-1,3-thiazole-4-carboxamide (Example Compound No. 60)



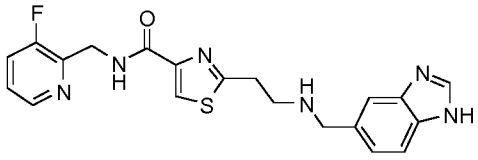
In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-(1H-1,3-benzodiazol-2-ylmethyl)-1,3-thiazole-4-carboxamide **(112)** (111 mg, 0.368 mmol) and 1H-benzimidazole-2-carbaldehyde (59 mg, 0.405 mmol) in DCE (12 ml) at room temperature for 2 h, followed by addition of $NaBH(OAc)_3$ (109 mg, 0.516 mmol) gave the title compound (15 mg, 9%) as a yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.23 (s, 2H), 8.89 (t, J = 5.9 Hz, 1H), 8.18 (s, 1H), 7.49 (s, 4H), 7.13 (tt, J = 7.0, 3.5 Hz, 4H), 4.69 (d, J = 5.9 Hz, 2H), 3.98 (s, 2H), 3.21 (t, J = 6.8 Hz, 2H), 3.00 (t, J = 6.8 Hz, 2H)
HPLCMS (Method B): [*m/z*]: 430.3 $[M-H]^+$

2-(2-{[(6-Fluoro-1H-1,3-benzodiazol-2-yl)methyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 114)



In a similar fashion to general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (200 mg, 0.49 mmol), 6-fluoro-1H-benzimidazole-2-carbaldehyde (89 mg, 0.539 mmol) and DIPEA (0.342 ml, 1.961 mmol) in MeOH (10 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (28 mg, 0.735 mmol) gave the title compound (83 mg, free base) as a brown solid after purification by basic basic prep-HPLC. The freebase and 12M HCl (1 ml) in MeOH (4 ml) were stirred at room temperature to give the title compound (111 mg, 42%) after solvent evaporation *in vacuo*.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.52 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.53 (s, 1H), 7.34 (s, 1H), 4.97 (s, 2H), 4.92 (s, 2H), 3.84 (s, 2H), 3.64 (t, J = 6.1 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 429.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-5-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 139)

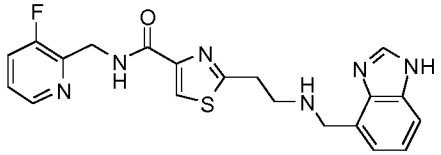


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (400 mg, 0.64 mmol, 56% purity), 1H-1,3-benzodiazole-5-carbaldehyde (112 mg, 0.77 mmol) and DIPEA (0.56 ml, 3.19 mmol) in MeOH (10 ml) at room temperature for 18 h, followed by by the addition of $NaBH_4$ (36 mg, 0.96 mmol) gave the title compound (207 mg, 75.9%) as a cream solid following purification by flash column chromatography (KP-NH, eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.31 - 8.29 (m, 1H), 8.14 (s, 1H), 8.10 (s, 1H), 7.64 - 7.53 (m, 3H), 7.37 – 7.33 (m, 1H), 7.29 (dd, J = 8.3, 1.3 Hz, 1H), 4.79 (d, J = 1.6 Hz, 2H), 3.96 (s, 2H), 3.28 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 411.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-4-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 140)

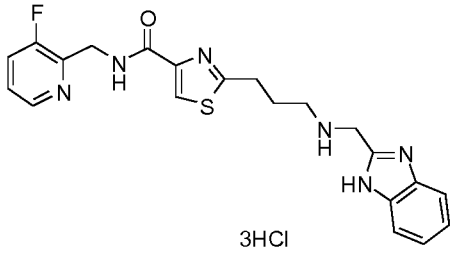


In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (400 mg, 0.64 mmol, 56.3% purity), 1H-1,3-benzodiazole-4-carbaldehyde (112 mg, 0.77 mmol) and DIPEA (0.56 ml, 3.19 mmol) in MeOH (10 ml) at room temperature for 18 h, followed by by the addition of $NaBH_4$ (36 mg, 0.96 mmol) gave the title compound (255 mg, 96.4%) as an off-white solid after purification by flash column chromatography (KP-NH, eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.41 (s, 1H), 8.65 (t, J = 5.5 Hz, 1H), 8.39 - 8.36 (m, 1H), 8.17 (br s, 1H), 8.12 (br s, 1H), 7.72 - 7.67 (m, 1H), 7.43 - 7.37 (m, 1H), 7.22 - 7.08 (m, 2H), 4.66 (dd, J = 5.7, 1.4 Hz, 2H), 4.13 (s, 1H), 4.04 (s, 1H), 3.18 (t, J = 6.5 Hz, 2H), 2.97 - 2.87 (m, 2H)

HPLCMS (Method C): [*m/z*]: 411.2 $[M+H]^+$

2-{3-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]propyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 134)

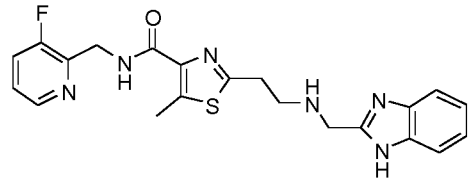


In a similar fashion to general procedure 3, 2-(3-aminopropyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(115)** (150 mg, 0.261 mmol, 64% purity), 1H-benzimidazole-2-carbaldehyde (46 mg, 0.314 mmol), DIPEA (0.18 ml, 1.05 mmol) in MeOH (2 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (15 mg, 0.39 mmol) afforded the freebase compound (53 mg, 48%) as a colouress oil after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 12.16 (s, 1H), 8.66 (t, J = 5.5 Hz, 1H), 8.38 (dt, J = 4.7, 1.4 Hz, 1H), 8.13 (s, 1H), 7.70 (ddd, J = 10.0, 8.4, 1.2 Hz, 1H), 7.61- 7.27 (m, 2H), 7.11 (dd, J = 6.0, 3.1 Hz, 2H), 4.65 (dd, J = 5.5, 1.4 Hz, 2H), 3.91 (s, 2H), 3.09 (t, 2H), 2.64 (t, J = 6.8 Hz, 2H), 1.92 (m, 2H)
HPLCMS (Method D): [*m/z*]: 425.2 $[M+H]^+$

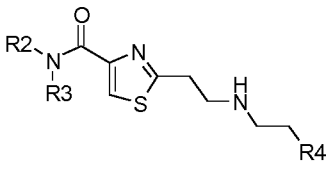
The freebase (35 mg, 0.082 mmol) and 12M HCl (20 µL, 0.247 mmol) were stirred in MeOH (2 ml) at room temperature to afford the title compound (44 mg, quant.) as a white solid after the solvent was removed*in vacuo*.
1H-NMR (D_2O, 500 MHz): d[ppm]= 8.50 (dd, J = 5.4, 1.2 Hz, 1H), 8.19 - 8.12 (m, 2H), 7.89 - 7.78 (m, 3H), 7.66 (dt, J = 6.3, 3.3 Hz, 2H), 4.89 (s, 2H), 4.85 (d, J = 1.3 Hz, 2H), 3.46- 3.39 (m, 2H), 3.26 (t, J = 7.2 Hz, 2H), 2.33 (m, 2H)
HPLCMS (Method D): [*m/z*]: 425.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-thiazole-4-carboxamide (Example Compound No. 164)



In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-thiazole-4-carboxamide dihydrochloride **(113)** (274 mg, 0.75 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (109 mg, 0.75 mmol), DIPEA (0.45 ml, 2.61 mmol) and anhydrous $MgSO_4$ (200 mg) in MeOH (10 ml) and DCM (10 ml) at room temperature for 20 h, followed by addition of $NaBH_4$ (60 mg,1.48 mmol) afforded the title compound (140 mg, 44%) as a pale yellow solid after purification by prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H), 8.36 (dt, J = 4.7, 1.4 Hz, 1H), 7.70 (ddd, J = 9.9, 8.4, 1.1 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.40 (dt, J = 8.5, 4.4 Hz, 1H), 7.13 (p, J = 6.6 Hz, 2H), 4.65 - 4.59 (m, 2H), 3.96 (s, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H), 2.68 (s, 3H)
HPLCMS (Method C): [*m/z*]: 425.2 $[M+H]^+$

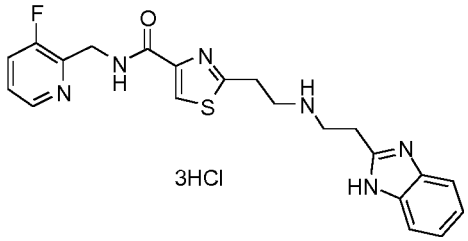
General procedure 7: 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 94)



2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (2.0 g, 3.96 mmol) was added to a solution of 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (1.12 g, 5.15 mmol) and DIPEA (10.6 ml, 59.45 mmol) in DMF (60 ml). The reaction mixture was allowed to stir at 30°C for 6 d (reaction was monitored by LCMS). The mixture was concentrated *in vacuo* and the residue was neutralised using sat. $NaHCO_3$ (aq). The aqueous layer was extracted using 4:1 $CHCl_3$ / IPA (4 x 100 ml) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude residue was purified by flash column chromatography (kp-NH, eluting with a gradient of 60-100% EtOAc / heptane followed by 0-20% MeOH / EtOAc) follow by neutral reverse-phase column chromatography (gradient elution 0-60% MeCN / water) to give the title compound (0.173 g, 10%) as a yellow oil.

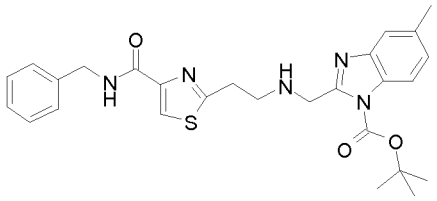
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.31 (d, J = 4.6 Hz, 1H), 8.02 (s, 1H), 7.57 (t, J = 9.1 Hz, 1H), 7.45 - 7.40 (m, 2H), 7.36 (dd, J = 8.6, 4.3 Hz, 1H), 7.17 (dd, J = 6.0, 3.2 Hz, 2H), 4.68 (s, 2H), 3.26 (d, J = 6.8 Hz, 2H), 3.15 - 3.07 (m, 6H)
HPLCMS (Method D): [*m/z*]: 425.1 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 94– HCl salt)



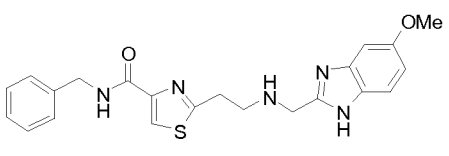
4M HCl in 1,4-dioxane (2.38 ml, 9.82 mmol) was added to a solution of 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(Example Compound No. 94)** (1.30 g, 2.98 mmol) in MeOH (15 ml) and the reaction mixture was stirred at room temperature for 2 h. The mixture was evaporated *in vacuo* to afford the title compound (1.16 g, 70%) as an off-white solid.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.48 (s, 1H), 8.25 (s, 1H), 8.07 (s, 1H), 7.79 (dt, J = 6.9, 3.4 Hz, 2H), 7.73 (s, 1H), 7.61 (dd, J = 6.2, 3.1 Hz, 2H), 4.91 (s, 2H), 3.82 (s, 4H), 3.75 (t, J = 6.4 Hz, 2H), 3.61 (t, J = 6.4 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 425.1 $[M+H]^+$

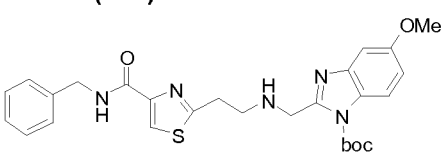
Tert-butyl 2-[({2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}amino)methyl]-5-methyl-1H-1,3-benzodiazole-1-carboxylate (116)



To a solution of 2-(2-aminoethyl)-N-benzyl-1,3-thiazole-4-carboxamide **(104)** (186 mg, 0.71 mmol) in DMF (5 ml) was added DIPEA (0.138 ml, 1 mmol), followed by addition of tert-butyl 2-(chloromethyl)-5-methyl-1H-1,3-benzodiazole-1-carboxylate **(F)** (200 mg, 0.71 mmol) and the reaction heated at 90°C. Upon completion (LCMS) the mixture was concentrated *in vacuo*. Residue was purified by flash column chromatography (eluting with DCM / MeOH, 95:5) as a yellow oil (85 mg, 24%).
1H-NMR ($CDCl_3$, 400 MHz): d[ppm]= 7.95 (s, 1H), 7.61 (s, 1H), 7.31 (dd, J = 24.4, 4.2 Hz, 6H), 7.07 (d, J = 8.2 Hz,1H), 4.61 (d, J = 6.1 Hz, 2H), 4.58 (s, 2H), 3.74 (t, J = 6.6 Hz, 2H), 3.20 (t, J = 6.6 Hz, 2H), 2.46 (s, 3H), 1.36 (s, 9H),
HPLCMS (Method I): [*m/z*]: 506.6 $[M+H]^+$

Tert-butyl 2-[({2-[4-(benzylcarbamoyl)-1,3-thiazol-2-yl]ethyl}amino)methyl]-5-methoxy-1H-1,3-benzodiazole-1-carboxylate (117) and N-benzyl-2-(2-{[(5-methoxy-1H-1,3-benzodiazol-2-yl)methyl]amino}ethyl)-1,3-thiazole-4-carboxamide (118)

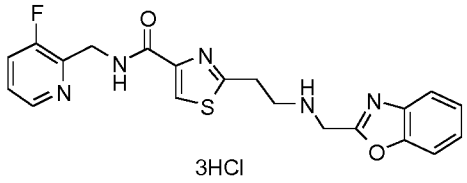




In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-benzyl-1,3-thiazole-4-carboxamide (**104**) (0.4 g, 2 mmol), tert-butyl 2-(chloromethyl)-5-methoxy-1H-1,3-benzodiazole-1-carboxylate **(F)** (0.45 g, 2 mmol), DIPEA (0.4 g, 3 mmol) and NaI (0.23 g, 2 mmol) in MeCN (30 ml) under argon at 90°C for 18 h, gave a mixture of a red solid, (boc deprotected product, 350 mg, 27%) and the expected product as a white solid (133 mg, 21%) after purification by flash column chromatography (eluting with a gradient DCM/ MeOH 5-7%).

HPLCMS (Method I): [*m/z*]: 522.6 $[M+H]^+$ and 422.6 $[M+H]^+$

2-{2-[(1,3-Benzoxazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 115)



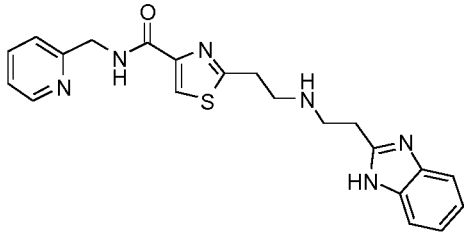
3HCl

In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (300 mg, 0.735 mmol), 2-(chloromethyl)-1,3-benzoxazole (160 mg, 0.956 mmol), DIPEA (1.922 ml, 11.03 mmol) and DMF (15 ml) at 30°C for 24 h, gave the title compound (102 mg, 34%) as a yellow oil after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.30 (d, J = 4.7 Hz, 1H), 8.08 (s, 1H), 7.66 - 7.62 (m, 1H), 7.60 - 7.54 (m, 2H), 7.39 - 7.32 (m, 3H), 4.77 (d, J = 1.6 Hz, 2H), 4.14 (s, 2H), 3.27 (d, J = 6.3 Hz, 2H), 3.18 (t, J = 6.6 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 412.1 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 58)

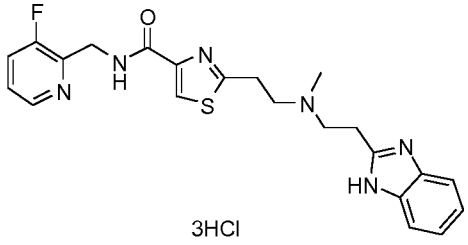


In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(105)** (240 mg, 0.72 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole (259 mg, 1.43 mmol) and DIPEA (2.17 ml, 12.53 mmol) in DMF (10 ml) afforded the title compound (64 mg 22%) as a brown solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM followed by 0.8 M ammonia in MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.87 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 4.6 Hz, 1H), 8.10 (s, 1H), 7.74 (td, J = 7.7, 1.7 Hz, 1H), 7.44 (s, 2H), 7.33 - 7.21 (m, 2H), 7.10 (dd, J = 5.9, 3.2 Hz, 2H), 4.55 (d, J = 6.0 Hz, 2H), 3.15 (t, J = 6.7 Hz, 2H), 3.02 (t, J = 6.7 Hz, 2H), 2.90– 2.96 (m, 4H)

HPLCMS (Method G): [*m/z*]: 407.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl](methyl)amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 112)



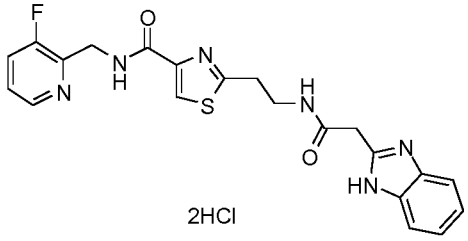
3HCl

2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride **(Example Compound No. 94)** (114 mg, 0.205 mmol), Et_3N (0.143 ml, 1.025 mmol) and DMF (1 ml) were stirred at room temperature for 1 h. MeI (0.059 ml, 0.949 mmol) was added and stirred at room temperature for 140 h. Water (10 ml) was added and the solvent reduced *in vacuo*. The crude product was purified by basic prep-HPLC to give the free base (18 mg). MeOH (2 ml) and 4 M HCl in dioxane (0.05 ml, 0.205 mmol) were added and stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* to give the title compound (24 mg, 21%) as a yellow solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.48 - 8.39 (br m, 1H), 8.26 (s, 1H), 8.02 - 7.84 (br m, 1H), 7.82 - 7.76 (m, 2H), 7.67 - 7.54 (m, 3H), 4.84 (s, 2H, obscured by H_2O peak), 3.99 - 3.84 (m, 6H), 3.71 (t, J = 6.8 Hz, 2H), 3.16 (s, 3H)

HPLCMS (Method D): [*m/z*]: 439.1 $[M+H]^+$

2-{2-[2-(1H-1, 3-Benzodiazol-2-yl)acetamido]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (Example Compound No. 113)



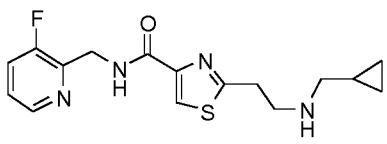
2HCl

In a similar fashin to general procedure 6, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (150 mg, 0.368 mmol), 2-(1H-1,3-Benzodiazol-2-yl)acetic acid (114 mg, 0.552 mmol), DIPEA (0.384 ml, 2.206 mmol) and HATU (210 mg, 0.52 mmol) in THF (20 ml) at room temperature for 2 h , gave the freebase compound (73 mg) after purified by basic prep-HPLC. The freebase and 12M HCl (2 ml) in MeOH (6 ml) were stirred at room temperature for 2 h. The reaction was concentrated *in vacuo* to give the title compound (97 mg, 51%) as a brown solid.

^{1}H NMR (Methanol-d4, 500 MHz): d[ppm]= 8.60 (dd, J = 5.5, 1.2 Hz, 1H), 8.32 (td, J = 8.9, 1.1 Hz, 1H), 8.15 (s, 1H), 7.96 - 7.90 (m, 1H), 7.81 - 7.75 (m, 2H), 7.63 - 7.58 (m, 2H), 4.93 (d, J = 1.1 Hz, 2H), 4.27 (s, 2H), 3.76 (t, J = 6.7 Hz, 2H), 3.32 (t, J = 6.6 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 439.1 $[M+H]^+$

2-{2-[(Cyclopropylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4 carboxamide (119)

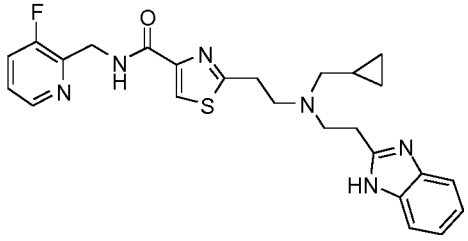


In a similar fashin to general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (56% purity, 500 mg, 0.793 mmol), cyclopropanecarbaldehyde (67 mg, 0.951 mmol) and DIPEA (0.552 ml, 3.17 mmol) in MeOH (7 ml) at room temperature for 16 h, followed by the addition of $NaBH_4$ (45 mg, 1.19 mmol) gave the title compound (149 mg, 51%) as a colourless oil after purification by flash column chromatography (kp-NH, eluting with a gradient 0-10% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.65 (t, J = 5.7 Hz, 1H), 8.39 (dt, J = 4.5, 1.3 Hz, 1H), 8.12 (s, 1H), 7.71 (ddd, J = 10.0, 8.3, 1.3 Hz, 1H), 7.41 (dt, J = 8.6, 4.5 Hz, 1H), 4.66 (dd, J = 5.7, 1.4 Hz, 2H), 3.13 (t, J = 6.7 Hz, 2H), 2.92 (t, J = 6.7 Hz, 2H), 2.43 (d, J = 6.6 Hz, 2H), 1.92 (s, 1H), 0.93 - 0.81 (m, 1H), 0.43 - 0.35 (m, 2H), 0.13 - 0.06 (m, 2H)

HPLCMS (Method F): [*m/z*]: 335.8 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl](cyclopropylmethyl)amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 148)

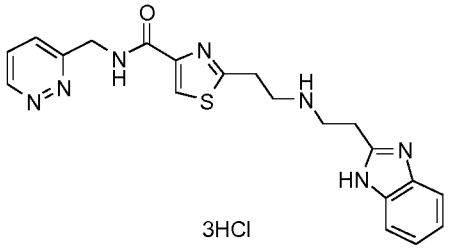


In a similar fashion to general procedure 7, 2-{2-[(cyclopropylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(119)** (149 mg, 0.45 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (116 mg, 0.53 mmol) and DIPEA (0.4 ml, 2.23 mmol) at 30°C for 32 h afforded the title compound (5 mg, 2%) as a yellow oil after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-10% MeOH in DCM then 0-10% 7 M ammonia in MeOH / DCM).

1H-NMR (Acetone-d6, 500 MHz): d[ppm]= 8.48 (s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.98 (s, 1H), 7.66 - 7.54 (m, 1H), 7.49 - 7.33 (m, 3H), 7.10 (dd, J = 6.0, 3.2 Hz, 2H), 4.75 (dd, J = 5.3, 1.5 Hz, 2H), 3.33 (t, J = 6.7 Hz, 2H), 3.30 - 3.11 (m, 6H), 2.67 (d, J = 6.7 Hz, 2H), 1.10 - 0.94 (m, 1H), 0.60 - 0.43 (m, 2H), 0.26 - 0.22 (m, 2H)

HPLCMS (Method B): [*m/z*]: 479.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 122)



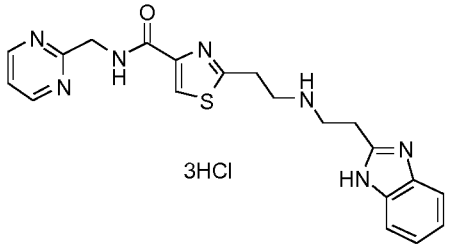
In a similar fashion using general procedure 7, 2-(2-aminoethyl)-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(106)** (409 mg, 1.22 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (316.9 mg, 1.46 mmol) and DIPEA (3.18 ml, 0.02 mol) in DMF (5 ml) at room temperature for 5 d gave the freebase product after purification by flash column chromatography using a gradient elution of 0-20% MeOH / DCM followed by further purification by basic prep-HPLC.

The freebase product was re-dissolved in MeOH (5 ml) and treated with 12 M HCl (1 ml) for 1 h to give the title compound (132 mg, 21%) as a pale yellow solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 9.52 (dd, J = 5.2, 1.2 Hz, 1H), 8.59 (dd, J = 8.7, 1.2 Hz, 1H), 8.46 (dd, J = 8.7, 5.2 Hz, 1H), 8.28 (s, 1H), 7.83 (dd, J = 6.2, 3.1 Hz, 2H), 7.65 (td, J =6.2, 5.5, 2.2 Hz, 2H), 5.04 (s, 2H), 3.90 - 3.82 (m, J = 4.2 Hz, 4H), 3.79 (t, J = 6.4 Hz, 2H), 3.64 (t, J = 6.4 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 408.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 129)



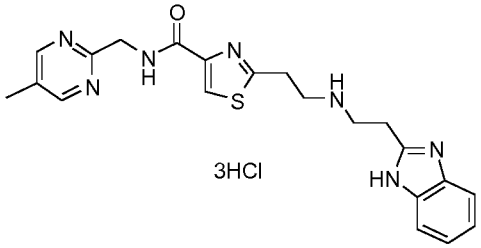
In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(108)** (300 mg, 0.89 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (193.7 mg, 0.89 mmol) and DIPEA (3.11 ml, 17.8 mmol) in DMF (10 ml) at room temperature for 9 d gave the freebase product after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM) followed by further purification by basic prep-HPLC.

The freebase product was re-dissolved in MeOH (5 ml) and treated with 12M HCl for 30 min to give the title compound (26 mg, 6%) as a pale yellow solid.

1H-NMR (D_2O, 500 MHz): d[ppm]= 8.66 (d, J = 5.1 Hz, 2H), 8.15 (s, 1H), 7.67 (dt, J = 6.7, 3.4 Hz, 2H), 7.53 (td, J = 6.2, 5.5, 2.1 Hz, 2H), 7.40 (t, J = 5.1 Hz, 1H), 4.60 (s, 2H), 3.76- 3.65 (m, 6H), 3.54 (t, J = 6.4 Hz, 2H)

HPLCMS (Method E): [*m/z*]: 408.1 $[M+H]^+$

General procedure 8: 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 155)

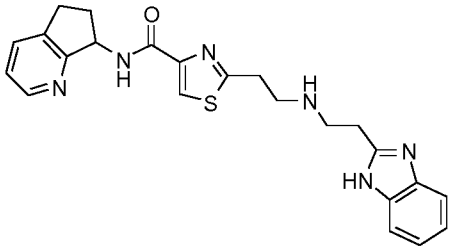


DBU (15.37 µl, 0.1mmol) was added to a suspension of 2-(2-aminoethyl)-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(109)** (36 mg, 0.1 mmol) in MeCN (3 ml). N-(2-nitrophenyl)prop-2-enamide **(D)** (19mg, 0.1 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (5 ml) and washed with 10% $NaHCO_3$ (5 ml), water (5 ml), brine (5 ml), dried (MgSO4), filtered and evaporated to give a crude intermediate which was further reacted with iron powder (3 mg, 0.05 mmol) in AcOH (3 ml) at 80°C for 3 h. The reaction mixture was diluted with water (5 ml), then made basic by slow addition of 10M NaOH (aq). The mixture was then further diluted with water (10 ml) and extracted with 4:1 chloroform / IPA (4 x 30 ml). The combined organic layers were separated, dried ($MgSO_4$) and evaporated under vacuum. The crude material was purified by basic prep-HPLC to give the title compound (8 mg, 67%) as a colourless film.

1H-NMR (Acetone-d6, 500MHz): d[ppm]= 8.58 (s, 2H), 8.44 (s, 1H), 8.03 (s, 1H), 7.45 (s, 2H), 7.14- 7.05 (m, 2H), 4.72 (d, J = 4.3 Hz, 2H), 3.24 (t, J = 6.5 Hz, 2H), 3.13 (m, 4H), 3.07 (t, J = 6.2 Hz, 2H), 2.29 (s, 3H)

HPLCMS (Method C): [*m/z*]: 422.0 $[M+H]^+$

N-{5H,6H,7H-Cyclopenta[b]pyridin-7-yl}-2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxamide (Example Compound No. 158)

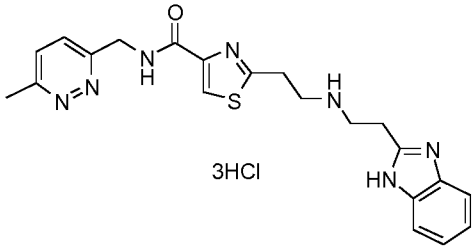


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1,3-thiazole-4-carboxamide dihydrochloride **(110)** (660 mg, 1.83 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (344 mg, 1.79 mmol) and DBU (0.8 ml, 5.37 mmol) in MeCN (8 ml) gave a crude intermediate which was further reacted with iron powder (180 mg, 3.22 mmol) in AcOH (10 ml) to afford the title compound (176 mg, 25%) as a pale yellow foam after purification by flash column chromatography (eluting with a gradient of 5-10% 3 M ammonia in MeOH / DCM) followed by basic prep-HPLC.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.27 (d, J = 4.7 Hz, 1H), 8.17 (s, 1H), 8.07 (br s, 1H), 7.43 (br s, 2H), 7.37 – 7.32 (m, 1H), 7.19 (dt, J = 8.5, 4.4 Hz, 1H), 7.15– 7.11 (m, 2H), 4.73 (dd, J = 5.0, 1.3 Hz, 2H), 3.18 (t, J = 6.2 Hz, 2H), 3.17 – 3.08 (m, 4H), 3.04 (t, J = 6.2 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 433.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(6-methylpyridazin-3-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 174)



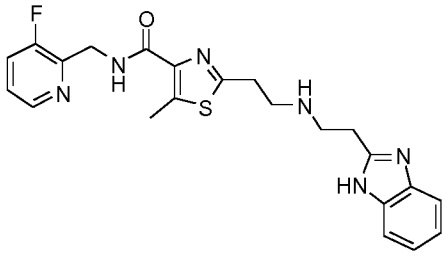
In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(6-methylpyridazin-3-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(107)** (382 mg, 0.932 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (161 mg, 0.839 mmol) and DBU (0.300 ml, 2.01 mmol) in MeCN (15 ml) at room temperature for 2h gave the required Michael intermediate (163 mg, 31 %) as a yellow oil after purification by flash column chromatography (0-3% MeOH / DCM) followed by a second purification using an isolute silica column with a gradient of 0-2% 7M NH_3 / MeOH in DCM.

The Michael intermediate (163 mg, 0.288 mmol) was reacted with iron powder (32 mg) in AcOH (3 ml) at 80°C for 1 h to give the title compound (15 mg, 12 %) as a beige solid after purification by basic prep-HPLC followed kp-NH silica column chromatography.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 9.00 (t, J = 6.0 Hz, 1H), 8.10 (s, 1H), 7.52 - 7.42 (m, 4H), 7.13 - 7.09 (m, 2H), 4.70 (d, J = 6.1 Hz, 2H), 3.15 (t, J = 6.7 Hz, 2H), 3.04 - 3.00 (m, 2H), 3.00 - 2.94 (m, 4H), 2.59 (s, 3H)

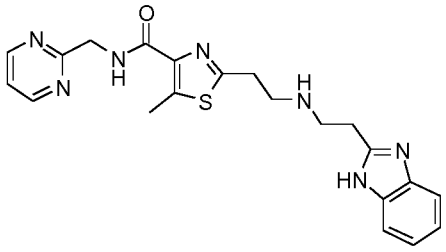
HPLCMS (Method B): [*m/z*]: 422.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-thiazole-4-carboxamide (Example Compound No. 165)



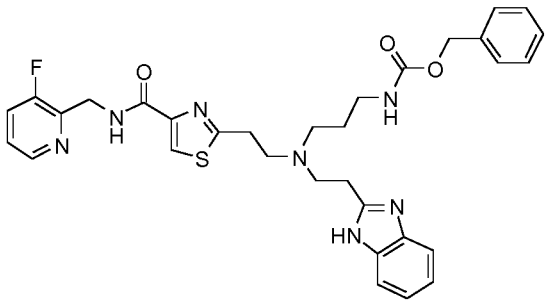
In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-thiazole-4-carboxamide dihydrochloride **(113)** (528 mg, 1.44 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (276 mg, 1.44 mmol) and DBU (0.64 ml, 0 mol) in MeCN (20 ml) at room temperature for 16 h gave the crude Michael intermediate (50%, 697 mg, 0.72 mmol) which was then reacted with iron powder (40 mg) in AcOH (4 ml) at 80°C for 1.5 h to give the title compound (99 mg, 32%) as a pale yellow solid after purification by flash column chromatography eluting 2-40% MeOH in DCM followed by prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.57 (t, J = 5.6 Hz, 1H), 8.38 (dt, J =4.3, 1.3 Hz, 1H), 7.73 - 7.66 (m, 1H), 7.45 (dd, J = 5.7, 3.2 Hz, 2H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.13- 7.08 (m, 2H), 4.61 (d, J = 5.5 Hz, 2H), 3.06 (q, J = 6.3 Hz, 4H), 2.97 (q, J = 6.7 Hz, 4H), 2.60 (s, 3H)
HPLCMS (Method C): [*m/z*]: 439.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-5-methyl-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 188)



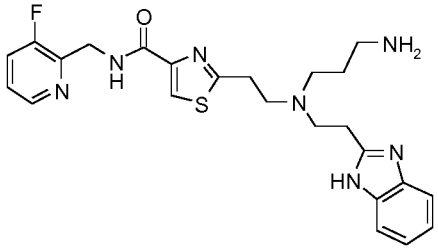
In a similar fashion to general procedure 8, 2-(2-aminoethyl)-5-methyl-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(114)** (315 mg, 0.594 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (114 mg, 0.594 mmol) and DBU (0.266 ml, 1.781 mmol) in MeCN (12 ml) at room temperature for 3 h gave the required Michael intermediate (142 mg, 42%) as a yellow oil after purification using isolute silica column eluting with a gradient of 0-6% MeOH in DCM.
The Michael intermediate (142 mg, 0.248 mmol) was reacted with iron powder (42 mg) in AcOH (3 ml) at 80°C for 1.5 h to give the title compound (7 mg, 7%) as a brownsolid after purification by basic prep-HPLC followed by isolute silica column chromatography eluting with a gradient of 0-8% MeOH in DCM.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.72 (d, J = 4.9 Hz, 2H), 7.43 (dt, J = 6.6, 3.3 Hz, 2H), 7.35 (t, J = 4.9 Hz, 1H), 7.19 (dt, J = 6.0, 3.4 Hz, 2H), 4.65 (s, 2H), 3.24 (t, J = 6.8 Hz, 2H), 3.22- 3.17 (m, 4H), 3.15 (t, J = 6.6 Hz, 2H), 2.68 (s, 3H)
HPLCMS (Method D): [m/z]: 422.2 $[M+H]^+$

Benzyl N-(3-{[2-(1H-1,3-benzodiazol-2-yl)ethyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}propyl)carbamate (Example Compound No. 179)



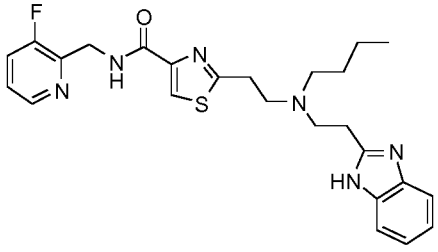
In a similar fashion to general procedure 3, 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (**Example Compound No. 94**– freebase) (166 mg, 0.391 mmol), benzyl (3-oxopropyl)carbamate (97 mg, 0.469 mmol) and DIPEA (0.12 ml, 0.587 mmol) in MeOH (1 ml) at room temperature for 1 h, followed by the addition of $NaBH_4$ (22 mg, 0.587 mmol) afforded the title compound (94 mg, 39%) as a pale yellow oil after purification by flash chromatography (eluting with a gradient of 0-5% MeOH / DCM).
HPLCMS (Method F): [*m/z*]: 616.2 $[M+H]^+$

2-{2-[(3-Aminopropyl)[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 163)



A solution of benzyl N-(3-{[2-(1H-1,3-benzodiazol-2-yl)ethyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}propyl)carbamate **(Example Compound No. 179)** (45 mg, 0.073 mmol) in AcOH / HBr (1:1, 1 ml) was stirred at 50°C for 2 h. The reaction mixture was evaporated*in vacuo*. Purification by basic prep-HPLC afforded the title compound (16 mg, 45%) as a colourless oil.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.32 (d, J = 4.7 Hz, 1H), 7.90 (s, 1H), 7.63 - 7.52 (m, 1H), 7.44 (dt, J = 6.6, 3.3 Hz, 2H), 7.35 (dt, J = 8.6, 4.4 Hz, 1H), 7.17 (dt, J = 6.0, 3.3 Hz, 2H), 4.75 (d, J = 1.5 Hz, 2H), 3.20 (t, J = 6.6 Hz, 2H), 3.04 (s, 4H), 2.98 (t, J = 6.6 Hz, 2H), 2.65 (m, 4H),1.67 (m, 2H)
HPLCMS (Method D): [*m/z*]: 482.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl](butyl)amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 157)

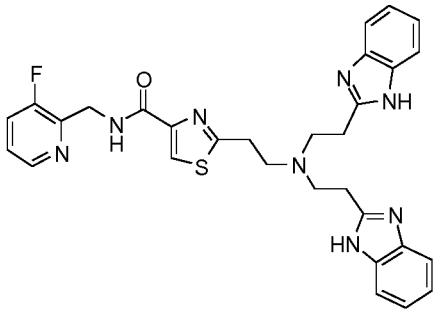


In a similar fashion to general procedure 3, 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (**Example Compound No. 94**– freebase) (60 mg, 0.141 mmol), butanal (12 mg, 0.174 mmol) and DIPEA (98 µl, 0.56 mmol) in MeOH (1 ml) at room temperature for 1 h followed by the addition of $NaBH_4$ (8 mg, 0.21 mmol) afforded the title compound (50 mg, 73%) as a yellow oil after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.13 (s, 1H), 8.66 (t, J = 5.6 Hz, 1H), 8.37 (d, J = 4.7 Hz, 1H), 8.06 (s, 1H), 7.69 (ddd, J = 9.9, 8.4, 1.2 Hz, 1H), 7.57 - 7.32 (m, 3H), 7.17 - 7.01 (m, 2H), 4.65 (d, J = 4.6 Hz, 2H), 3.17 (t, J = 6.7 Hz, 2H), 2.96 (m, 4H), 2.88 (t, J = 6.7 Hz, 2H), 2.58- 2.51 (m, 2H), 1.40 (m, 2H), 1.23 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H)

HPLCMS (Method D): [*m/z*]: 481.3 $[M+H]^+$

2-(2-{bis[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 152)

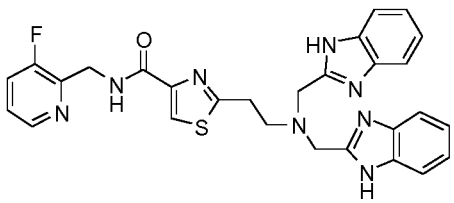


In a similar fashion to general procedure 7, 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (**Example Compound No. 94**– freebase) (400 mg, 1.13 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (492 mg, 2.27 mmol) and DIPEA (3.03 ml, 17 mol) in DMF (5 ml) at 30°C for 3 d, afforded the title compound (10 mg, 1.5%) as an off-white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM followed by 0-10% 7N ammonia in MeOH / DCM) and a second basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.28 (s, 1H), 8.66 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.4 Hz, 1H), 8.06 (s, 1H), 7.69 (ddd, J = 10.0, 8.3, 1.3 Hz, 1H), 7.61- 7.46 (m, 3H), 7.39 (dq, J = 8.6, 4.2 Hz, 2H), 7.23 - 7.04 (m, 4H), 4.77 - 4.52 (m, 4H), 3.27 (t, J = 7.2 Hz, 2H), 3.15- 3.04 (m, 2H), 3.02 - 2.90 (m, 4H), 2.87 (t, J = 6.7 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 569.3 $[M+H]^+$

2-{2-[bis(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 166)

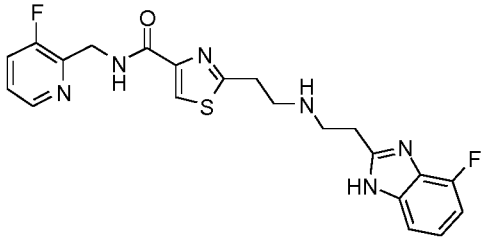


In a similar fashion to general procedure 7, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(Example Compound No. 40)** (110 mg, 0.268 mmol), 2-(chloromethyl)-1H-1,3-benzodiazole (45 mg, 0.268 mmol), DIPEA (0.467 ml, 2.68 mmol) in DMF (1 ml) at 45°C for 3 h then at 55°C for 1 h, afforded the title compound (10 mg, 7%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM followed by 0-10% 7N ammonia in MeOH / DCM).

1H-NMR (Acetone-d6, 500 MHz): d[ppm]= 11.99 (s, 1H), 8.43 (s, 1H), 8.33 (d, J = 4.7 Hz, 1H), 8.02 (s, 1H), 7.71 - 7.55 (m, 3H), 7.51 (s, 2H), 7.37 (dt, J = 8.5, 4.4 Hz, 1H), 7.17 (d, J = 5.7 Hz, 4H), 4.80 - 4.70 (m, 2H), 4.17 (s, 4H), 3.37 (t, J = 6.9 Hz, 2H), 3.20 (t, J = 6.9 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 541.3 $[M+H]^+$

2-(2-{[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 243)

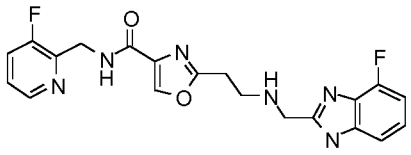


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (662 mg, 1.87 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (394 mg, 1.87 mmol) and DBU (924 µl, 6.18 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (286 mg, 5.12 mmol) in AcOH (15 ml) to afford the title compound (203 mg, 34%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.66 (t, J = 5.6 Hz, 1H), 8.39 (dt, J = 4.7, 1.3 Hz, 1H), 8.08 (s, 1H), 7.70 (ddd, J = 10.0, 8.4, 1.1 Hz, 1H), 7.40 (dt, J = 8.7, 4.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.10 (td, J = 8.0, 4.9 Hz, 1H), 6.92 (dd, J = 11.1, 8.0 Hz, 1H), 4.68- 4.62 (m, 2H), 3.16 (t, J = 6.7 Hz, 2H), 3.05 (t, J = 6.7 Hz, 2H), 2.99 (t, J = 6.6 Hz, 4H)

HPLCMS (Method B): [*m/z*]: 443.2 $[M+H]^+$

2-(2-{[(4-fluoro-1H-1,3-benzodiazol-2-yl)methyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 253)

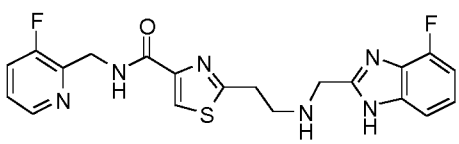


In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (100 mg, 0.3 mmol), 2-(chloromethyl)-7-fluoro-1H-1,3-benzodiazole hydrochloride (66 mg, 0.3 mmol) and DIPEA (258 µl, 1.48 mmol) in DMF (2.5 ml) was stirred at 40°C for 73 h, to afforded the title compound (23 mg, 18%) as a brown glassy solid after purification by reverse phase Biotage (A = water / 0.1% NH_3; B = MeCN / 0.1% NH_3; eluting with a gradient of 10% A / B for 2 column volumns, 10% to 30% A / B for 4 column volumns, 30% to 60% A/ B for 10 column volumes and 60% to 100% for 5 column volumes).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.49 (br s, 1H), 8.54 - 8.47 (m, 2H), 8.39 - 8.34 (m, 1H), 7.73 - 7.65 (m, 1H), 7.42 – 7.37 (m, 1H), 7.34 - 7.24 (m, 1H), 7.15 - 7.06 (m, 1H), 6.92 (t, 1H), 4.63 - 4.57 (m, 2H), 3.99 - 3.91 (m, 2H), 3.02 - 2.94 (m, 4H), 2.63 (br s, 1H)

HPLCMS (Method D): [*m/z*]: 413.2 $[M+H]^+$

2-(2-{[(4-fluoro-1H-1,3-benzodiazol-2-yl)methyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 274)



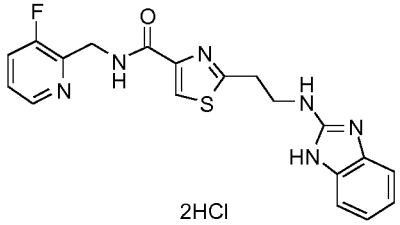
In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (200 mg, 0.57 mmol), 2-(chloromethyl)-7-fluoro-1H-1,3-benzodiazole hydrochloride (125 mg, 0.57 mmol) and DIPEA (493 µl, 2.83 mmol) in DMF (5.5 ml) was heated at 40°C for 18 h, stirred at room temperature for 2 d and then heated at 40°C for 4 h to give the title compound (7 mg, 3%) as a glassy brown solid after purification by reverse phase chromatography [(eluting with a gradient of 10-100% (water+0.1% ammonia) / (MeCN+0.1% ammonia)]

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.50 (s, 1H), 8.70 - 8.61 (m, 1H), 8.39 - 8.32 (m, 1H), 8.13 (s, 1H), 7.72 - 7.66 (m, 1H), 7.42 - 7.36 (m, 1H), 7.34 - 7.25 (m, 1H), 7.15 - 7.08 (m, 1H), 6.93 (m, 1H), 4.68 - 4.62 (m, 2H), 4.00 - 3.94 (m, 2H), 3.22 - 3.15 (m, 2H), 3.01 - 2.93 (m, 2H), 2.71 (s, 1H)

HPLCMS (Method D): [*m/z*]: 429.1 $[M+H]^+$

General Scheme 6 above:

General procedure 9: 2-{2-[(1H-1,3-Benzodiazol-2-yl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (Example Compound No. 121)

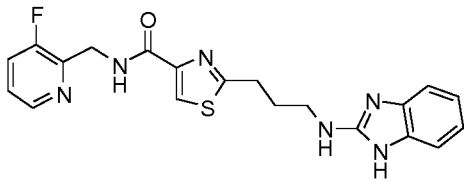


A solution of 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (1.65 g, 2.62 mmol, 56% purity), 2-chloro-1H-benzimidazole (0.1 g, 0.66 mmol) and DIPEA (0.571 ml, 3.277 mmol) in n-butanol (3 ml) and MeOH (0.1 ml) was heated at 150°C under microwave irradiation for 2.5 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in saturated $NaHCO_3$ solution, diluted with water (20 ml) and extracted with 4:1 chloroform / IPA (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / EtOAc) followed by basic prep-HPLC. The residue obtained was dissolved in MeOH (4 ml) and treated with 12 M HCl (1 ml) for 2 h. Evaporation *in vacuo* afforded the title compound (0.131 g, 43%) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.60 (d, J = 5.5 Hz, 1H), 8.31 (t, J = 8.3 Hz, 1H), 8.19 (s, 1H), 7.93 (br, J = 3.8 Hz, 1H), 7.38 (dt, J = 7.1, 3.5 Hz, 2H), 7.28 (dd, J = 5.9, 3.2 Hz, 2H), 4.93 (s, 2H), 3.99 (t, J = 6.4 Hz, 2H), 3.49 (t, J = 6.4 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 397.1 $[M+H]^+$

2-{3-[(1H-1,3-Benzodiazol-2-yl)amino]propyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 135)



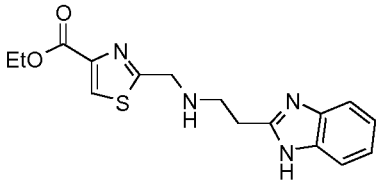
In a similar fashion to general procedure 9, 2-(3-aminopropyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(115)** (173 mg, 0.472 mmol), 2-chloro-1H-benzimidazole (60 mg, 0.393 mmol), DIPEA (0.21 ml, 1.18 mmol), n-BuOH (2 ml) and DMF (0.5 ml) at 150°C in the microwave for 1 h, gave the title compound (26 mg, 16%) as an off-white solid after urification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.74 (s, 1H), 8.68 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.7, 1.4 Hz, 1H), 8.15 (s, 1H), 7.70 (ddd, J = 10.0, 8.3, 1.3 Hz, 1H), 7.40 (dt, J= 8.6, 4.4 Hz, 1H), 7.11 (dd, J = 14.8, 7.6

Hz, 2H), 6.96 - 6.75 (m, 2H), 6.67 (t, J = 5.7 Hz, 1H), 4.65 (dd, J = 5.7, 1.4 Hz, 2H), 3.39 (q, J = 6.7 Hz, 2H), 3.18 - 3.07 (m, 2H), 2.07 (m, 2H)
HPLCMS (Method D): [*m/z*]: 411.2 $[M+H]^+$

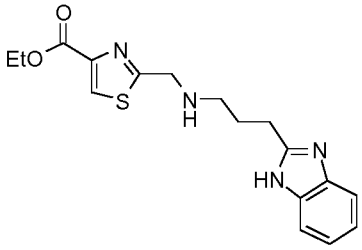
General Scheme 7 above:

Ethyl 2-({[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}methyl)-1,3-thiazole-4-carboxylate (120)



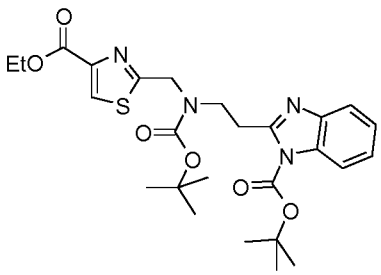
In a similar fashion to general procedure 3, 2-(1H-benzimidazol-2-yl)ethanamine dihydrochloride (379 mg, 1.62 mmol), ethyl 2-formyl-1,3-thiazole-4-carboxylate (300 mg, 1.62 mmol), DIPEA (1.13 ml, 6.48 mmol) and $MgSO_4$ (100 mg) in DCM (10 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (92 mg, 2.43 mmol) gave the title compound (201 mg, 35%) as a white solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-15% MeOH / EtOAc).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.40 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.1 Hz, 1H), 7.16 - 7.07 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.05 (m, 2H), 3.04 (m, 2H), 299 (t, J = 5.8 Hz, 2H), 2.52 (s, 2H), 1.29 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 331.0 $[M+H]^+$

Ethyl 2-({[3-(1H-1,3-benzodiazol-2-yl)propyl]amino}methyl)-1,3-thiazole-4-carboxylate (121)



In a similar fashion to general procedure 3, 3-(1H-benzimidazol-2-yl)propan-1-amine (568 mg, 3.24 mmol), ethyl 2-formyl-1,3-thiazole-4-carboxylate (600 mg, 3.24 mmol), DIPEA (2.26 ml, 12.96 mmol) and $MgSO_4$ (300 mg) in DCM (20 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (184 mg, 4.86 mmol) afforded the title compound (570 mg, 31%, 62% purity) as a white solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / EtOAc).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.14 (s, 1H), 8.39 (s, 1H), 7.50 (d, J = 6.9 Hz, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.14 - 7.05 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.99 (m, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.94 (q, J = 7.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 345.00 $[M+H]^+$

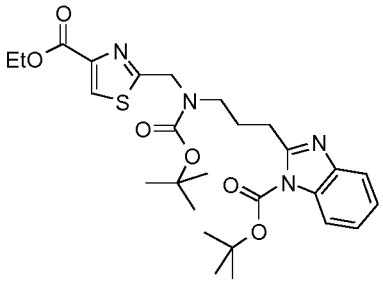
Tert-butyl 2-(2-{[(tert-butoxy)carbonyl]({[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl})amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate (122)



In a similar fashion to general procedure 4, ethyl 2-({[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}methyl)-1,3-thiazole-4-carboxylate **(120)** (201 mg, 0.608 mmol), Boc_2O (146 mg, 0.669 mmol) and TEA (0.08 ml, 0.608 mmol) in THF (10 ml) at room temperature for 20 h, gave the afforded the title compound (345 mg, 94%) as a colourless oil after purification by flash column chromatography (eluting with a gradient of 40-100% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 531.15 $[M+H]^+$

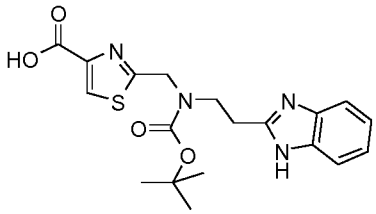
Tert-butyl 2-(3-{[(tert-butoxy)carbonyl]({[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl})amino}propyl)-1H-1,3-benzodiazole-1-carboxylate (123)



In a similar fashion to general procedure 4, ethyl 2-({[3-(1H-1,3-benzodiazol-2-yl)propyl]amino}methyl)-1,3-thiazole-4-carboxylate **(121)** (0.570 g, 1.018 mmol, 62% purity), Boc_2O (1.56 g, 7.124 mmol) and TEA (0.671 ml, 5.089 mmol) in THF (40ml) at room temperature for 72 h, following further Boc_2O (0.444 g, 2.036 mmol) for 4 h and further addition of Boc_2O (0.444 g, 2.036 mmol) for more 16 h, gave the title compound (1.162 g, 48% purity, quant.) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-60% EtOAc / heptane).

HPLCMS (Method A): [*m/z*]: 545.15 $[M+H]^+$

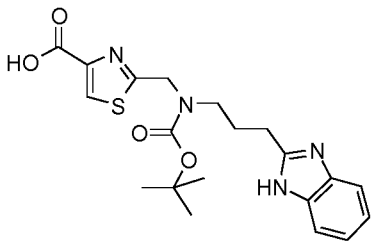
2-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylic acid (124)



In a similar fashion to general procedure 5, tert-butyl 2-(2-{[(tert-butoxy)carbonyl]({[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl})amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate **(122)** (385 mg, 0.73 mmol) and LiOH (87 mg, 3.63 mmol) in THF / water (25 ml / 5 ml) afforded the title compound (350 mg, 99%, 83% purity) as a white solid.

HPLCMS (Method A): [*m/z*]: 403.00 $[M+H]^+$

2-({[3-(1H-1,3-Benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylic acid (125)

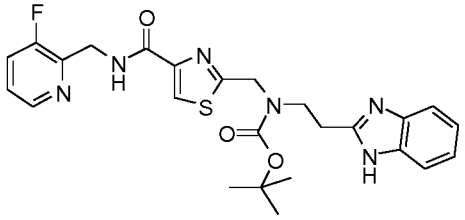


In a similar fashion to general procedure 5, tert-butyl 2-(3-{[(tert-butoxy)carbonyl]({[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]methyl})amino}propyl)-1H-1,3-benzodiazole-1-carboxylate **(123)** (1.16 g, 1.02 mmol, 48% purity) and LiOH (122 mg, 5.09 mmol) in THF / water (20 ml / 5 ml) afforded the crude title compound (811 mg, 52% purity) as an off-white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.39 (s, 1H), 7.65 (br s, 2H), 7.37 (br s, 2H), 4.68 (br s, 2H), 3.38 (br s, 2H), 3.00 (br s, 2H), 2.08 (br s, 2H), 1.34 (s, 9H)

HPLCMS (Method A): [*m/z*]: 417.05 $[M+H]^+$

Tert-butyl N-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate (126)

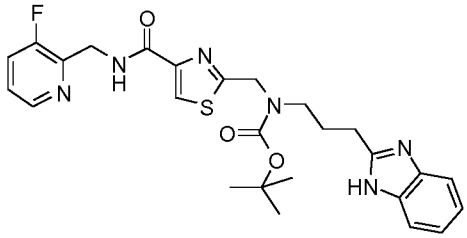


In a similar fashion to general procedure 6, 2-({[2-(1H-1,3-benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylic acid **(124)** (175 mg, 0.36 mmol, 83% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (108 mg, 0.54 mmol), DIPEA (0.25 ml, 1.44 mmol) and HATU (206 mg, 0.54 mmol) in DMF (4 ml) afforded the title compound (81 mg, 44%) as a colourless solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.24 (s, 1H), 8.75 (s, 1H), 8.36 (s, 1H), 8.22 (s, 1H), 7.73 - 7.66 (m, 1H), 7.50 (s, 1H), 7.46 - 7.37 (m, 2H), 7.11 (s, 2H), 4.72 (s, 2H), 4.66 (d, J = 4.4 Hz, 2H), 3.76 (m, 2H), 3.20 - 3.05 (m, 2H), 1.30 (s, 9H)

HPLCMS (Method A): [*m/z*]: 511.10 $[M+H]^+$

Tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate (127)

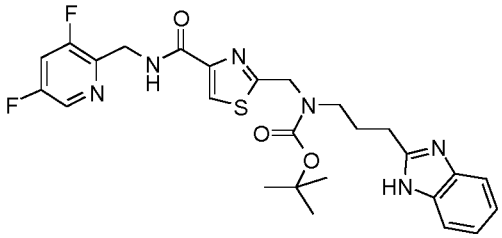


In a similar fashion to general procedure 6, 2-({[3-(1H-1,3-benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylic acid **(125)** (406 mg, 0.51mmol, 52% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (152 mg, 0.76 mmol), DIPEA (0.36 ml, 2.04 mmol) and HATU (291 mg, 0.76 mmol) in DMF (4 ml) afforded the title compound (215 mg, 75%) as a white solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 70-100% EtOAc / heptane).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.68 (t, J = 5.5 Hz, 1H), 8.36 (s, 1H), 8.22 (s, 1H), 7.69 (t, J = 9.3 Hz, 1H), 7.52 - 7.45 (m, 1H), 7.42 - 7.34 (m, 2H), 7.09 (s, 2H), 4.71 (s, 2H), 4.65 (d, J = 5.5 Hz, 2H), 3.41 (s, 2H), 2.81 (t, J = 7.3 Hz, 2H), 2.04 (m, 2H), 1.34 (s, 9H)

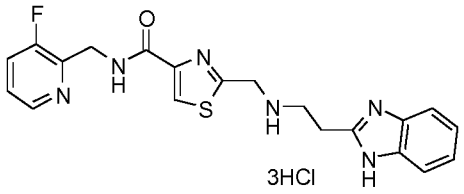
HPLCMS (Method A): [*m/z*]: 525.15 $[M+H]^+$

Tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate (128)



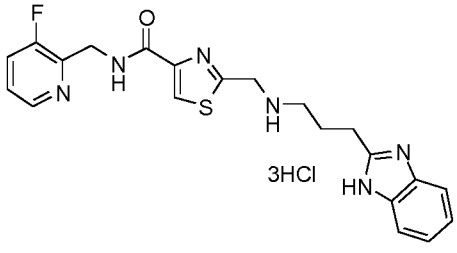
In a similar fashion to general procedure 6, 2-({[3-(1H-1,3-benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}methyl)-1,3-thiazole-4-carboxylic acid **(125)** (0.146 g, 0.351 mmol), (3,5-difluoropyridin-2-yl)methanamine dihydrochloride (0.114 g, 0.526 mmol), DIPEA (0.305 ml, 1.753 mmol) and HATU (0.227 g, 0.526 mmol) in DMF (3 ml) at room temperature for 2 h afforded the title compound (0.071 g, 37 %) as a glassy solid after purification by basic prep-HPLC.
^{1}H NMR (DMSO-d6, 500 MHz): d[ppm]= 12.14 (s, 1H), 8.73 - 8.66 (m, 1H), 8.47 - 8.41 (m, 1H), 8.24 - 8.18 (m, 1H), 7.95 - 7.87 (m, 1H), 7.52 - 7.45 (m, 1H), 7.41 - 7.35 (m, 1H), 7.15 - 7.05 (m, 2H), 4.70 (s, 2H), 4.61 (d, *J* = 5.7 Hz, 2H), 3.45 - 3.38 (m, 2H), 2.85 - 2.77 (m, 2H), 2.07 - 1.99 (m, 2H), 1.34 (s, 9H)
HPLCMS (Method A): [*m/z*]: 543.15 $[M+H]^+$

2-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 118)



In a similar fashion to general procedure 2, tert-butyl N-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate **(126)** (81 mg, 0.159 mmol) and 12M HCl (0. 53 ml) in MeOH (5 ml) at room temperature for 4 d and then at 40°C for 4 h afforded the title compound (49 mg, 58%) as a white solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.81 (s, 1H), 8.41 (s, 1H), 8.36 (dt, J = 4.7, 1.4 Hz, 1H), 7.78 (dd, J = 6.1, 3.1 Hz, 2H), 7.72 (ddd, J = 10.0, 8.4, 1.2 Hz, 1H), 7.53 (dd, J = 6.0, 3.1 Hz, 2H), 7.40 (dd, J = 8.4, 4.3 Hz, 1H), 4.73 (s, 2H), 4.69 (d, J = 5.1 Hz, 2H), 3.79 (br s, 2H), 3.73 (br s, 2H)
HPLCMS (Method D): [*m/z*]: 411.1 $[M+H]^+$

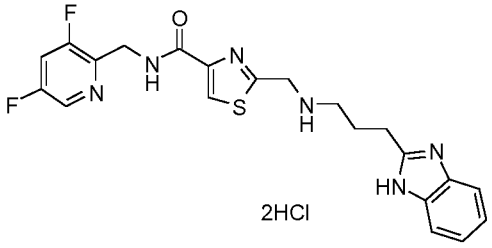
2-({[3-(1H-1,3-Benzodiazol-2-yl)propyl]amino}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 119)



In a similar fashion to general procedure 2, 12M HCl (0. 635ml) was added to a solutionof tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate **(127)** (215 mg, 0.381 mmol) in MeOH (5 ml) and the mixture stirred for 16 h. Further 12M HCl (0. 635ml, 7.623 mmol) was added and the mixture stirred for a further 20 h. The reaction mixture was evaporated *in vacuo* to afford the title compound (139 mg, 68%) as a white solid.

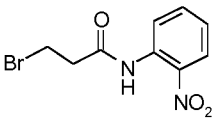
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 9.96 (br s, 1H), 8.78 (br s, 1H), 8.40 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 7.80 - 7.76 (m, 2H), 7.73 (t, J = 8.1 Hz, 1H), 7.55 - 7.51 (m, 2H), 7.44 - 7.39 (m, 1H), 4.70 (d, J = 4.6 Hz, 2H), 4.64 (s, 2H), 3.35 (t, J = 7.2 Hz, 2H), 3.23 (t, J = 7.4 Hz, 2H), 2.39 - 2.33 (m, 2H)
HPLCMS (Method D): [*m/z*]: 425.2 $[M+H]^+$

2-({[3-(1H-1,3-Benzodiazol-2-yl)propyl]amino}methyl)-N-[(3,5-difluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (Example Compound No. 124)



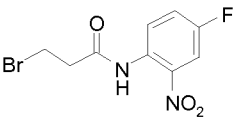
In a similar fashion to general procedure 2, 12M HCl (0.524 ml, 6.28 mmol) was added to a solution tert-butyl tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)methyl]carbamate **(128)** (0.071 g, 0.131 mmol) in MeOH (3 ml) at 45°C for 4 h, to give the title compound (0.036 g, 53 %) as a white solid.
^{1}H NMR (Methanol-d4, 500 MHz): d[ppm]= 8.37 (s, 1H), 8.35 - 8.30 (m, 1H), 7.81 - 7.76 (m, 2H), 7.66 - 7.57 (m, 3H), 4.79 (s, 2H), 4.74 (s, 2H), 3.45 - 3.36 (m, 4H), 2.51 - 2.41 (m, 2H)
HPLCMS (Method D): [*m/z*]: 443.2 $[M+H]^+$

General Scheme 8 above:
General procedure 10: 3-Bromo-N-(2-nitrophenyl)propanamide (129)



3-Bromopropanoyl chloride (1.59 ml, 15.75 mmol) was added dropwise to an ice-cold solution of 2-nitroaniline (2.18 g, 15.75 mmol) and TEA (2.63 ml, 18.9 mmol) in toluene (50 ml) and themixture stirred for 2 h. The reaction mixture was concentrated *in vacuo* and the residue triturated with water (10 ml) to give a brown precipitate which was collected by filtration. Purification by flash column chromatography (eluting with a gradient of 0-10% EtOAc / heptane) afforded the title compound (0.988 g, 23%) as a yellow crystalline solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 10.45 (s, 1H), 8.81 (dd, J = 8.5, 1.2 Hz, 1H), 8.25 (dd, J = 8.5, 1.6 Hz, 1H), 7.78 - 7.61 (m, 1H), 7.24 (ddd, J = 8.5, 7.3, 1.3 Hz, 1H), 3.74 (t, J = 6.5 Hz, 2H), 3.11 (t, J = 6.5 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 272.95 / 274.90 $[M+H]^+$

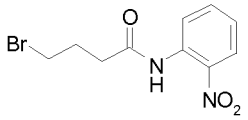
3-Bromo-N-(4-fluoro-2-nitrophenyl)propanamide (130)



In a similar ashion to general procedure 10, 3-bromopropanoyl chloride (2.29 ml, 23.06 mmol), 4-fluoro-2-nitroaniline (3 g, 19.22 mmol) and TEA (3.124 ml, 23.06 mmol) in toluene (35 ml) at room temperature for 40 h afforded the title compound (3.04 g, 42%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 0-40 % EtOAc / heptane).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.38 (s, 1H), 7.91 (dd, J = 8.6, 2.5 Hz, 1H), 7.65 - 7.60 (m, 2H), 3.68 (t, J = 6.4 Hz, 2H), 2.97 (t, J = 6.4 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 290.75 / 292.75 $[M+H]^+$

4-Bromo-N-(2-nitrophenyl)butanamide (131)

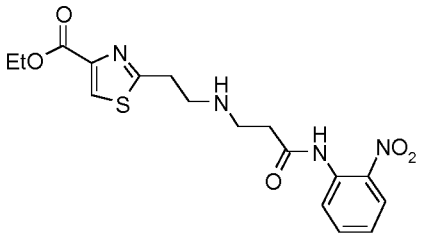


In a similar ashion to general procedure 10, 4-bromobutanoyl chloride (1.56 ml, 13.48 mmol), 2-nitroaniline (1.55 g, 11.24 mmol) and TEA (1.566 ml, 11.2 mmol) in toluene (25 ml) at room temperature for 16 h, gave the title compound (2.35 g, 41%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-40% EtOAc / heptane).

^{1}H NMR (DMSO-d6, 500 MHz): d[ppm]= 10.33 (s, 1H), 7.93 (dd, J = 8.2, 1.4 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.58 (dd, J = 8.1, 1.2 Hz, 1H), 7.38 - 7.34 (m, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.51 (t, J = 6.6 Hz, 2H, obscured by DMSO), 2.13 - 2.06 (m, 2H)

HPLCMS (Method A): [*m/z*]: 288.75 $[M+H]^+$

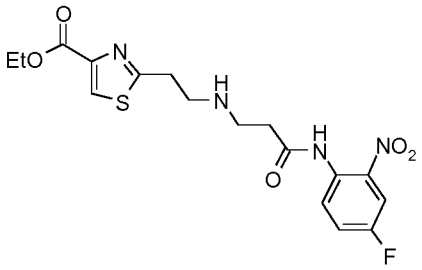
General procedure 11: Ethyl 2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxylate (132)



To a solution of 3-Bromo-N-(2-nitrophenyl)propanamide **(129)** (1.04 g, 3.8 mmol) in DMF (10 ml) was added dropwise over 20 min to a mixture of ethyl 2-(2-aminoethyl)-1,3-thiazole-4-carboxylate hydrochloride (1 g, 3.8 mmol, 90% purity) and Na_2CO_3 (0.48 g, 4.56 mmol) in DMF (30 ml). The reaction mixture was stirred for 16 h at room temperature. Water (10 ml) was added and the mixture extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude title compound (1.5 g, 70%, 70% purity) which was used without purification.

HPLCMS (Method A): [*m/z*]: 393.1 $[M+H]^+$

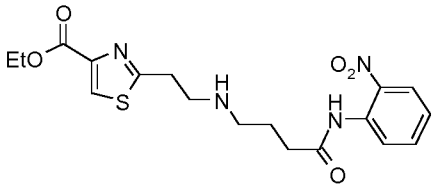
Ethyl 2-[2-({2-[(4-fluoro-2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxylate (133)



In a similar fashion to general procedure 11, 3-bromo-N-(4-fluoro-2-nitrophenyl)propanamide **(130)** (1 g, 2.68 mmol), ethyl 2-(2-aminoethyl)-1,3-thiazole-4-carboxylate hydrochloride (0.634 g, 2.68 mmol) and Na_2CO_3 (0.426 g, 4.02 mmol) in DMF (10 ml) at room temperature for 24 h gave the crude title compound (2.26 g, 80%, 39% purity) which was used without purification.

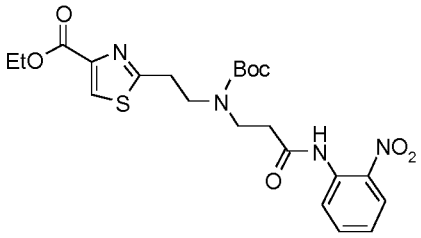
HPLCMS (Method A): [*m/z*]: 411 $[M+H]^+$

Ethyl 2-[2-({3-[(2-nitrophenyl)carbamoyl]propyl}amino)ethyl]-1,3-thiazole-4-carboxylate (134)



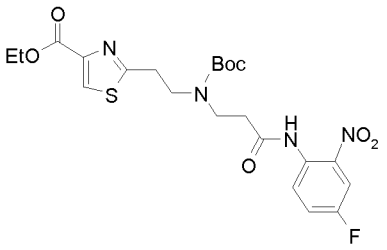
In a similar fashion to general procedure 11, 4-Bromo-N-(2-nitrophenyl)butanamide **(131)** (2.35 g, 4.65 mmol), ethyl 2-(2-aminoethyl)-1,3-thiazole-4-carboxylate hydrochloride (1.10 g, 4.66 mmol), Na_2CO_3 (0.74 g, 6.98 mmol) and DMF (25 ml) at room temperature for 16 h gave the crude title compound (3.0 g, quant.) as yellow oil, which was used in the next setp without purification.
HPLCMS (Method A): [*m/z*]: 407 $[M+H]^+$

Ethyl 2-(2-{[(tert-butoxy)carbonyl]({2-[(2-nitrophenyl)carbamoyl]ethyl})amino}ethyl)-1,3-thiazole-4-carboxylate (135)



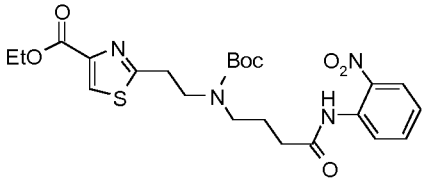
In a similar fashion to general procedure 4, ethyl 2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxylate **(132)** (1.3 g, 1.99 mmol, 60% purity), Boc_2O (477 mg, 2.19 mmol) and TEA (413 µl, 2.9 mmol) in THF (50 ml) were stirred at room temperature for 16 h. Additional Boc_2O (477 mg, 2.19 mmol) and TEA (413 µl, 2.98 mmol) were added and the mixture was stirred for a further 4 h. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in EtOAc (10 ml) and washed with water (3 x 5 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 10-100% EtOAc / heptane) afforded the title compound (132 mg, 12%) as a yellow oil.
HPLCMS (Method A): [*m/z*]: 493.15 $[M+H]^+$

Ethyl 2-(2-{[(tert-butoxy)carbonyl]({2-[(4-fluoro-2-nitrophenyl)carbamoyl]ethyl})amino}ethyl)-1,3-thiazole-4-carboxylate (136)



In a similar fashion to general procedure 4, 2-[2-({2-[(4-fluoro-2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxylate **(133)** (2.26 g, 2.145 mmol), Boc_2O (1.87 g, 8.58 mmol) and TEA (0.848 ml, 6.43 mmol) in THF (60 ml at room temperature for 16 h gave the title compound (0.43 g, 38%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 10-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.30 (s, 1H), 8.41 (s, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.62 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.54 (m, 2H), 3.41 (t, J = 7.1 Hz, 2H), 3.22 (t, J = 7.0 Hz, 2H), 2.58 (m 2H), 1.35–1.27 (m, 12H)
HPLCMS (Method A): [*m/z*]: 511.1 $[M+H]^+$

Ethyl 2-(2-{[(tert-butoxy)carbonyl]({3-[(2-nitrophenyl)carbamoyl]propyl})amino}ethyl)-1,3-thiazole-4-carboxylate (137)

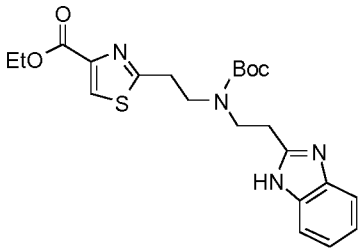


In a similar fashion to general procedure 4, ethyl 2-[2-({3-[(2-nitrophenyl)carbamoyl]propyl}amino)ethyl]-1,3-thiazole-4-carboxylate **(134)** (3.0 g, 5.32 mmol, 72% purity), Boc_2O (2.44 g, 11.17 mmol) and TEA (2.10 ml, 15.96 mmol) in THF (50 ml) were stirred at room temperature for 24 h. additional Boc_2O (2.32 g, 10.64 mmol) and TEA (0.7 ml, 5.32 mmol) were added and the reaction stirred at room temperature for 96 h, to give the title compound (0.287 g, 10%) as a yellow oil after purification by reverse-phase column chromatography (eluting with a gradient of 0-100 % MeCN / water) gave

^{1}H NMR (DMSO-d6, 500 MHz): d[ppm]= 10.23 (s, 1H), 8.40 (s, 1H), 7.93 (dd, J = 8.2, 1.4 Hz, 1H), 7.71 - 7.66 (m, 1H), 7.62 (dd, J = 8.1, 1.4 Hz, 1H), 7.37 - 7.32 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.53 (t, J = 6.9 Hz, 2H), 3.25 - 3.15 (m, 4H), 2.32 (t, J = 7.4 Hz, 2H), 1.81 – 1.72 (m, 2H), 1.40 – 1.29 (br m, 9H), 1.28 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 507.1 $[M+H]^+$

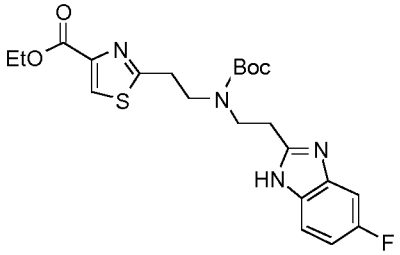
Ethyl 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate (138)



A suspension of ethyl 2-(2-{[(tert-butoxy)carbonyl]({2-[(2-nitrophenyl)carbamoyl]ethyl})amino}ethyl)-1,3-thiazole-4-carboxylate **(135)** (175 mg, 0.36 mmol) and iron powder (238 mg, 4.26 mmol) in AcOH was heated at 80°C for 1 h. The reaction mixture was cooled to room temperature, diluted with DCM (10 ml) and neutralised with sat. $NaHCO_3$. The aqueous phase was extracted with DCM (3 x 10 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo* to afford the title compound (121 mg, 76%) as a pale yellow oil.

HPLCMS (Method A): [*m/z*]: 445.15 $[M+H]^+$

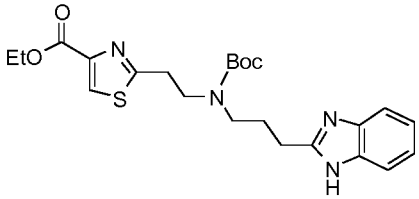
Ethyl 2-(2-{[(tert-butoxy)carbonyl][2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxylate (139)



A suspension of ethyl 2-(2-{[(tert-butoxy)carbonyl]({2-[(4-fluoro-2-nitrophenyl)carbamoyl]ethyl})amino}ethyl)-1,3-thiazole-4-carboxylate **(136)** (0.43 g, 0.825 mmol) and iron powder (0.533 g, 9.905 mmol) in AcOH (40 ml) was heated at 80°C for 2 h. The reaction mixture was cooled to room temperature and neutralised by slow addition sat. Na_2CO_3. The mixture was extracted with

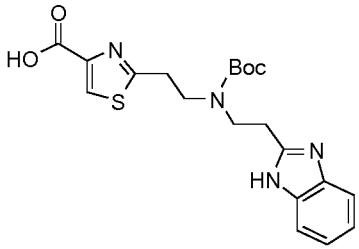
DCM (4 x 40 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford the title compound as an off-white glassy solid (0.445 g, quant).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.34 (s, 1H), 8.40 (s, 1H), 7.27 (s, 2H), 6.96 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.55 (br s, 2H), 3.22 (br s, 2H), 3.00 (br s, 2H), 1.34- 1.20 (m, 12H)
HPLCMS (Method A): [*m/z*]: 463.1 $[M+H]^+$

Ethyl 2-(2-{[3-(1H-1,3-benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate (140)



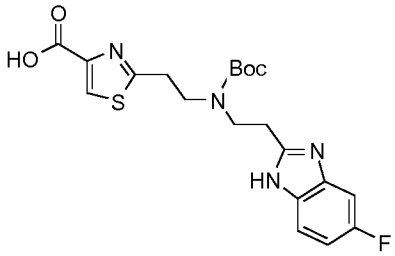
Iron powder (0.368 g, 6.595 mmol) was added to ethyl 2-(2-{[(tert-butoxy)carbonyl]({3-[(2-nitrophenyl)carbamoyl]propyl})amino}ethyl)-1,3-thiazole-4-carboxylate **(137)** (0.287 g, 0.55 mmol, 97% purity) in AcOH (10 ml). The reaction was stirred at 80°C for 1 h. The reaction was allowed to cool to room temperature. Water (50 ml) was added followed by Na_2CO_3 until pH ~9. The aqueous layer was extracted with DCM (4 x 50 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated to give the title compound (0.291 g, quant) as a pale orange oil.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.39 (s, 1H), 7.53- 7.47 (m, 1H), 7.43 - 7.35 (m, 1H), 7.14 - 7.06 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.58 - 3.51 (m, 2H), 3.26 - 3.21 (m, 4H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.01 - 1.91 (m, 2H), 1.30 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 459.1 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid (141)



In a similar fashion to general procedure 5, ethyl 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(138)** (156 mg, 0.35 mmol) and LiOH (33 mg, 1.35 mmol) in THF / water (5 ml / 1 ml) gave the title compound (100 mg, 68%) as a tan solid after acidification with AcOH, extraction with 3:1 THF / EtOAc (3 x 10 ml), drying ($MgSO_4$), filtration and evaporation *in vacuo*.
HPLCMS (Method A): [*m/z*]: 417.1 $[M+H]^+$

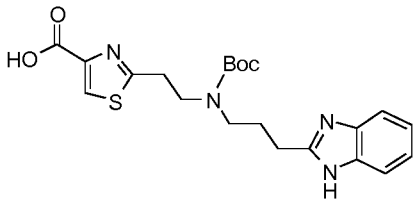
2-(2-{[(Tert-butoxy)carbonyl][2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid (142)



In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl][2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(139)** (380 mg, 0.83 mmol) and LiOH (59 mg, 2.48 mmol) in THF / water (45 ml / 15 ml) afforded the title compound (319 mg, 82%, 92% purity) as a white solid.

HPLCMS (Method A): [*m/z*]: 435.05 $[M+H]^+$

2-(2-{[3-(1H-1,3-Benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid (143)

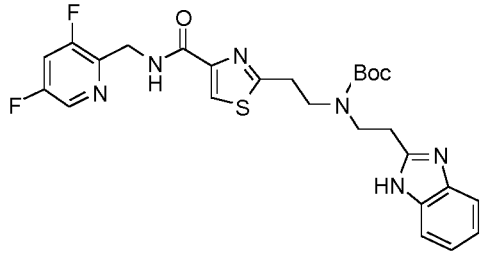


In a similar fashion to general procedure 5, ethyl 2-(2-{[3-(1H-1,3-benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(140)** (291 mg, 0.550 mmol, 87% purity) and LiOH (39 mg, 1.649 mmol) in THF / water (25 ml / 10 ml) at room temperature for 24 h, gave the title compound (219 mg, 72%) as a glassy solid.

1H-NMR (Acetone-d_6, 500 MHz): d[ppm]= 7.87 (s, 1H), 7.06 - 6.96 (m, 2H), 6.70 - 6.63 (m, 2H), 3.90 - 3.85 (m, 2H), 3.10 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 1.57 - 1.49 (m, 2H), 0.85 (s, 9H)

HPLCMS (Method A): [*m/z*]: 431.1 $[M+H]^+$

Tert-butyl N-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (144)

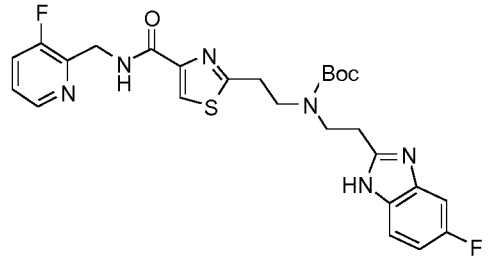


In a similar manner to general procedure 6, 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(141)** (100 mg, 0.24 mmol), (3,5-difluoropyridin-2-yl)methanamine dihydrochloride (78 mg, 0.36 mmol), DIPEA (0.21 ml, 1.2 mmol) and HATU (137 mg, 0.36 mmol) in DMF (3 ml) afforded the title compound (77 mg, 59%) as a white solid after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.30 (br s, 1H), 8.09 (s, 1H), 7.55 (br s, 1H), 7.48 (s, 2H), 7.20 (d, J = 3.3 Hz, 2H), 4.82 (s, 2H), 4.73 (s, 2H), 3.70 (m, 4H), 3.08 (m, 2H), 1.16 (s, 9H)

HPLCMS (Method A): [*m/z*]: 543.15 $[M+H]^+$

Tert-butyl N-[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (145)

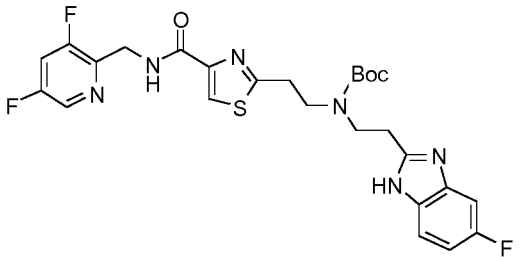


In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl][2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(142)** (160 mg, 0.34 mmol, 92% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (101 mg, 0.51 mmol), DIPEA (0.18 ml, 1.01 mmol) and HATU (192 mg, 0.51 mmol) in DMF (4 ml) afforded the title compound (112 mg, 61%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-50% MeOH / EtOAc).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.33 (br s, 1H), 8.66 (br s, 1H), 8.36 (br s, 1H), 8.17 (br s, 1H), 7.72 - 7.66 (m, 1H), 7.53 - 7.36 (m, 2H), 7.33 - 7.21 (m, 1H), 7.00 - 6.91 (m, 1H), 4.66 (d, J = 4.5 Hz, 2H), 3.63 (t, J = 7.0 Hz, 2H), 3.58 (t, J = 6.9 Hz, 2H), 3.24 (t, J = 6.9 Hz, 2H), 3.02 (m, 2H), 1.35- 1.18 (m, 9H)

HPLCMS (Method A): [*m/z*]: 543.1 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]-N-[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]carbamate (146)

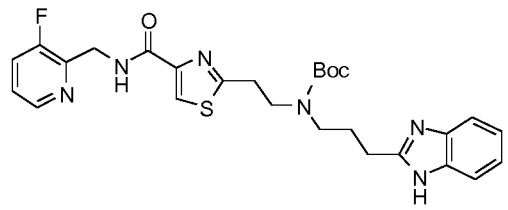


In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl][2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(142)** (12 mg, 0.28 mmol), (3,5-difluoropyridin-2-yl)methanamine dihydrochloride (90 mg, 0.41 mmol), DIPEA (0.24 ml, 1.38 mmol) and HATU (158 mg, 0.41 mmol) in DMF (3 ml) afforded the title compound (72 mg, 47%) as a colourless glassy solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.33 (br s, 1H), 8.68 (br s, 1H), 8.44 (br s, 1H), 8.16 (br s, 1H), 7.90 (d, J = 11.0 Hz, 1H), 7.27 (br s, 2H), 6.96 (br s, 1H), 4.62 (d, J =5.7 Hz, 2H), 3.65 – 3.57 (m, 4H), 3.22 (m, 2H), 3.01 (br s, 2H), 1.24 (m, 9H)

HPLCMS (Method A): [*m/z*]: 561.15 $[M+H]^+$

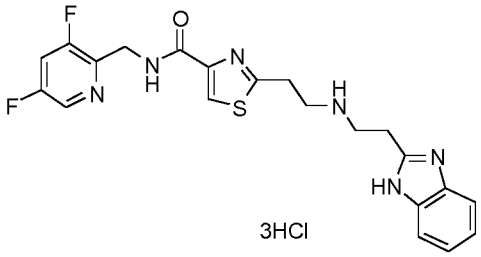
Tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (147)



In a similar fashion to general procedure 6, 2-(2-{[3-(1H-1,3-benzodiazol-2-yl)propyl][(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylic acid **(143)** (219 mg, 0.39 mmol, 78% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (118 mg, 0.59 mmol), DIPEA (0.346 ml, 1.98

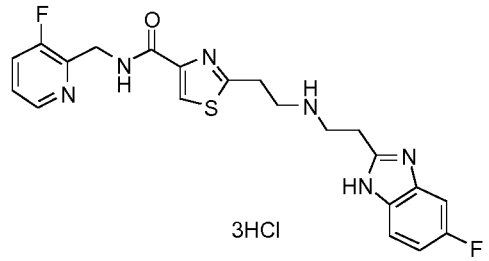
mmol) and HATU (226 mg, 0.59 mmol) in DMF (3 ml) at room temperature for 2 h gave the title compound (111 mg, 52%) as a colourless oil after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.66 (br s, 1H), 8.36 (d, J = 4.3 Hz, 1H), 8.16 (s, 1H), 7.73 - 7.63 (m, 1H), 7.52 - 7.45 (m, 1H), 7.45 - 7.34 (m, 2H), 7.18 - 7.01 (m, 2H), 4.65 (d, J = 5.5 Hz, 2H), 3.59 (t, J = 7.0 Hz, 2H), 3.29 - 3.23 (m, 4H), 2.78 (t, J = 7.5 Hz, 2H), 2.05 - 1.92 (m, 2H), 1.30 (s, 9H)
HPLCMS (Method A): [*m/z*]: 539.15 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3,5-difluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 116)



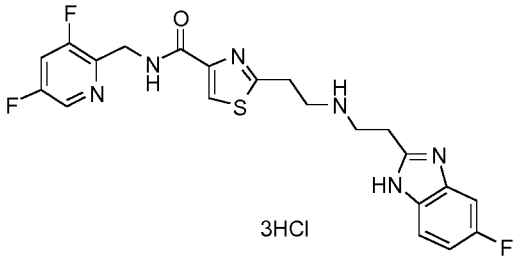
In a similar fashion to general procedure 2, 12M HCl (0.378ml, 4.541mmol) and tert-butyl N-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(144)** (77 mg, 0.142 mmol) in MeOH (3 ml) at room temperature for 5 h and at 40°C for 20 h gave the title compound (60 mg, 73%) as a yellow solid.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.29 (d, J = 2.3 Hz, 1H), 8.23 (s, 1H), 7.79 (dd, J = 6.1, 3.2 Hz, 2H), 7.64 - 7.59 (m, 3H), 4.77 (s, 2H), 3.78 (s, 4H), 3.72 (t, J = 6.4 Hz, 2H), 3.59 (d, J = 5.9 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 443.1 $[M+H]^+$

2-(2-{[2-(5-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 120)



In a similar fashion to general procedure 2, 12 M HCl (0.344 ml, 4.128 mmol) and N-[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(145)** (112 mg, 0.206 mmol) in MeOH (4 ml) at room temperature for 16 h, following the addition of 12M HCl (0.344 ml, 4.128 mmol) at room temperature for further 20 h and at 40°C for 3 h, gave the title compound (80 mg, 67 %) as a white solid.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.57 (d, J = 5.4 Hz, 1H), 8.28 (t, J = 8.8 Hz, 1H), 8.25 (s, 1H), 7.89 (dt, J = 9.5, 5.0 Hz, 1H), 7.81 (dd, J = 9.0, 4.3 Hz, 1H), 7.58 (dd, J = 8.1, 2.3 Hz, 1H), 7.42 (td, J = 9.3, 2.4 Hz, 1H), 4.97 (s, 2H), 3.85 - 3.79 (m, 4H), 3.75 (t, J = 6.3 Hz, 2H), 3.62 (t, J = 6.3 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 443.2 $[M+H]^+$

N-[(3,5-Difluoropyridin-2-yl)methyl]-2-(2-{[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 123)

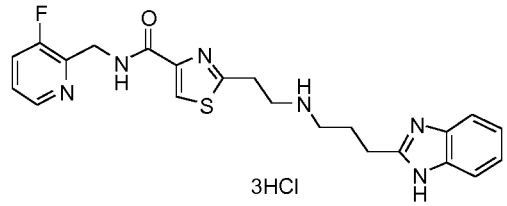


In a similar fashion to general procedure 2, 12 M HCl (0257 ml, 3.08 mmol) and tert-butyl N-[2-(4-{[(3,5-difluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]-N-[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]carbamate **(146)** (72 mg, 0.128 mmol) in MeOH (3 ml) at room temperature for 16 h, following additional 12M HCl (0.257 ml, 3.08 mmol) and the mixture stirred at 45°C for 4 h, gave the title compound (28 mg, 38%) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.28 (d, J = 2.3 Hz, 1H), 8.23 (s, 1H), 7.79 (dd, J = 9.0, 4.3 Hz, 1H), 7.60 (m, 1H), 7.56 (dd, J = 8.1, 2.3 Hz, 1H), 7.40 (td, J = 9.3, 2.4 Hz, 1H), 4.76 (s, 2H), 3.77 (m, 4H), 3.73 (t, J = 6.4 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 461.2 $[M+H]^+$

2-(2-{[3-(1H-1,3-Benzodiazol-2-yl)propyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 125)

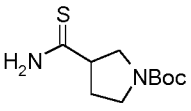


In a similar fashion to general procedure 2, 12M HCl (0.405 ml, 4.864 mmol) and tert-butyl N-[3-(1H-1,3-benzodiazol-2-yl)propyl]-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(147)** (131 mg, 0.243 mmol) in MeOH (3 ml) at 40°C for 16 h, gave the title compound (48 mg, 35 %) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.48 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 8.07 - 8.00 (m, 1H), 7.80 - 7.76 (m, 2H), 7.74 - 7.66 (m, 1H), 7.63 - 7.58 (m, 2H), 4.91 (s, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.57 (t, J = 6.6 Hz, 2H), 3.41 - 3.32 (m, 4H), 2.49 - 2.40 (m, 2H)

HPLCMS (Method D): [*m/z*]: 439.2 $[M+H]^+$

General procedure 11: Tert-butyl 3-carbamothioylpyrrolidine-1-carboxylate (148)

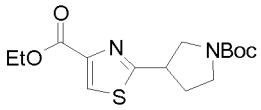


Lawesson reagent (0.42 g, 1.03 mmol) was added in one portion to tert-butyl 3-carbamoylpyrrolidine-1-carboxylate (0.4 g, 1.87 mmol) in DCM (5 ml) and the reaction was stirred at room temperature for 2 h. The reaction mixture was directly loaded onto silica and purified by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) to give the title compound (0.36 g, 79%) as an off-white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.46 (d, J = 8.6 Hz, 1H), 7.01 (br s , 1H), 3.75 - 3.66 (m, 1H), 3.65 - 3.54 (m, 1H), 3.59 (dd, 11 and 8.1 Hz, 1H), 3.37 (q, J = 8.7 Hz, 1H), 3.27 (p, J = 7.8 Hz, 1H), 2.24- 2.12 (m, 3H), 1.46 (s, 9H)

HPLCMS (Method A): [*m/z*]: 252.95 $[M+Na]^+$

Ethyl 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}-1,3-thiazole-4-carboxylate (149)

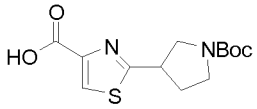


In a similar fashion to general procedure 1, ethyl 3-bromo-2-oxopropanoate (2.5 ml, 19.75 mmol), tert-butyl 3-carbamothioylpyrrolidine-1-carboxylate **(148)** (3.96 g, 17.19 mmol) and $CaCO_3$ (0.87 g, 8.73 mmol) in EtOH (50 ml) at room temperature for 21 h, gave the title compound (2.84 g, 51.9%) as a yellow oil which solidified on standing, after purification by flash column chromatography (eluting with a gradient of 0-70% EtOAc / heptane).

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.08 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.96 - 3.76 (m, 2H), 3.73 - 3.51 (m, 2H), 3.51 - 3.35 (m, 1H), 2.35 - 2.44 (m, 1H), 2.28 - 2.14 (m, 1H), 1.46 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 349.05 $[M+Na]^+$

2-{1-[(Tert-butoxy)carbonyl]pyrrolidin-3-yl}-1,3-thiazole-4-carboxylic acid (150)

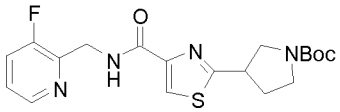


In a similar fashion to general procedure 5, LiOH (1.04 g, 43.5 mmol) and ethyl 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}-1,3-thiazole-4-carboxylate **(149)** (2.84 g, 8.7 mmol) in THF (30 ml) / water (30 ml) gave the title compound (2.48 g, 93.6%) as a yellow solid. Compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 12.94 (s, 1H), 8.37 (s, 1H), 3.94 - 3.78 (m, 1H), 3.78 - 3.68 (m, 1H), 3.49 - 3.39 (m, 2H), 2.44 - 2.24 (m, 1H), 2.19 - 1.98 (m, 1H), 1.41 (s, 9H). A CH signal was obscured by the H_2O peak

HPLCMS (Method A): [*m/z*]: 321.05 $[M+Na]^+$ and 297.1 $[M+H]^+$

Tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate (151)

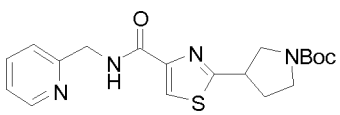


In a similar fashion using general procedure 6, 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}-1,3-thiazole-4-carboxylic acid **(150)** (1 g, 3.35 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (1 g, 5.03 mmol), DIPEA (1.93 ml, 11.06 mmol), HATU (1.9 g, 5.03 mmol) in DMF (14 ml) gave the title compound (1.27 g, 86%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) followed by re-purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.71 (t, J = 5.6 Hz, 1H), 8.38 (dt, J = 4.7, 1.4 Hz, 1H), 8.20 (s, 1H), 7.70 (ddd, J = 10.2, 8.3, 1.3 Hz, 1H), 7.40 (dt, J = 8.5, 4.4 Hz, 1H), 4.66 (dd, J = 5.7, 1.5 Hz, 2H), 3.94 – 3.81 (m, 1H), 3.82 - 3.66 (m, 1H), 3.58 – 3.40 (m, 2H), 2.43 – 2.26 (m, 1H), 2.25 - 2.04 (m, 1H), 1.40 (s, 9H). A CH signal was obscured by the H_2O peak

HPLCMS (Method A): [*m/z*]: 407.1 $[M+H]^+$

Tert-butyl 3-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}pyrrolidine-1-carboxylate (152)

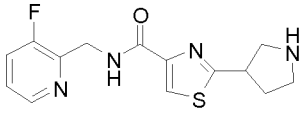


In a similar fashion using general procedure 6, 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}-1,3-thiazole-4-carboxylic acid **(150)** (1 g, 3.35 mmol), pyridin-2-ylmethanamine (0.52 ml, 5.03 mmol), DIPEA (1.17 ml, 6.7 mmol) and HATU (1.9 g, 5.03 mmol) in DMF (14 ml) gave the title compound (1.54 g, 100%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.90 (s, 1H), 8.52 (d, J = 4.0 Hz, 1H), 8.22 (s, 1H), 7.76 (td, J = 7.7, 1.8 Hz, 1H), 7.36 - 7.21 (m, 2H), 4.58 (d, J = 6.0 Hz, 2H), 3.92 - 3.82 (m, 1H), 3.84 - 3.71 (m, 1H), 3.68 - 3.42 (m, 3H), 2.34 – 2.25 (m, 1H), 2.27 - 2.11 (m, 1H)

HPLCMS (Method A): [*m/z*]: 389.15 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-2-(pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide dihydrochloride (153)



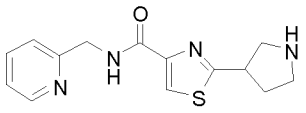
2HCl

In a similar fashion using general procedure 2, 12M HCl (6 ml) and tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)pyrrolidine-1-carboxylate **(151)** (1.27 g, 2.87 mmol) in MeOH (25 ml) at 40°C for 4 h gave the title compound (1.11 g, 96.7%) as a cream foam. Compound was used in the next step without further purification.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.58 (dd, J = 5.4, 1.2 Hz, 1H), 8.28 - 8.18 (m, 2H), 7.87 (dt, J = 8.6, 4.8 Hz, 1H), 4.94 (d, J = 1.3 Hz, 2H), 4.25 - 4.11 (m, 1H), 3.82 (dd, J = 11.8, 4.6 Hz, 1H), 3.72 - 3.43 (m, 3H), 2.67 - 2.46 (m, 1H), 2.39 - 2.23 (m, 1H)

HPLCMS (Method A): [*m/z*]: 307.05 $[M+H]^+$

N-(Pyridin-2-ylmethyl)-2-(pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide dihydrochloride (154)



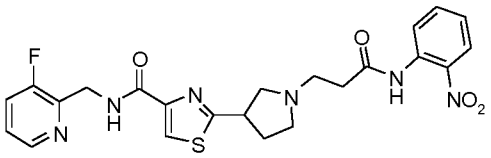
2HCl

In a similar fashion using general procedure 2, 12M HCl (7 ml) and and tert-butyl 3-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}pyrrolidine-1-carboxylate **(152)** (1.54 g, 3.35 mmol) in MeOH (30 ml) at 40°C for 4 h gave the title compound (1.42 g, 99%) as a pale brown foam. Compound was used in the next step without further purification.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.77 (d, J = 5.9 Hz, 1H), 8.65 - 8.54 (m, 1H), 8.25 (s, 1H), 8.12 (d, J = 8.1 Hz, 1H), 7.99 (t, J = 6.8 Hz, 1H), 4.96 (s, 2H), 4.17 (ddd, J = 11.5, 7.3, 4.3 Hz, 1H), 3.86 (dd, J = 11.9, 4.2 Hz, 1H), 3.79 - 3.41 (m, 3H), 2.56 (dq, J = 13.4, 8.3 Hz, 1H), 2.41 - 2.21 (m, 1H)

HPLCMS (Method A): [*m/z*]: 289.05 $[M-H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-2-(1-{2-[(2-nitrophenyl)carbamoyl]ethyl}pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide (155)



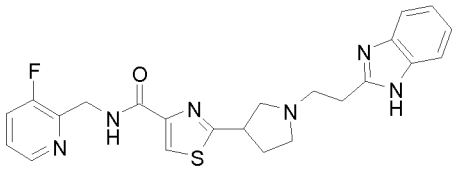
In a similar fashion to general procedure 8, N-[(3-fluoropyridin-2-yl)methyl]-2-(pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide dihydrochloride **(153)** (1.11 g, 2.78 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (0.59 g,

3.06 mmol), DBU (1.41 ml, 9.45 mmol) in MeCN (20 ml) at room temperature for 19 h, gave the title compound (1.53 g, 99%) as a yellow oil after work up.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.69 (s, 1H), 8.67 (t, J = 5.7 Hz, 1H), 8.38 (dt, J = 4.6, 1.4 Hz, 1H), 8.11 (s, 1H), 7.96 (dd, J = 8.2, 1.5 Hz, 1H), 7.79 (dd, J = 8.2, 1.2 Hz, 1H), 7.73- 7.67 (m, 2H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.33 (ddd, J = 8.5, 7.4, 1.4 Hz, 1H), 4.63 (d, J = 4.6 Hz, 2H), 3.87 - 3.77 (m, 1H), 2.99 (dd, J = 9.2, 7.4 Hz, 1H), 2.88 - 2.74 (m, 4H), 2.70 - 2.62 (m, 1H), 2.57 (td, J = 6.7, 1.9 Hz, 2H), 2.43 - 2.34 (m, 1H), 2.08 - 1.99 (m, 1H)

HPLCMS (Method A): [*m/z*]: 499.1 $[M+H]^+$

Tert-butyl 3-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}pyrrolidine-1-carboxylate (Example Compound No. 214)

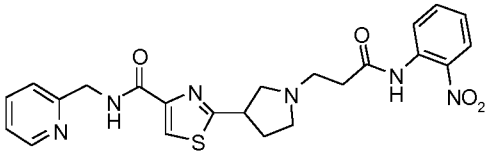


In a similar fashion to general procedure 8, N-[(3-fluoropyridin-2-yl)methyl]-2-(1-{2-[(2-nitrophenyl)carbamoyl]ethyl}pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide **(155)** (1.53 g, 2.78 mmol), AcOH (15 ml) and iron powder (0.62 g, 11.11 mmol) at 80°C for 2 h, gave the title compound (94 mg, 8%) as a pale brown solid after purification by flash column chromatography (KP-NH, eluting with a grading of 0-25% MeOH / DCM) gave a residue (207 mg) which was re-purified by flash column chromatography (KP-NH, eluting with a gradient of 0-3% MeOH / DCM).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.33 (d, J = 4.7 Hz, 1H), 7.94 (s, 1H),7.58 (app t, J = 9.1 Hz, 1H), 7.47 (br s, 2H), 7.40 - 7.32 (m, 1H), 7.24 - 7.16 (m, 2H), 4.75 (d, J = 1.4 Hz, 2H), 3.87 - 3.80 (m, 1H), 3.17 - 3.11 (m, 2H), 3.11 - 2.96 (m, 5H), 2.78 - 2.69 (m, 1H), 2.48 - 2.38 (m, 1H), 2.18 - 2.04 (m, 1H)

HPLCMS (Method C): [*m/z*]: 451.1 $[M+H]^+$

2-(1-{2-[(2-Nitrophenyl)carbamoyl]ethyl}pyrrolidin-3-yl)-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide (156)

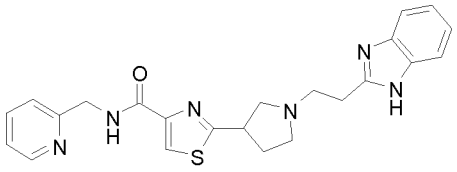


In a similar fashion to general procedure 8, DBU (1.52 ml, 10.19 mmol), N-(pyridin-2-ylmethyl)-2-(pyrrolidin-3-yl)-1,3-thiazole-4-carboxamide dihydrochloride **(154)** (84.6%, 1.28 g, 3.0 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (0.63 g, 3.3 mmol) in MeCN (25 ml) room temperature for 19 h gave the title compound (1.43 g, 99%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-12% MeOH / DCM).

^{1}H NMR (DMSO-d6, 500 MHz): d[ppm]= 10.67 (s, 1H), 8.83 (t, J = 6.0 Hz, 1H), 8.51 (d, J = 4.2 Hz, 1H), 8.12 (s, 1H), 7.96 (dd, J = 8.2, 1.4 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.74 (td, J= 7.7, 1.8 Hz, 1H), 7.69 (td, J = 8.5, 8.0, 1.5 Hz, 1H), 7.36 - 7.24 (m, 3H), 4.55 (d, J = 6.1 Hz, 2H), 3.87 - 3.78 (m, 1H), 3.04 - 2.98 (m, 1H), 2.89 - 2.74 (m, 4H), 2.71 - 2.65 (m, 1H), 2.57 (td, J = 6.7, 1.7 Hz, 2H), 2.44 - 2.33 (m, 1H), 2.09 - 2.01 (m, 1H)

HPLCMS (Method A): [*m/z*]: 481.35 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]pyrrolidin-3-yl}-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 215)



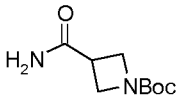
In a similar fashion to general procedure 8, 2-(1-{2-[(2-nitrophenyl)carbamoyl]ethyl}pyrrolidin-3-yl)-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide **(156)** (1.43 g, 2.77 mmol) and iron powder (0.62 g, 11.07 mmol) in AcOH (15 ml) at 80°C for 2 h, gave the title compound (116 mg, 10%) as an off-white solid after purification by flash column chromatography (x 3) (eluting with a gradient of 0-40% MeOH / DCM followed gradient of 0-3% MeOH / DCM and then a gradient of 0-10% MeOH / DCM).

1H-NMR (Methanol-d4, 500 MHz) d[ppm]= 8.48 (d, J = 4.4 Hz, 1H), 7.95 (s, 1H), 7.79 (app t, J = 7.1Hz, 1H), 7.48 (s, 2H), 7.39 (d, J = 7.8 Hz, 1H), 7.36 - 7.26 (m, 1H), 7.25 - 7.12 (m, 2H), 4.67 (s, 2H), 3.89 - 3.78 (m, 1H), 3.18 - 3.11 (m, 2H), 3.11 - 2.96 (m, 5H), 2.73 (q, J = 8.6 Hz, 1H), 2.49 - 2.39 (m, 1H), 2.19-2.06 (m,1H)

HPLCMS (Method C): [m/z]: 433.1 $[M+H]^+$

General Scheme 9 above:

General procedure 12: Tert-butyl 3-carbamoylazetidine-1-carboxylate (157)

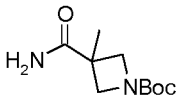


1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (4.96 g, 24.65 mmol) and TEA (5.84 ml, 42.0 mmol) were dissolved in THF (60 ml) and cooled to -20°C. Isobutyl chloroformate (4.8 ml, 37.0 mmol) was added slowly and the reaction mixture stirred at <-10°C for 15 min. 28% aqueous ammonia (7.46 ml, 394 mmol) was added and the mixture allowed to warm to room temperature and stirred for 1 h. Thereaction mixture was quenched with sat. $NaHCO_3$(aq) and extracted with DCM (3 x 100 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated in *vacuo*. Purification by flash chromatography using a gradient elution of 20-100% EtOAc / heptane followed by 1-4% MeOH / EtOAc afforded the title compound (3.99 g, 81%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.47 (s, 2H), 4.22 - 4.01 (m, 4H), 3.34 - 3.15 (m, 1H), 1.46 (s, 9H)

HPLCMS (Method A): [*m/z*]: 222.95 $[M+Na]^+$

Tert-butyl 3-carbamoyl-3-methylazetidine-1-carboxylate (158)

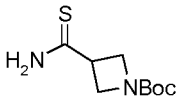


In a similar fashion to general procedure 12, 1-[(tert-butoxy)carbonyl]-3-methylazetidine-3-carboxylic acid (110 mg, 0.51 mmol), TEA (90 mg, 0.87 mmol), isobutyl chloroformate (0.1 ml, 0.77 mmol) and NH_3 (28% aqueous solution, 0.15 ml, 10 mmol) in THF (10 ml) gave the title compound (102 mg, 93%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 5.63 (s, 1H), 5.37 (s, 1H), 4.21 (d, J = 8.4 Hz, 2H), 3.72 (d, J = 8.4 Hz, 2H), 1.58 (s, 3H), 1.47 (s, 9H)

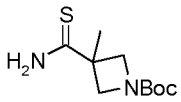
HPLCMS (Method A): [*m/z*]: 237 $[M+Na]^+$

Tert-butyl 3-carbamothioylazetidine-1-carboxylate (159)



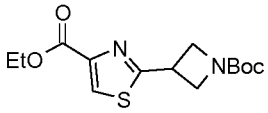
In a similar fashion to general procedure 11, Lawesson reagent (4.43 g, 11.0 mmol), tert-butyl 3-carbamoylazetidine-1-carboxylate **(157)** (3.99 g, 19.9 mmol) in DCM (60 ml) at room temperature for 30 min gave the title compound (4.47 g) as a pale yellow residue after being flushed through a plug of silica using a gradient elution of 10-80% EtOAc / heptane.
HPLCMS (Method A): [*m/z*]: 238.9 $[M+Na]^+$

Tert-butyl 3-carbamothioyl-3-methylazetidine-1-carboxylate (160)



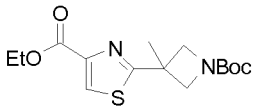
In a similar fashion to general procedure 11, tert-butyl 3-carbamoyl-3-methylazetidine-1-carboxylate **(158)** (1.0 g, 4.67 mmol) and Lawesson reagent (1.04 g, 3.0 mmol) in DCM (30 ml) gave the title compound (1.07 g) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.47 (s, 1H), 6.88 (s, 1H), 4.33 (d, J = 8.3 Hz, 2H), 3.81 (d, J = 8.3 Hz, 2H), 1.72 (s, 3H), 1.47 (s, 9H)
HPLCMS (Method A): [*m/z*]: 253.05 $[M+Na]^+$

Ethyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylate (161)



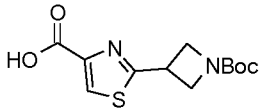
In a similar fashion to general procedure 1, tert-butyl 3-carbamothioylazetidine-1-carboxylate **(159)** (4.47 g, 20.67 mmol), ethyl 3-bromo-2-oxopropanoate (2.85 ml, 22.73 mmol) and calcium carbonate (1.12 g, 11.0 mmol) in EtOH (40 ml) afforded the title compound (3.54 g, 54%) as a yellow oil after purification by flash chromatography using a gradient elution from 10-50% EtOAc / heptane.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.49 (s, 1H), 4.37 - 4.23 (m, 5H), 4.00 (m, 2H), 1.41 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 335 $[M+Na]^+$

Ethyl 2-{1-[(tert-butoxy)carbonyl]-3-methylazetidin-3-yl}-1,3-thiazole-4-carboxylate (162)



In a similar fashion to general procedure 1, tert-butyl 3-carbamothioyl-3-methylazetidine-1-carboxylate **(160)** (0.82 g, 3.56 mmol), ethyl 3-bromo-2-oxopropanoate (0.49 ml, 4.0 mmol) and calcium carbonate (0.2 g, 2.0 mmol) in EtOH (20 ml) gave the title compound (1.0 g) as a pale yellow oil.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.14 (s, 1H), 4.44 (q, J = 7.1 Hz, 2H), 4.39 (d, J = 8.0 Hz, 2H), 3.98 (d, J = 8.0 Hz, 2H), 1.83 (s, 3H), 1.48 (s, 9H), 1.43 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 349.15 $[M+Na]^+$

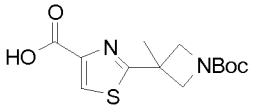
2-{1-[(Tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylic acid (163)



In a similar fashion to general procedure 5, ethyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylate **(161)** (2.52 g, 7.91 mmol) and LiOH (0.57 g, 23.72 mmol) in THF (40 ml) and water (40 ml) afforded the title compound (2.23 g, 87% purity, 86%) as an orange solid.

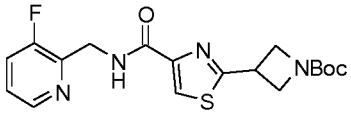
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 13.03 (s, 1H), 8.40 (s, 1H), 4.31 - 4.23 (m, 2H), 4.23 - 4.17 (m, 1H), 4.05 - 3.93 (m, 2H), 1.40 (s, 9H)
HPLCMS (Method A): [*m/z*]: 306.85 $[M+Na]^+$

2-{1-[(Tert-butoxy)carbonyl]-3-methylazetidin-3-yl}-1,3-thiazole-4-carboxylic acid (164)



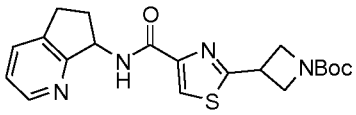
In a similar fashion to general procedure 5, ethyl 2-{1-[(tert-butoxy)carbonyl]-3-methylazetidin-3-yl}-1,3-thiazole-4-carboxylate **(162)** (1.0 g, 3.06 mmol) and LiOH (0.22 g, 10.0 mmol) in THF (30 ml) and water (15 ml) gave the title compound (853 mg, 93%) as a pale yellow foam.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.44 (s, 1H), 4.16 (d, J = 8.2 Hz, 2H), 3.90 (d, J = 8.2 Hz, 2H), 1.72 (s, 3H), 1.41 (s, 9H)
HPLCMS (Method A): [*m/z*]: 321.05 $[M+Na]^+$

Tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate (165)



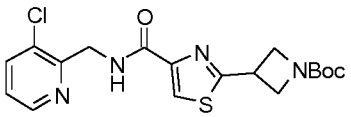
In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylic acid **(163)** (87%, 2.23 g, 6.69 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (1.6 g, 8.03 mmol), DIPEA (4.66 ml, 26.77 mmol) and HATU (3.05 g, 8.03 mmol) in DCM (40 ml) afforded the title compound (2.51 g, 82% purity, 79%) as an orange oil after purification by flash column chromatography using an elution gradient 20-100% EtOAc / heptane.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.79 (t, J = 5.7 Hz, 1H), 8.38 (dt, J = 4.6, 1.4 Hz, 1H), 8.24 (s, 1H), 7.76 - 7.62 (m, 1H), 7.46 - 7.35 (m, 1H), 4.66 (dd, J = 5.7, 1.5 Hz, 2H), 4.34 - 4.17 (m, 3H), 4.16 - 4.05 (m, 2H), 1.39 (s, 9H)
HPLCMS (Method A): [*m/z*]: 393 $[M+H]^+$

Tert-butyl 3-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1,3-thiazol-2-yl]azetidine-1-carboxylate (166)



In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylic acid **(163)** (300 mg, 1.06 mmol), 5H,6H,7H-cyclopenta[b]pyridin-7-amine dihydrochloride (284 mg, 1.37 mmol), DIPEA (0.61 ml, 3.5 mmol) and HATU (0.52 g, 1.4 mmol) in DCM (20 ml) afforded the crude title compound (1.32 g, 30% purity, 94%) which was used into the next step without purification.
HPLCMS (Method A): [*m/z*]: 401.1 $[M+H]^+$

Tert-butyl 3-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate (167)

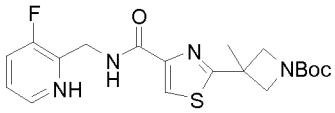


In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylic acid **(163)** (364 mg, 1.28 mmol), (3-chloropyridin-2-yl)methanamine dihydrochloride (359 mg, 1.66 mmol), DIPEA (0.74 ml, 4.2 mmol) and HATU (0.63 g, 1.7 mmol) in DCM (20 ml) afforded the title compound (493 mg, 94%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.79 (t, J = 5.5 Hz, 1H), 8.51 (dd, J = 4.7, 1.4 Hz, 1H), 8.27 (s, 1H), 7.96 (dd, J = 8.1, 1.4 Hz, 1H), 7.39 (dd, J = 8.1, 4.7 Hz, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.38- 4.18 (m, 3H), 4.09 (q, J = 3.9 Hz, 2H), 1.41 (s, 9H)

HPLCMS (Method A): [*m/z*]: 409.05 $[M+H]^+$

Tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-3-methylazetidine-1-carboxylate (168)

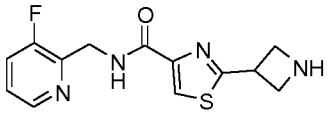


In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]-3-methylazetidin-3-yl}-1,3-thiazole-4-carboxylic acid **(164)** (546 mg, 1.83 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (400 mg, 2.01 mmol), DIPEA (1.05 ml, 6.0 mmol) and HATU (830 mg, 2.0 mmol) in DCM (20 ml) gave the crude title compound (824 mg) as a pale yellow oil. The crude material was used in the next step without further purification.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.38 - 8.33 (m, 1H), 8.28 (s, 1H), 8.02 (s, 1H), 7.37 - 7.31 (m, 1H), 7.23 - 7.17 (m, 1H), 4.81 - 4.76 (m, 2H), 4.30 (d, J = 7.5 Hz, 2H), 3.88 (d, J = 7.5 Hz, 2H), 1.52 (s, 3H), 1.40 (s, 9H)

HPLCMS (Method A): [*m/z*]: 407.2 $[M+H]^+$

2-(Azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (169)



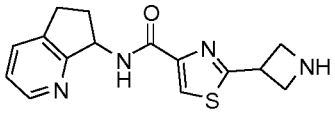
2HCl

In a similar fashion to general procedure 4, tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate **(165)** (82%, 2.51 g, 5.26 mmol) and 12 M HCl (8.8 ml) in MeOH (25 ml) afforded the title compound (2.26 g, 85% purity, quant.) as a light brown solid.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.56 (d, J = 5.2 Hz, 1H), 8.27 (s, 1H), 8.24 - 8.07 (m, 1H), 7.87 - 7.73 (m, 1H), 4.96 - 4.91 (m, 2H), 4.57 - 4.41 (m, 5H)

HPLCMS (Method A): [*m/z*]: 292.95 $[M+H]^+$

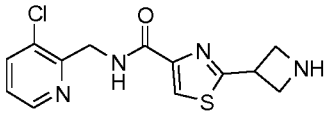
2-(Azetidin-3-yl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1,3-thiazole-4-carboxamide (170)



In a similar fashion to general procedure 4, crude tert-butyl 3-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1,3-thiazol-2-yl]azetidine-1-carboxylate **(166)** (1.32 g, 30% purity, 1.06 mmol) and 12 M HCl (1 ml) in MeOH (10 ml) afforded the title compound (322 mg, quant.) as a white solid after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.

HPLCMS (Method A): [*m/z*]: 300.95 $[M+H]^+$

2-(Azetidin-3-yl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (171)

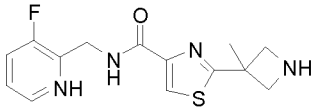


In a similar fashion to general procedure 4, tert-butyl 3-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate **(167)** (423 mg, 1.03 mmol) and 12 M HCl (2 ml) in MeOH (30 ml) afforded the title compound (330 mg, 99%) as a white solid after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.71 (t, J = 5.5 Hz, 1H), 8.52 (dd, J = 4.7, 1.4 Hz, 1H), 8.24 (s, 1H), 7.96 (dd, J = 8.0, 1.4 Hz, 1H), 7.39 (dd, J = 8.0, 4.7 Hz, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.24 (m, 1H), 3.92 – 3.87 (m, 2H), 3.76 – 3.73 (m, 2H)

HPLCMS (Method A): [*m/z*]: 308.95 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-2-(3-methylazetidin-3-yl)-1,3-thiazole-4-carboxamide (172)

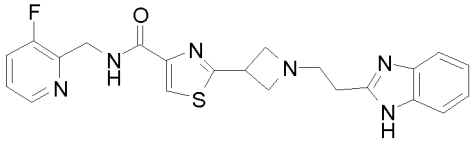


In a similar fashion to general procedure 4, tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-3-methylazetidine-1-carboxylate **(168)** (824 mg, 2.03 mmol) and 12 M HCl (2 ml) in MeOH (20ml) gave the title compound (476 mg, 74%) after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.71 (t, J = 5.7 Hz, 1H), 8.39 (dt, J = 4.6, 1.3 Hz, 1H), 8.21 (s, 1H), 7.71 (ddd, J = 10.0, 8.3, 1.3 Hz, 1H), 7.46 - 7.36 (m, 1H), 4.68 (m, 2H), 3.85 (d, J = 7.5 Hz, 2H), 3.52 (d, J = 7.5 Hz, 2H), 1.72 (s, 3H)

HPLCMS (Method A): [*m/z*]: 307.20 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 193)

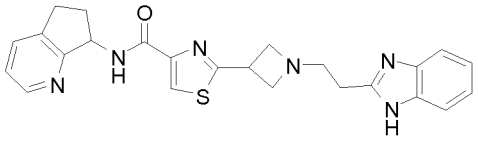


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(169)** (85%, 2.26 g, 5.26 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (1.21 g, 6.31 mmol) and DBU (2.35 ml, 15.77 mmol) in MeCN (30 ml) afforded a crude intermediate which was further reacted with iron powder (0.51 g, 9.0 mmol) and AcOH (5 ml) to afford the title compound (122 mg, 7%) as a cream solid after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.33 (dt, J = 4.7, 1.3 Hz, 1H), 8.12 (s, 1H), 7.62 - 7.56 (m, 1H), 7.53 - 7.47 (m, 2H), 7.39 - 7.34 (m, 1H), 7.22 - 7.17 (m, 2H), 4.79 (d, J = 1.7 Hz, 2H), 4.11 - 4.03 (m, 1H), 3.80 (t, J = 7.9 Hz, 2H), 3.55 - 3.50 (m, 2H), 3.07 - 3.02 (m, 2H), 3.01 - 2.96 (m, 2H)

HPLCMS (Method G): [*m/z*]: 437 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1,3-thiazole-4-carboxamide (Example Compound No. 194)

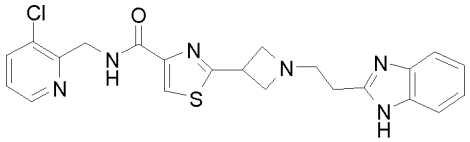


In a similar manner to general procedure 8, 2-(azetidin-3-yl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1,3-thiazole-4-carboxamide **(170)** (322 mg, 1.07 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (227 mg, 1.18 mmol) and DBU (0.21 ml, 1.4 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (0.15 g, 2.6 mmol) in AcOH (4 ml) to afford the title compound (139 mg, 48%) as a white solid after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.35 (d, J = 5.0 Hz, 1H), 8.15 (s, 1H), 7.78 - 7.74 (m, 1H), 7.50 (br s, 2H), 7.29 (dd, J = 7.6, 5.0 Hz, 1H), 7.24 - 7.18 (m, 2H), 5.58 (t, J = 8.3 Hz, 1H), 4.05 (tt, J = 7.9, 6.4 Hz, 1H), 3.77 (t, J = 7.9 Hz, 2H), 3.56 - 3.49 (m, 2H), 3.11 (ddd, J = 16.3, 9.1, 2.8 Hz, 1H), 3.05 - 3.00 (m, 3H), 3.00 - 2.94 (m, 2H), 2.73 (m, 1H), 2.11 (m, 1H)

HPLCMS (Method C): [*m/z*]: 445.3 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 195)

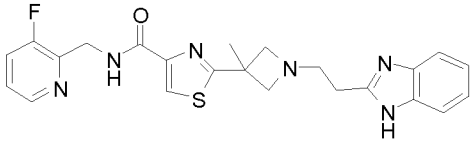


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(171)** (330 mg, 1.07 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (226 mg, 1.18 mmol) and DBU (0.21 ml, 1.4 mmol) in MeCN (10 ml) gave the required crude intermediate which was further reacted with iron powder (150 mg, 2.6 mmol) in AcOH (4 ml) to afford the title compound (80 mg, 27%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-12% MeOH / DCM).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.45 (dd, J = 4.7, 1.4 Hz, 1H), 8.15 (s, 1H), 7.88 (dd, J = 8.1, 1.4 Hz, 1H), 7.51 (br s, 2H), 7.32 (dd, J = 8.1, 4.7 Hz, 1H), 7.24 - 7.19 (m, 2H), 4.85 - 4.82 (m, 2H), 4.11 (m, 1H), 3.84 (t, J = 7.9 Hz, 2H), 3.59 - 3.53 (m, 2H), 3.10 - 3.05 (m, 2H), 3.03 - 2.98 (m, 2H)

HPLCMS (Method C): [*m/z*]: 453.2 $[M+H]^+$

2-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]-3-methylazetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 212)



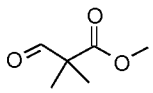
In a similar fashion to general procedure 8, N-[(3-fluoropyridin-2-yl)methyl]-2-(3-methylazetidin-3-yl)-1,3-thiazole-4-carboxamide **(172)** (476 mg, 1.55 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (328 mg, 1.71 mmol) and DBU (0.26 ml, 2 mmol) in MeCN (15 ml) gave the required crude intermediate which was further reacted with iron powder (350 mg, 10.0 mmol) in AcOH (5 ml). Purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM) gave the title compound (162 mg, 23%) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.34 - 8.27 (m, 1H), 8.14 (s, 1H), 7.60 (ddd, J = 9.7, 8.5, 1.2 Hz, 1H), 7.51 (s, 2H), 7.37 - 7.32 (m, 1H), 7.24 - 7.18 (m, 2H), 4.80 (d, J = 1.3 Hz, 2H), 3.78 (d, J = 7.7 Hz, 2H), 3.47 (d, J = 7.7 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 1.78 (s,3H)

HPLCMS (Method C): [*m/z*]: 451.1 $[M+H]^+$

General Scheme 10 above:

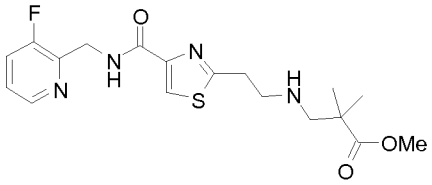
Methyl 2,2-dimethyl-3-oxopropanoate (173)



To an ice-cooled (0°C) solution of methyl 3-hydroxy-2,2-dimethylpropanoate (1.45 ml, 11.35 mmol) and TEA (4.75 ml, 34.05 mmol) in DCM (45 ml) and DMSO (8 ml, 113.5 mmol) was added pyridine sulfur trioxide complex (5.42 g, 34.05 mmol). The resulting mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated NH_4Cl (30 ml). The layers were separated and the aqueous layer was extracted with DCM (40 ml). The organic layer was washed sequentially with 2M HCl (2 x 20 ml) and brine (15 ml), dried ($MgSO_4$), filtered and evaporated to give the title compound (0.35 g, 99%) as an orange oil.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 9.66 (s, 1H), 5.30 (s, 1H), 3.75 (s, 3H), 1.35 (s, 6H)

Methyl 3-{[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoate (174)

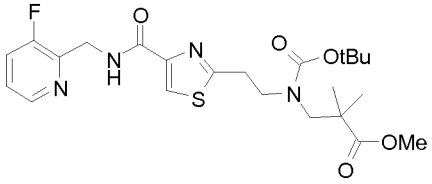


DIPEA (1.8 ml, 10.32 mmol) was added to 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(103)** (0.97 g, 2.58 mmol) and methyl 2,2-dimethyl-3-oxopropanoate **(173)** (0.52 g, 3.36 mmol) in MeOH (20 ml). The reaction was stirred at room temperature for 18 h. The reaction was cooled to 0°C and $NaBH_4$ (146 mg, 3.87 mmol) was added portionwise. The reaction was allowed to warm to room temperature and stirred for 3.5 h. The solvent evaporated and water (10 ml) added. The aqueous layer extracted with EtOAc (3 x 20 ml). The combined organic layers were dried (MgSO4), filtered and evaporated to give an orange oil (1.1 g). Purification by flash column chromatography (eluting with a gradient of 0-15% MeOH / DCM) gave the title compound (0.95 g, 79%) as a pale yellow oil.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.43 - 8.38 (m, 2H), 8.02 (s, 1H), 7.45 - 7.36 (m, 1H), 7.26 - 7.20 (m, 1H), 4.85 (dd, J = 5.3, 1.7 Hz, 2H), 3.63 (s, 3H), 3.20 (t, J = 5.6 Hz, 2H), 3.10 (t, J = 5.8 Hz, 2H), 2.79 (s, 2H), 1.22 (s, 6H)

HPLCMS (Method A): [m/z]: 395.05 $[M+H]^+$

3-{[(Tert-butoxy)carbonyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoate (175)

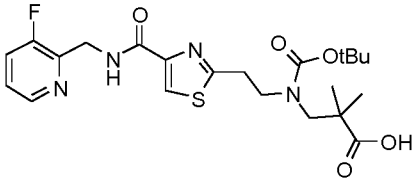


TEA (0.5 ml, 3.62 mmol) was added to methyl 3-{[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoate **(174)** (0.95 g, 2.41 mmol) in DCM (10 ml). The reaction was stirred for 5 min at room temperature, di-tert-butyl dicarbonate (0.63 g, 2.9 mmol) in DCM (10 ml) was added dropwise and the reaction stirred at room temperature for 20 h. The solvent was evaporated and purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) to give the title compound (0.94 g, 90%) as a clear oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.42 (d, J = 4.3 Hz, 2H), 8.01 (s, 1H), 7.44- 7.37 (m, 1H), 7.26 (m, 1H, obscured by solvent peak), 4.85 (dd, J = 5.1, 1.7 Hz, 2H), 3.70 (s, 3H), 3.55 (t, J = 7.0 Hz, 2H), 3.48-3.41 (br m, 2H), 3.31 - 3.14 (m, 2H), 1.45 (s, 9 H), 1.19 (s, 6H)

HPLCMS (Method A): [m/z]: 495.15 $[M+H]^+$

3-{[(Tert-butoxy)carbonyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoic acid (176)

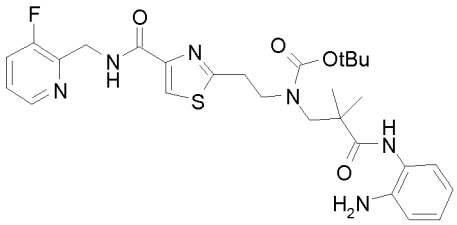


In a similar fashion using general procedure 5, LiOH (0.27 g, 11.1 mmol) and 3-{[(tert-butoxy)carbonyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoate **(175)** (0.94 g, 1.85 mmol) in THF (6 ml) / water (1.5 ml) gave the title compound (0.91 g, 96%) as an offwhite solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.41 (s, 1H), 8.63 (s, 1H), 8.39 (s, 1H), 8.17 (s, 1H), 7.71 (ddd, J = 10.0, 8.3, 1.2 Hz, 1H), 7.41 (dt, J = 8.6, 4.4 Hz, 1H), 4.67 (dd, *J* = 5.6, 1.3 Hz, 2H), 3.53 (t, J = 7.1 Hz, 2H), 3.38 (s, 2H), 3.23 (t, J = 7.1 Hz, 2H), 1.34 (s, 9H), 1.07 (s, 6H)

HPLCMS (Method A): [m/z]: 481.15 $[M+H]^+$

Tert-butyl N-{2-[(2-aminophenyl)carbamoyl]-2,2-dimethylethyl}-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (177)

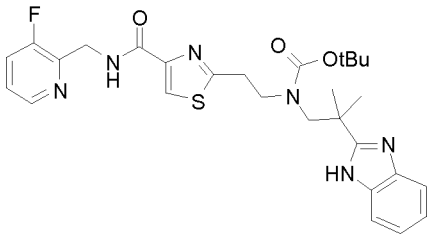


In a similar fashion using general procedure 6, 3-{[(tert-butoxy)carbonyl][2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]amino}-2,2-dimethylpropanoic acid **(176)** (0.5 g, 0.98 mmol), benzene-1,2-diamine (0.14 g, 1.3 mmol), TEA (0.18 ml, 1.3 mmol) and HATU (0.49 g, 1.3 mmol) in DMF (10 ml) gave the title compound (0.51 g, 83%) as a yellow oil after purification by flash column chromatography using a gradient of 0-100% EtOAc / heptane.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.84 (s, 1H), 8.61 (s, 1H), 8.37 (d, J = 4.5 Hz, 1H), 8.16 (s, 1H), 7.70 (ddd, J = 10.1, 8.3, 1.2 Hz, 1H), 7.41 (dt, J = 8.6, 4.4 Hz, 1H), 7.02 - 6.86 (m, 2H), 6.78 - 6.68 (m, 1H), 6.57 - 6.45 (m, 1H), 4.66 (d, J = 4.4 Hz, 2H), 3.55 (t, J = 6.9 Hz, 2H), 3.50 (s, 2H), 3.24 (t, J = 6.9 Hz, 2H), 1.35 (s, 9H), 1.21 (s, 6H)

HPLCMS (Method A): [m/z]: 571.2 $[M+H]^+$

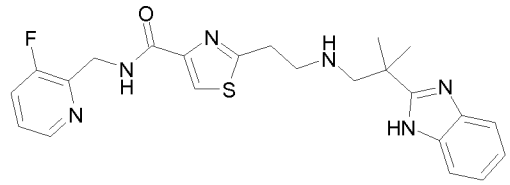
Tert-butyl N-[2-(1H-1,3-benzodiazol-2-yl)-2-methylpropyl]-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (178)



Tert-butyl N-{2-[(2-aminophenyl)carbamoyl]-2,2-dimethylethyl}-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(177)** (260 mg, 0.415 mmol) in glacial AcOH (4 ml) was heated to 80°C for 35 min. The reaction was cooled, concentrated *in vacuo* and the residue partitioned between EtOAc (10 ml) and saturated K_2CO_3 (10 ml). The layers were separated and the aqueous layer

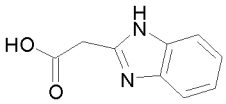
extracted with EtOAc (2 x 10 ml). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to give a brown oil. Purification by flash column chromatography (KP-NH column eluting with a gradient of 0-100% DCM / heptane) gave the title compound (172 mg, 71%) as a pale brown oil.
^{1}H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.43 (br s, 1H), 8.42 (dt, J = 4.6 and 1.2 Hz, 2H), 7.99 (s, 1H), 7.82-7.69 (m, 1H), 7.47 - 7.42 (m, 1H), 7.40 - 7.34 (m, 1H), 7.25 - 7.18 (m, 2H), 4.91 (d, J = 4.5 Hz, 2H), 3.75 - 3.69 (br m, 2H), 3.59 - 3.39 (br m, 2H), 3.11 (t, J = 6.3 Hz, 2H), 1.59 (s, 9H), 1.45 (s, 6H)
HPLCMS (Method A): [m/z]: 553.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)-2-methylpropyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 199)



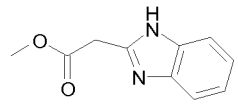
In a similar fashion to general procedure 2, TFA (2 ml) was added to tert-butyl N-{2-[(2-aminophenyl)carbamoyl]-2,2-dimethylethyl}-N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(178)** (172 mg, 0.25 mmol) in DCM (2 ml) aqnd stirred at room temperature for 3 h, to give the title compound (79 mg, 70%) as a beige solid after purification by Isolute SCX-2 cartridge, eluted with DCM (2 CV), DCM/MeOH (1:1, 1 CV), MeOH (2 CV) and then 7M NH_3 in MeOH (2 CV).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.01 (s, 1H), 8.62 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.7 and 1.5 Hz, 1H), 8.02 (s, 1H), 7.74 - 7.63 (m, 1H), 7.53 - 7.35 (m, 2H), 7.42 - 7.38 (m, 1 H), 7.14 - 7.06 (m, 2H), 4.64 (dd, J = 5.6, 1.4 Hz, 2H), 3.11 (t, J = 6.5 Hz, 2H), 2.91 - 2.87 (m, 4H), 1.39 (s, 6H)
HPLCMS (Method D): [m/z]: 453.2 $[M+H]^+$

2-(1H-1,3-Benzodiazol-2-yl)acetic acid (179)



2M NaOH (90.7 ml, 181 mmol) was added to 2-(1H-1,3-benzodiazol-2-yl)acetonitrile (9.5 g, 60.4 mmol). The reaction heated at 100°C for 3 h. The reaction mixture was cooled to room temperature and acidified to pH 5-6 with 4 M HCl. The resulting precipitate was filtered, washed with water and dried *in vacuo* to give the title compound (9.7 g, 77%) as light brown solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 7.52 - 7.46 (m, 1H), 7.45 - 7.39 (m, 1H), 7.17 - 7.11 (m, 1H), 7.11 - 7.06 (m, 1H), 2.47 (s, 2H)
HPLCMS (Method F): [m/z]: 177.0 $[M+H]^+$

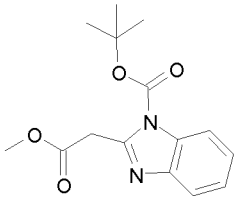
Methyl 2-(1H-1,3-benzodiazol-2-yl)acetate (180)



Thionyl dichloride (0.7 ml, 9.65 mmol) was added dropwise to an ice-cooled (0°C) suspension of 2-(1H-1,3-benzodiazol-2-yl)acetic acid **(179)** (0.7 g, 3.97 mmol) in MeOH (30 ml). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was poured onto saturated $NaHCO_3$ (40 ml) and extracted with DCM (3 x 20 ml). The combined organic layers were washed with brine (30 ml), dried ($NaSO_4$), filtered and evaporated to give the title compound (0.65 g, 86%) as a cream solid.

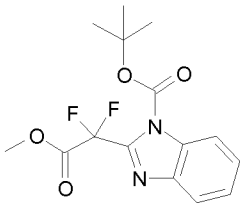
1H-NMR (CDCl3, 500 MHz): d[ppm]= 10.10 (br s, 1H), 7.72 (br s, 1H), 7.46 (br s, 1H), 7.29- 7.23 (m, 2H), 4.09 (s, 2H), 3.82 (s, 3H)
HPLCMS (Method F): [m/z]: 191.2 $[M+H]^+$

Tert-butyl 2-(2-methoxy-2-oxoethyl)-1H-1,3-benzodiazole-1-carboxylate (181)



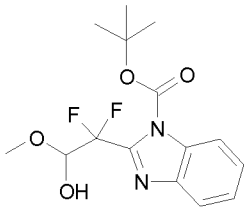
In a similar fashion to general procedure 4, methyl 2-(1H-1,3-benzodiazol-2-yl)acetate **(180)** (650 mg, 3.42 mmol), TEA (0.5 ml, 3.59 mmol), Boc_2O (890 mg, 4.11 mmol) and DMAP (84 mg, 0.68 mmol) in THF (30 ml) at room temperature for 18 h, gave the title compound (940 mg, 95%)as a cream solid after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.96 - 7.90 (m, 1H), 7.74 - 7.68 (m, 1H), 7.38 - 7.31 (m, 2H), 4.28 (s, 2H), 3.73 (s, 3H), 1.69 (s, 9H)
HPLCMS (Method A): [m/z]: 291 $[M+H]^+$

Tert-butyl 2-(1,1-difluoro-2-methoxy-2-oxoethyl)-1H-1,3-benzodiazole-1-carboxylate (182)



KHMDS (1.5 g, 7.61 mmol) in THF (15 ml) was cooled to -78°C. tert-Butyl 2-(2-methoxy-2-oxoethyl)-1H-1,3-benzodiazole-1-carboxylate **(181)** (0.74 g, 2.54 mmol) was added and the mixture was stirred at -78°C for 45 min. A combined mixture of 18-crown-6 (2.01 g, 7.61 mmol) and N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (2.2 g, 7.1 mmol) was added. The mixture was stirred at -78°C for 30 min. Additional KHMDS (0.75 g, 3.76 mmol) was added and stirred for 20 min. Additional N-fluoro-N-(phenylsulfonyl)benzenesulfonamide (1.1 g, 3.49 mmol) and 18-crown-6 (1 g, 3.78 mmol) were added. The reaction mixture was then allowed to slowly warm to room temperature and stirred for 18 h to give a ratio of 1.6:1 bis:mono fluorinated products. Saturated NH_4Cl (12 ml) was added followed by water (20 ml). The organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc (3 x 50ml). The combined organic layers were washed with brine (100 ml), dried ($NaSO_4$), filtered and evaporated to give a pink semi-solid (3 g). Purification by flash column chromatography (eluting with a gradient of 0-50% TBME / heptane followed by 100% TBME) gave the title compound (0.47 g, 48%) as a yellow oil which solidified on standing.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.00 - 7.81 (m, 2H), 7.55 - 7.34 (m, 2H), 3.91 (s, 3H), 1.70 (s, 9H).
HPLCMS (Method A): [m/z]: 226.9 $[M-BOC+H]^+$

Tert-butyl 2-(1,1-difluoro-2-hydroxy-2-methoxyethyl)-1H-1,3-benzodiazole-1-carboxylate (183)

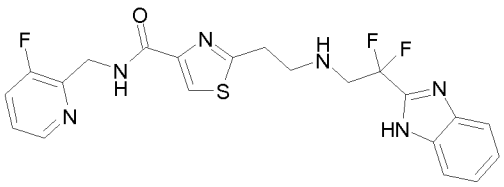


$NaBH_4$ (44 mg, 1.16 mmol) was added to an ice-cooled (0°C) solution of tert-butyl 2-(1,1-difluoro-2-methoxy-2-oxoethyl)-1H-1,3-benzodiazole-1-carboxylate **(182)** (295 mg, 0.76 mmol) in EtOH (3.5 ml). The reaction was stirred at 0°C for 1.5 h, quenched with dropwise addition of 1 M HCl (0.5 ml). Water (10 ml) was added and the aqueous layer extracted with EtOAc (3 x 10 ml). The combined organic layers dried ($NaSO_4$), filtered and evaporated to give a white solid (300 mg). Purification by flash column chromatography (eluting with a gradient of 0-40% EtOAc / heptane) gave the title compound (185 mg, 59%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.03 - 7.77 (m, 1H), 7.63 - 7.31 (m, 3H), 6.17 (dd, J = 6.4, 4.9 Hz, 1H), 3.69 (s, 3H), 1.52 (s, 9H)

HPLCMS (Method A): [m/z]: 329.05 $[M+H]^+$

4-(2-{[2-(1H-1,3-Benzodiazol-2-yl)-2,2-difluoroethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-2-carboxamide (Example Compound No. 196)



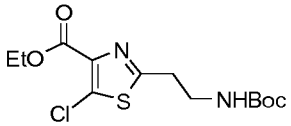
Tert-Butyl 2-(1,1-difluoro-2-hydroxy-2-methoxyethyl)-1H-1,3-benzodiazole-1-carboxylate **(183)** (160 mg, 0.4 mmol), 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(103)** (136 mg, 0.49 mmol) and activated molecular sieves in dry toluene (3 ml) was heated to 125°C for 18 h. The reaction was cooled to room temperature and $NaBH_4$ (40 mg, 1.06 mmol) was added followed by EtOH (4 ml). The reaction mixture was stirred for 1 h. The reaction was quenched with dropwise addition of 1 M HCl (10 drops). Once effervescence ceased, water (10 ml) was added and using 2M K_2CO_3, the pH was adjusted to 10. The mixture was filtered and the aqueous layer extracted with EtOAc (3 x 20 ml). The combined organic layers dried ($NaSO_4$), filtered and evaporated to give a brown oily solid (176 mg). Purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM) gave a brown solid (40 mg). Further purification by basic prep HPLC gave a yellow oil (21 mg). Re-purification by flash column chromatography (eluting with a gradient of 0-5% EtOH / DCM) gave the title compound (12 mg, 6%) as a pale yellow solid.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.38 - 8.32 (m, 1H), 7.90 (s, 1H), 7.65 - 7.55 (m, 3H), 7.42 - 7.36 (m, 1H), 7.36 - 7.30 (m, 2H), 4.73 (d, J = 1.6 Hz, 2H), 3.60 (t, J = 14.0 Hz, 2H), 3.20 - 3.08 (m, 4H)

HPLCMS (Method D): [m/z]: 461.2 $[M+H]^+$

General Scheme 11 above:

General procedure 12: Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylate (184)

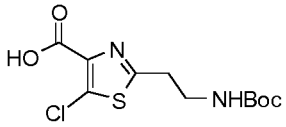


A solution of ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(1)** (2 g, 6.66 mmol) and hexachloroethane (1.49 g, 6.32 mmol) in THF (140 ml) was cooled to-78°C. 2 M NaHMDS (7.0 ml, 14.0 mmol) was added dropwise. The reaction mixturewas stirred at -78°C for 1 h, quenched with sat. NH_4Cl (aq) and allowed to warm to room temperature. The mixture was filtered and the residue was rinsed with THF (50 ml). The filtrates were evaporated *in vacuo* and the residue was partitioned between EtOAc and sat. NH_4Cl (aq). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica flash chromatography (eluting with a gradient of 0-30% EtOAc / DCM) gave the title compound (1.47 g, 65%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 4.91 (s, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.55 (q, *J* = 6.3 Hz, 2H), 3.18 (t, *J* = 6.4 Hz, 2H), 1.49 – 1.39 (m, 12H)

HPLCMS (Method A): [*m/z*]: 356.95 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid (185)

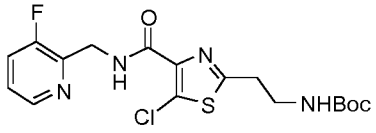


In a similar fashion using general procedure 5, LiOH (739 mg, 30.84 mmol) and ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylate **(184)** (1.47 g, 4.41 mmol) in THF (30 ml) / water (10 ml) gave the title compound (1.35 g, quant.) as a yellow oil. The compound was used in the next step without further purification.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 4.92 (s, 1H), 3.58 (q, J = 5.7 Hz, 2H), 3.18 (t, J = 5.8 Hz, 2H), 1.46 (s, 9H)

HPLCMS (Method A): [*m/z*]: 328.9 $[M+H]^+$

Tert-butyl N-[2-(5-chloro-4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (186)

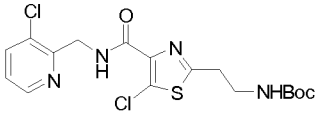


In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (800 mg, 2.61 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride - **(A2)** (623 mg, 3.13 mmol), DIPEA (1.5 ml, 10.0 mmol), HATU (1.19 g, 3.0 mmol) in DCM (30 ml) gave the title compound (1.08 g, 80%) as a white solid after purification by flash column chromatography(eluting with a gradient of 0-60% EtOAc / heptane). Compound was used in the next step without further purification.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.49 - 8.39 (m, 2H), 7.44 (ddd, J = 9.4, 8.4, 1.3 Hz, 1H), 7.34 - 7.23 (m, 3H), 4.94 (s, 1H), 4.84 (dd, J = 5.1, 1.7 Hz, 2H), 3.59 (q, J = 6.3 Hz, 2H), 3.15 (t, J = 6.4 Hz, 2H), 1.46 (s, 9H)

HPLCMS (Method A): [*m/z*]: 415 $[M+H]^+$

Tert-butyl N-[2-(5-chloro-4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (187)



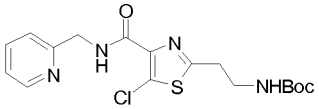
In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (220 mg, 0.72 mmol), (3-chloropyridin-2-yl)methanamine dihydrochloride

(154.55 mg, 0.72 mmol), DIPEA (0.26 ml, 2 mmol), HATU (0.33 g, 0.85 mmol) in tetrahydrofuran (10 ml) / DMF (2 ml) gave the title compound (360 mg, quant.) as a white solid after purification by flash column chromatography (eluting with a gradient of 20-60% EtOAc / heptane). Compound was used in the next step without further purification.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.66 (s, 1H), 8.56 - 8.52 (m, 1H), 7.74 (dd, J = 8.0, 1.4 Hz, 1H), 7.24 (dd, J = 8.0, 4.7 Hz, 1H), 4.98 (s, 1H), 4.85 (d, J = 4.8 Hz, 2H), 3.61 (q, J = 6.1Hz, 2H), 3.17 (t, J = 6.3 Hz, 2H), 1.46 (s, 9H).

HPLCMS (Method A): [*m/z*]: 431.1 [M+H]+

Tert-butyl N-(2-{5-chloro-4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (188)

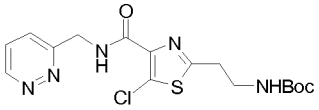


In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (216 mg, 0.7 mmol), pyridin-2-ylmethanamine (0.09 ml, 0.84 mmol), DIPEA (0.26 ml, 1 mmol), HATU (0.32 g, 0.84 mmol) in tetrahydrofuran (10 ml) were stirred at room temperature. Further pyridin-2-ylmethanamine (0.09 ml, 0.84 mmol), DIPEA (0.26 ml, 0 mol) and HATU (0.32 g, 0 mol) were added and the reaction continued. The title compound (227 mg, 78%) was isolated as a brown oil after purification by flash column chromatography (eluting with a gradient of 5-100% EtOAc / heptane). Compound was used in the next step without further purification.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.50 (d, J = 4.4 Hz, 1H), 7.81 (td, J = 7.8, 1.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.36 - 7.27 (m, 1H), 4.73 (s, 3H), 4.68 (s, 2H), 3.13 (t, J = 6.4 Hz, 2H), 1.41 (s, 9H).

HPLCMS (Method A): [*m/z*]: 397.10 $[M+H]^+$

Tert-butyl N-(2-{5-chloro-4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (189)



In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (220 mg, 0.72 mmol), pyridazin-3-ylmethanamine (0.12 g, 1 mmol), DIPEA (0.31 ml, 2 mmol), HATU (0.41 g, 1 mmol) in DCM (20 ml) gave the title compound (278 mg, 91%) as a yellow residue after purification by flash column chromatography (eluting with a gradient of 50-100% EtOAc / heptane, then 2-6% methanol/ethyl acetate). Compound was used in the next step without further purification.

HPLCMS (Method A): [*m/z*]: 398.05 $[M+H]^+$

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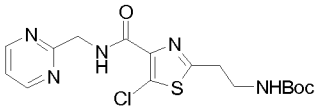
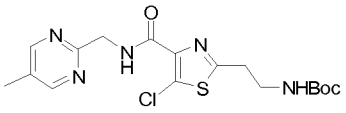
Tert-butyl N-(2-{5-chloro-4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate (190)



In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (579 mg, 1.54 mmol), 1-(pyrimidin-2-yl)methanamine (0.14 g, 1.28 mmol), DIPEA (0.67 ml, 3.85 mmol), HATU (0.585 g, 1.54 mmol) in tetrahydrofuran (10 ml) / DMF (2 ml) gave the title compound (0.483 g, 73 %) as a white solid after purification by flash column chromatography (eluting with a gradient of 50-100% EtOAc / heptane). Compound was used in the next step without further purification.

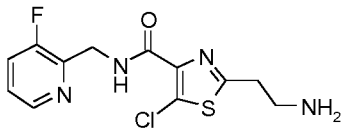
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.83 - 8.79 (m, 1H), 8.78 (d, J = 4.9 Hz, 2H), 7.41 (t, J = 4.9 Hz, 1H), 7.11 - 7.05 (m, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 1.37 (s, 9H).
HPLCMS (Method A): [*m/z*]: 398 $[M+H]^+$

Tert-butyl N-[2-(5-chloro-4-{[(5-methylpyrimidin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (191)



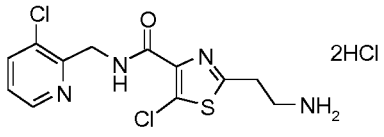
In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-chloro-1,3-thiazole-4-carboxylic acid **(185)** (556 mg, 1.48 mmol), (5-methylpyrimidin-2-yl)methanamine (0.14 g, 1.14 mmol), DIPEA (0.396 ml, 2.274 mmol), HATU (0.562 g, 1.478 mmol) in tetrahydrofuran (10 ml) / DMF (2 ml) gave the title compound (577 mg, 92 %) as a colourless oil after purification by flash column chromatography (eluting with a gradient of 70-100% EtOAc / heptane). Compound was used in the next step without further purification.
1H-NMR (DMSO-d6, 500 MHz) δ 8.77 (t, J = 5.8 Hz, 1H), 8.63 (s, 2H), 7.08 (s, 1H), 4.60 (d, J = 5.9 Hz, 2H), 3.09 (t, J = 6.6 Hz, 2H), 2.27 (s, 3H), 1.37 (s, 9H).
HPLCMS (Method A): [*m/z*]: 412.05 $[M+H]^+$

2-(2-Aminoethyl)-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (192)



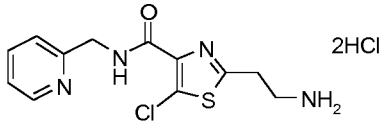
In a similar fashion using general procedure 2, 12M HCl (8 ml) and tert-butyl N-[2-(5-chloro-4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(186)** (1 g, 2.41 mmol) in MeOH (40 ml) at room temperature gave the title compound (703 mg, 93%) as a whitesolid after purification by SCX-2 cartridge (gradient elution 100% DCM, followed by 100% MeOH and then 7 N NH_3/MeOH).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.73 (t, J = 5.6 Hz, 1H), 8.40 (dt, J = 4.6, 1.4 Hz, 1H), 7.71 (ddd, J = 10.0, 8.3, 1.2 Hz, 1H), 7.42 (dt, J = 8.6, 4.4 Hz, 1H), 4.63 (dd, J = 5.7, 1.5 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.93 (t, J = 6.1 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 314.95 $[M+H]^+$

2-(2-Aminoethyl)-5-chloro-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (193)



In a similar fashion using general procedure 2, 12M HCl (2 ml) and tert-butyl N-[2-(5-chloro-4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(187)** (360 mg, 0.83 mmol) in MeOH (10 ml) at room temperature gave the title compound (320 mg, 95%) as a white solid.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.93 (t, J = 6.0 Hz, 1H), 8.52 (dd, J = 4.7, 1.3 Hz, 1H), 8.04 (s, 2H), 7.97 (dd, J = 8.1, 1.4 Hz, 1H), 7.40 (dd, J = 8.1, 4.7 Hz, 1H), 4.68 (d, J = 5.8 Hz, 2H), 3.36- 3.26 (m, 4H)
HPLCMS (Method A): [*m/z*]: 331.1 $[M+H]^+$

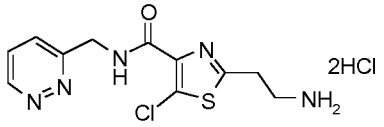
2-(2-Aminoethyl)-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (194)



In a similar fashion using general procedure 2, 12M HCl (2 ml) and tert-butyl N-(2-{5-chloro-4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(188)** (260 mg, 0.66 mmol) in MeOH (10 ml) at room temperature gave the title compound (198 mg, 82%) as a dark yellow gum. The crude product was used without further purification.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.80 (d, J = 5.4 Hz, 1H), 8.64 (td, J = 8.0, 1.3 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.03 (t, J = 6.7 Hz, 1H), 4.99 (s, 2H), 3.60 - 3.39 (m, 4H)

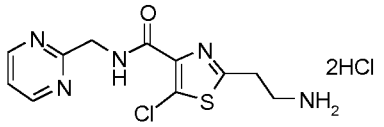
2-(2-Aminoethyl)-5-chloro-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (195)



In a similar fashion using general procedure 2, 12M HCl (1.86 ml) and tert-butyl N-(2-{5-chloro-4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(189)** (278 mg, 0.65 mmol) in MeOH (10 ml) at 60°C gave the crude title compound (296 mg) as a pale brown residue. Compound was taken to the next step without further purification.

HPLCMS (Method A): [*m/z*]: 298 $[M+H]^+$

2-(2-Aminoethyl)-5-chloro-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride (196)

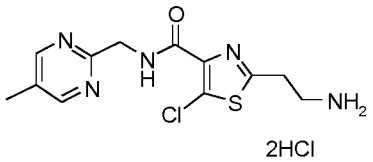


In a similar fashion using general procedure 2, 12M HCl (1.56 ml) and tert-butyl N-(2-{5-chloro-4-[(pyrimidin-2-ylmethyl)carbamoyl]-1,3-thiazol-2-yl}ethyl)carbamate **(190)** (483 mg, 0.938 mmol) in MeOH (3 ml) at 40°C gave the title compound (563 mg, 100%) as a beige solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.83 (d, J = 5.0 Hz, 2H), 7.49 (t, J = 5.0 Hz, 1H), 4.82 (s, 2H), 3.49 (t, J = 6.2 Hz, 2H), 3.39 (t, J = 6.2 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 297.9 $[M+H]^+$

2-(2-Aminoethyl)-5-chloro-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (197)

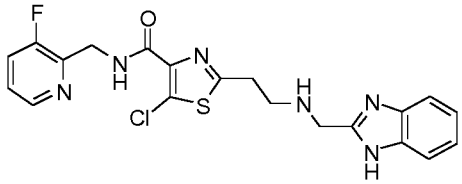


In a similar fashion using general procedure2, 12M HCl (1.74 ml) and tert-butyl N-[2-(5-chloro-4-{[(5-methylpyrimidin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(191)** (580 mg, 1.04 mmol) in MeOH (6 ml) at room temperature gave the title compound (447 mg, 100%) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.74 (s, 2H), 4.80 (s, 2H), 3.49 (t, J = 6.2 Hz, 2H), 3.38 (t, J = 6.2 Hz, 2H), 2.39 (s, 3H)

HPLCMS (Method A): [*m/z*]: 311.95 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 151)

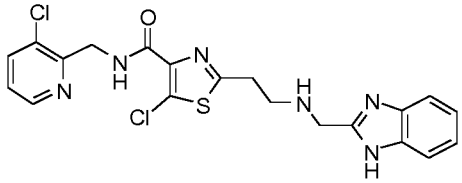


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(192)** (143 mg, 0.37 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (70.1 mg, 0.48 mmol), $MgSO_4$ (200 mg) in MeOH (10 ml) at room temperature for 3 d, followed by addition of $NaBH_4$ (28 mg, 0.74 mmol) gave the title compound (94 mg, 56%) as a white sdid after purification by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 8.71 (t, J = 5.6 Hz, 1H), 8.37 (dt, J = 4.6, 1.3 Hz, 1H), 7.70 (ddd, J = 10.0, 8.4, 1.1 Hz, 1H), 7.54 (d, J = 7.2 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.14 (t, J = 7.5 Hz, 2H), 4.66 - 4.58 (m, 2H), 3.97 (s, 2H), 3.12 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 445.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 159)

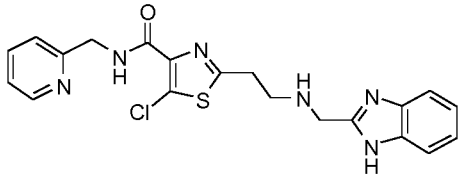


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-[(3-chloropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(193)** (320 mg, 0.79 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (127.3 mg, 0.87 mmol), DIPEA (0.32 ml, 2.0 mmol) and $MgSO_4$ (300 mg) in MeOH (20 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (60 mg, 1.59 mmol) gave the title compound (191 mg, 52%) as a white solid after purification by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 8.72 (t, J = 5.6 Hz, 1H), 8.49 (dd, J = 4.7, 1.3 Hz, 1H), 7.95 (dd, J = 8.1, 1.3 Hz, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.38 (dd, J = 8.1, 4.7 Hz, 1H), 7.17- 7.09 (m, 2H), 4.65 (d, J = 5.5 Hz, 2H), 3.98 (d, J = 4.1 Hz, 2H), 3.13 (t, J = 6.3 Hz, 2H), 2.95 (q, J = 6.1, 5.3 Hz, 2H), 2.74 (s, 1H)

HPLCMS (Method C): [*m/z*]: 461 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 160)

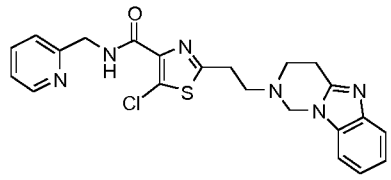


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(194)** (190 mg, 0.51 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (113 mg, 0.77 mmol), DIPEA (0.3 ml, 2.0 mmol) and $MgSO_4$ (400 mg) in DCM (10 ml) and MeOH (10 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (39 mg, 1.03 mmol) gave the title compound (60 mg, 27%) as a pale yellow solid after purification by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 8.90 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 5.5 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.58 - 7.42 (m, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.27 (dd, J =7.0, 5.3 Hz, 1H), 7.17 - 7.10 (m, 2H), 4.54 (d, J = 6.0 Hz, 2H), 3.98 (s, 2H), 3.12 (t, J = 6.3Hz, 2H), 2.95 (t, J = 6.3 Hz, 2H), 2.76 (s, 1H)

HPLCMS (Method C): [*m/z*]: 427.1 $[M+H]^+$

5-chloro-N-(pyridin-2-ylmethyl)-2-(2-{1,8,12-triazatricyclo[7.4.0.0²,7]trideca-2(7),3,5,8-tetraen-12-yl}ethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 189)

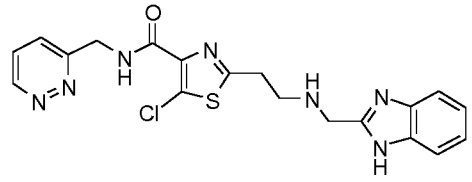


In a similar fashion to general procedure 8, 2-(2-Aminoethyl)-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(194)** (361.5 mg, 0.98 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (187.9 mg, 0.98 mmol), DBU (219 µl, 1.47 mmol) in MeCN (5 ml) at room temperature for 3 h, gave a mixture of mono and bis alkylated intermediates which were separated by flash column chromatography (eluting with a gradient of 0-10% MeOH / EtOAc followed by 0-10% MeOH / DCM). The mono alkylated intermediate (5-chloro-2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide) (66.0 mg, 0.135 mmol) was further reacted with iron powder (15.1 mg, 0.270 mmol) in AcOH (1 ml) at 80°C for 1 h to give the title compound (61 mg, 25%) as a brown oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

^{1}H NMR (Acetone-d6, 500 MHz): d[ppm]= 8.53 (d, J = 4.2 Hz, 2H), 7.76 (td, J = 7.7, 1.8 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.45 - 7.37 (m, 2H), 7.26 (dd, J = 7.0, 4.9 Hz, 1H), 7.22 - 7.14 (m, 2H), 5.14 (s, 2H), 4.66 (d, J = 5.7 Hz, 2H), 3.39 (t, J = 6.2 Hz, 2H), 3.36 - 3.28 (m, 2H), 3.20 (t, J = 6.3 Hz, 2H), 3.14 (t, J = 6.2 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 453.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 161)

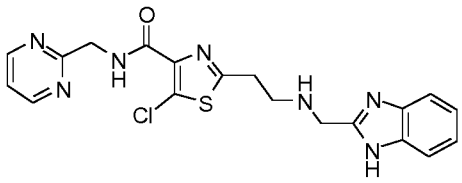


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(195)** (296 mg, 0.8 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (151.7 mg, 1.04 mmol), DIPEA (0.42 ml, 2.0 mmol) and $MgSO_4$ (400 mg) in DCM (10 ml) and MeOH (10 ml) at room temperature for 3 d, followed by addition of $NaBH_4$ (60 mg, 1.59 mmol) gave the title compound (96 mg, 28%) as a white solid after purification by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.18 (s, 1H), 9.14 (dd, J = 4.8, 1.5 Hz, 1H), 9.07 (t, J = 6.1 Hz, 1H), 7.66 (dd, J = 8.5, 4.8 Hz, 1H), 7.60 (dd, J = 8.5, 1.6 Hz, 1H), 7.54 (d, J = 7.4 Hz,1H), 7.45 (d, J = 7.7 Hz, 1H), 7.13 (p, J = 7.0, 6.6 Hz, 2H), 4.72 (d, J = 6.1 Hz, 2H), 3.97 (s, 2H), 3.12 (t, J = 6.3 Hz, 2H), 2.95 (t, J = 6.2 Hz, 2H), 2.75 (s, 1H)

HPLCMS (Method C): [*m/z*]: 428 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 175)

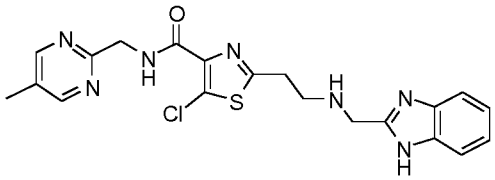


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-(pyrimidin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(196)** (563 mg, 0.94 mmol), 1H-benzimidazole-2-carbaldehyde (178 mg, 1.22 mmol), DIPEA (0.654 ml, 0.74 mmol) in MeOH (15 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (53 mg, 1.41 mmol) gave the title compound (224 mg, 54%)as a white solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.20 (br s, 1H), 8.80 - 8.74 (m, 3H), 7.50 (br s, 2H), 7.40 (t, J = 4.9 Hz, 1H), 7.21 - 7.07 (m, 2H), 4.64 (d, J = 5.9 Hz, 2H), 3.98 (s, 2H), 3.13 (t, J = 6.3 Hz,2H), 2.96 (t, J = 6.3 Hz, 2H), 2.76 (br s, 1H)

HPLCMS (Method G): [*m/z*]: 428.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-5-chloro-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 178)

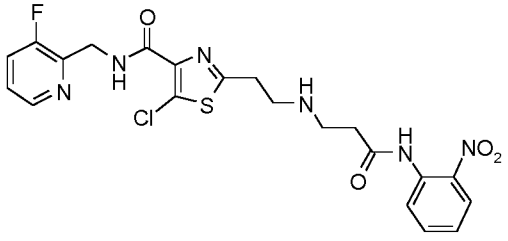


In a similar fashion to general procedure 3, 2-(2-aminoethyl)-5-chloro-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(197)** (223 mg, 0.52 mmol), 1H-benzimidazole-2-carbaldehyde (99 mg, 0.68 mmol), DIPEA (0.363 ml, 2.09 mmol) and $MgSO_4$ (400 mg) in MeOH (6 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (30 mg, 0.78 mmol) gave the title compound (120 mg, 52%) as a white solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.21 (s, 1H), 8.72 (t, J = 5.8 Hz, 1H), 8.63 - 8.57 (m, 2H), 7.50 (s, 1H), 7.14 (dd, J = 6.0, 2.7 Hz, 2H), 4.61 - 4.56 (m, 2H), 3.98 (s, 2H), 3.13 (t, J = 6.3 Hz, 2H), 2.95 (t, J = 6.3 Hz, 2H), 2.75 (s, 1H), 2.26 (s, 3H)

HPLCMS (Method C): [*m/z*]: 442 $[M+H]^+$

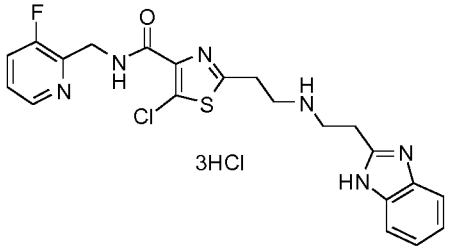
5-Chloro-N-[(3-fluoropyridin-2-yl)methyl]-2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxamid (198)



In a similar fashion to general procedure 8, 2-(2-aminoethyl)-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(192)** (700mg, 2.22 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (470 mg, 2.45 mmol) were combined in MeCN (40 ml) and DBU (0.37 ml, 2.0 mmol) was added. The mixture was stirred at room temperature for 3 d. The reaction mixture was evaporated directly onto silica. Purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM) gave the title compound (390 mg, 25%) as a yellow solid.

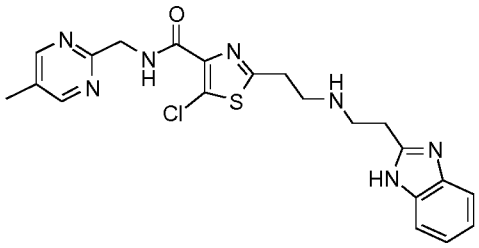
HPLCMS (Method A): [*m/z*]: 507 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 154)



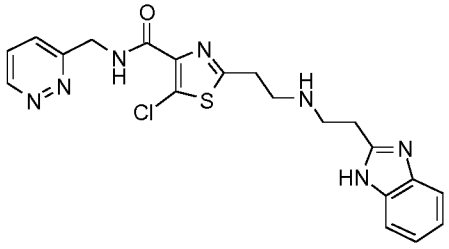
In a similar fashion to general procedure 8, 5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-thiazole-4-carboxamide **(198)** (390 mg, 0.77 mmol) and iron powder (172 mg, 3 mmol) in AcOH (5 ml) at 90°C for 30 min gave the crude product. The residue was flushed through a plug of silica, gradient elution 0.5-40% MeOH / DCM then 20% 7 M NH_3 in MeOH / DCM, followed by further purification by basic prep-HPLC to give the required product as the free base. The residue was re-dissolved in MeOH (10 ml) and treated with 12 M HCl (1 ml) for 1 h. The solvent was rigorously removed under vacuum to give the target compound as a pale yellow solid.
1H-NMR (D_2O, 500 MHz): d[ppm]= 8.33 - 8.30 (m, 1H), 7.87 (ddd, J = 9.6, 8.6, 1.2 Hz, 1H), 7.71 (dt, J = 6.8, 3.4 Hz, 2H), 7.59 (dt, J = 7.5, 4.2 Hz, 1H), 7.55 (dt, J = 6.3, 3.4 Hz, 2H), 3.72- 3.62 (m, 6H), 3.44 (t, J = 6.6 Hz, 2H). Note that a benzylic CH_2 signal is obscured by D2O
HPLCMS (Method A): [*m/z*]: 459.1 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-5-chloro-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 182)



In a similar fashion using general procedure 8, 2-(2-aminoethyl)-5-chloro-N-[(5-methylpyrimidin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(197)** (0.223 g, 0.522 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (0.090 g, 0.47 mmol) and DBU (0.171 ml, 1.148 mmol) in MeCN (10ml) gave the intermediate (355 mg, 0.46 mmol) which was further reacted with iron powder (104 mg, 1.86 mmol) in AcOH (5 ml) at 80°C for 2.5 h gave the title compound (6 mg, 3%) as an off-white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-5% MeOH / DCM).
1H-NMR (DMSO-d4, 500 MHz): d[ppm]= 8.54 (s, 2H), 7.47 - 7.41 (m, 2H), 7.20 - 7.14 (m, 2H), 4.62 (s, 2H), 3.23 - 3.16 (m, 4H), 3.15 - 3.10 (m, 4H), 2.28 (s, 3H)
HPLCMS (Method D): [*m/z*]: 456.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-5-chloro-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 183)

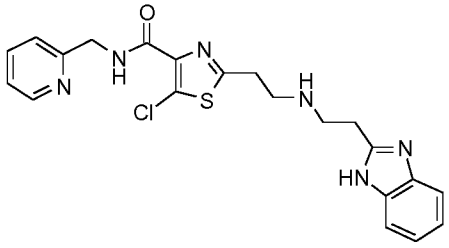


In a similar fashion using general procedure 8, 2-(2-aminoethyl)-5-chloro-N-(pyridazin-3-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(195)** (255mg, 0.689 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (132 mg, 0.689) and DBU (0.154 ml, 1.03 mmol) in MeCN (5 ml) gave the intermediate (112 mg, 0.16 mmol) which was further reacted with iron powder (18 mg, 0.33 mmol) in AcOH (1 ml) at 80°C for 2.5 h gave the title compound (6.4 mg, 8.5%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) followed by basic prep HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 9.08 (dd, J = 4.3, 2.3 Hz, 1H), 7.72 - 7.63 (m, 2H), 7.47 (dd, J = 5.9, 3.2 Hz, 2H), 7.23 - 7.15 (m, 2H), 4.80 (s, 2H), 3.16 - 3.02 (m, 8H)

HPLCMS (Method B): [*m/z*]: 440.4 $[M-H]^-$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 184)

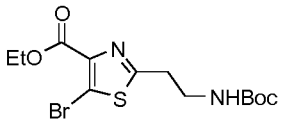


In a similar fashion using general procedure 8, 2-(2-aminoethyl)-5-chloro-N-(pyridin-2-ylmethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(194)** (361.6 mg, 0.978 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (187.9 mg, 0.978 mmol), DBU (0.219 ml, 1.467 mmol) in MeCN (5 ml) gave the intermediate (180 mg, 0.26 mmol) which was further reacted with iron powder (29 mg, 0.54 mmol) in AcOH (1 ml) at 80°C for 2 h gave the title compound (8.8 mg, 7.5%) as a yellow oil after purification by basic prep HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.47 (ddd, J = 5.0, 1.6, 0.9 Hz, 1H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.47 (dd, J = 5.9, 3.2 Hz, 2H), 7.37 (d, J = 7.9 Hz, 1H), 7.33 - 7.25 (m, 1H), 7.20 - 7.16 (m, 2H), 4.61 (s, 2H), 3.16 - 3.01 (m, 8H)

HPLCMS (Method B): [*m/z*]: 439.3 $[M-H]^-$

Ethyl 5-bromo-2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate (199)

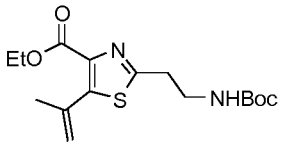


Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(1)** (1.56 g, 5.19 mmol) and 1,2-dibromo-1,1,2,2-tetrachloroethane (1.86 g, 10.0 mmol) were dissolved in THF (60 ml) and cooled to-78°C. 2 M NaHMDS (5.45 ml) was added dropwise and the mixture stirred at-78°C for 2 h. The reaction was quenched with sat. NH_4Cl (aq) (30 ml) and allowed to warm to room temperature. The mixture was extracted with DCM (3 x 100 ml) and the combined organic extracts dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography using a gradient elution 10-50% EtOAc / heptane gave the title compound (1.62 g, 80%) as a colourless oil.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 4.91 (s, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.56 (q, *J* = 6.3 Hz, 2H), 3.21 (t, *J* = 6.3 Hz, 2H), 1.50 – 1.42 (m, 12H)

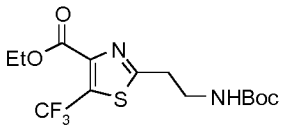
HPLCMS (Method A): [*m/z*]: 400.9 / 402.85 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxylate (200)



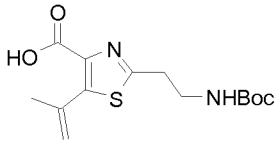
Ethyl 5-bromo-2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(199)** (626 mg, 1.65 mmol), $PdCl_2$(dppf) (120 mg, 0.17 mmol) and K_2CO_3 (460 mg, 3.0 mmol) were dissolved in MeCN (18 ml) and water (18 ml) under nitrogen and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.38 ml, 1.98 mmol) was added. The mixture was heated at 80°C for 30 min, cooled to room temperature and diluted with water. The mixture was extracted with DCM (3 x 80 ml) and the combined organic extracts dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash chromatography using a gradient elution 10-60% EtOAc / heptane gave the title compound (558 mg, 99%) as a yellow oil.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.23 (s, 1H), 5.12 (s, 1H), 4.94 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.47 (q, J = 6.5 Hz, 2H), 3.09 (t, J = 6.5 Hz, 2H), 2.07 (s, 3H), 1.37 (s, 9H), 1.31 (t,J = 7.2 Hz, 3H).
HPLCMS (Method A): [*m/z*]: 341.05 $[M+H]^+$

Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-(trifluoromethyl)-1,3-thiazole-4-carboxylate (201)



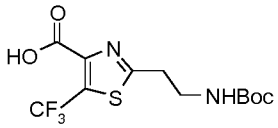
Ethyl 5-bromo-2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-thiazole-4-carboxylate **(199)** (0.54 g, 1.43 mmol) was dissolved in DMF (30 ml) under nitrogen and copper(I) iodide (1.36 g, 7.0 mmol), triphenylarsane (0.14 ml, 0.57 mmol), Pd_2dba_3 (0.065 g, 0.07 mmol) and methyl difluoro(fluorosulfonyl)acetate (0.23 ml, 1.85 mmol) were added. The mixture was heated at 100°C for 3 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between EtOAc and sat. $NaHCO_3$ (aq). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 80 ml) and the combined organic extracts were washed with brine (2 x 50 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 10-60% EtOAc / heptane) afforded the title compound (0.447 g, 84%) as a yellow oil.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 4.92 (s, 1H), 4.48 (q, J = 7.1 Hz, 2H), 3.60 (q, J = 6.2 Hz, 2H), 3.27 (t, J = 6.2 Hz, 2H), 1.46 (s, 9H), 1.44 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 391 $[M+Na]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxylic acid (202)



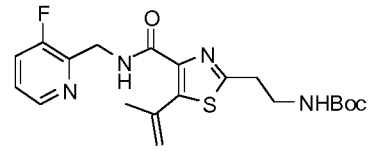
In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxylate **(200)** (550 mg, 1.62 mmol) and LiOH (390 mg, 16.0 mmol) in THF (20 ml) and water (20 ml) gave the crude title compound (569 mg, quant.) as a yellow oil.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 5.41 (s, 1H), 5.38 (s, 1H), 4.84 (s, 1H), 3.59 (m, 2H), 3.16 (t, J = 6.4 Hz, 2H), 2.23 (s, 3H), 1.47 (s, 9H)
HPLCMS (Method A): [*m/z*]: 312.9 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-(trifluoromethyl)-1,3-thiazole-4-carboxylic acid (203)



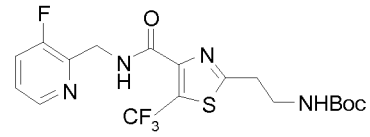
In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-(trifluoromethyl)-1,3-thiazole-4-carboxylate **(201)** (447 mg, 1.21 mmol) and LiOH (320 mg, 13.0 mmol) in THF (15 ml) and water (15 ml) afforded the title compound (365 mg, 88%) as a pale yellow solid.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 4.81 (s, 1H), 3.53 (q, J = 6.0 Hz, 2H), 3.18 (br s, 2H), 1.37 (s, 9H)
HPLCMS (Method A): [*m/z*]: 362.95 $[M+Na]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-(prop-1-en-2-yl)-1,3-thiazol-2-yl)ethyl]carbamate (204)



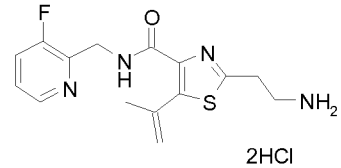
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxylic acid **(202)** (569 mg, 1.82 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (435 mg, 2.19 mmol), DIPEA (1.11 ml, 6.0 mmol) and HATU (830 mg, 2.0 mmol) in DCM (20 ml) gave the title compound (544 mg, 71%) as a colourless oil after purification by flash column chromatography (eluting with a gradient of 0-60% EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.51 - 8.43 (m, 2H), 7.45 - 7.38 (m, 1H), 7.30 - 7.24 (m, 1H), 5.34 (m, 1H), 5.27 (s, 1H), 4.83 (dd, J = 5.1, 1.6 Hz, 2H), 3.61 (m, 2H), 3.15 (m, 2H), 2.25 (s, 3H), 1.46 (s, 9H).
HPLCMS (Method A): [*m/z*]: 421.05 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-(trifluoromethyl)-1,3-thiazol-2-yl)ethyl]carbamate (205)



In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-(trifluoromethyl)-1,3-thiazole-4-carboxylic acid **(203)** (365 mg, 1.07 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (256.2 mg, 1.29 mmol), DIPEA (0.65 ml, 4 mmol) and HATU (490 mg, 1.3 mmol) in DCM (20 ml) gave the title compound (344 mg, 72%) after purification by flash column chromatography (eluting with a gradient of 20-30% EtOAc / heptane).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.49 (s, 1H), 8.35 (dt, J = 4.6, 1.3 Hz, 1H), 7.35 (ddd, J = 9.4, 84, 1.3 Hz, 1H), 7.25 - 7.15 (m, 1H), 4.85 (s, 1H), 4.77 (dd, J = 5.0, 1.6 Hz, 2H), 3.54 (q, J = 6.3 Hz, 2H), 3.17 (t, J = 6.3 Hz, 2H), 1.37 (s, 9H)
HPLCMS (Method A): [*m/z*]: 449.05 $[M+H]^+$

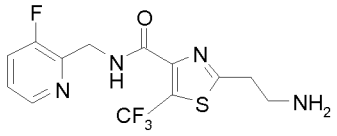
2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxamide dihydrochloride (206)



2HCl

In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-(prop-1-en-2-yl)-1,3-thiazol-2-yl)ethyl]carbamate **(204)** (544 mg, 1.29 mmol) and 12 M HCl (2 ml) in MeOH (10 ml) gave the title compound (486 mg, 94%) as a white solid.
HPLCMS (Method A): [*m/z*]: 321 $[M+H]^+$

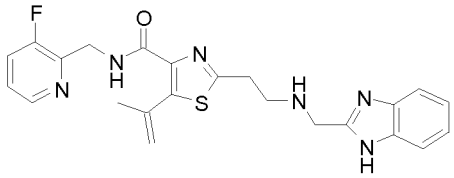
2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(trifluoromethyl)-1,3-thiazole-4-carboxamide dihydrochloride (207)



2HCl

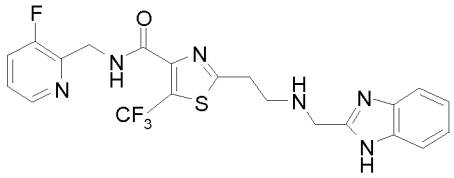
In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-(trifluoromethyl)-1,3-thiazol-2-yl)ethyl]carbamate **(205)** (347 mg, 0.77 mmol) and 12 M HCl (2 ml) in MeOH (10 ml) gave the title compound (330 mg, quant.) as a white solid.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 9.22 (t, J = 5.6 Hz, 1H), 8.40 (dt, J = 4.6, 1.4 Hz, 1H), 8.16 (s, 3H), 7.74 (ddd, J = 10.1, 8.4, 1.4 Hz, 1H), 7.43 (dt, J = 8.4, 4.4 Hz, 1H), 4.68 (dd, J = 5.8, 1.5 Hz, 2H), 3.42 - 3.22 (m, 4H)
HPLCMS (Method A): [*m/z*]: 349 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxamide (Example Compound No. 177)



In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxamide dihydrochloride **(206)** (260 mg, 0.66 mmol), 1H-benzimidazole-2-carbaldehyde (96.6 mg, 0.66 mmol), DIPEA (0.36 ml, 2.0 mmol) and $MgSO_4$ (300 mg) in MeOH (20 ml) at room temperature for 18 h, followed by addition of $NaBH_4$ (500 mg, 1.3 mmol) afforded the title compound (148 mg, 50%) as pale yellow solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.19 (s, 1H), 8.67 (t, J = 5.5 Hz, 1H), 8.36 (d, J = 4.6 Hz, 1H), 7.69 (t, J = 8.8 Hz, 1H), 7.58 - 7.43 (m, 2H), 7.40 (m, 1H), 7.16 - 7.09 (m, 2H), 5.21 (s, 1H), 5.15 (s, 1H), 4.61 (d, J = 5.5 Hz, 2H), 3.97 (s, 2H), 3.11 (t, J = 6.7 Hz, 2H), 2.96 (t, J = 6.7 Hz, 2H), 2.08 (s, 3H)
HPLCMS (Method C): [*m/z*]: 451.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-5-(trifluoromethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 176)

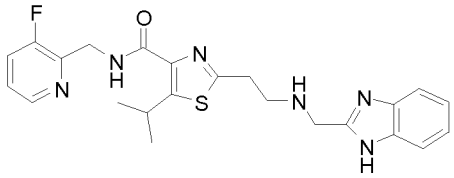


In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(trifluoromethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(207)** (130 mg, 0.31 mmol), 1H-benzimidazole-2-carbaldehyde (67.6 mg, 0.46 mmol), DIPEA (0.16 ml, 0.93 mmol) and $MgSO_4$ (300 mg) in MeOH (10 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (23 mg, 0.62 mmol) gave the title compound (81 mg, 55%) as pale yellow solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.21 (s, 1H), 8.96 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.3 Hz, 1H), 7.71 (ddd, J = 10.0, 8.3, 1.3 Hz, 1H), 7.53 (s, 1H), 7.45 (s, 1H), 7.41 (dt, J = 8.3, 4.4 Hz, 1H), 7.14 (s, 2H), 4.65 (dd, J = 5.7, 1.4 Hz, 2H), 3.99 (s, 2H), 3.22 (t, J = 6.3 Hz, 2H), 2.99 (t, J = 6.3 Hz, 2H), 2.80 (s, 1H)

HPLCMS (Method C): [*m/z*]: 479.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-5-(propan-2-yl)-1,3-thiazole-4-carboxamide (Example Compound No. 180)

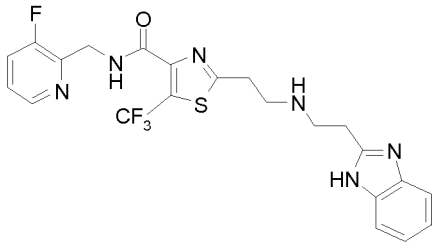


2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-5-(prop-1-en-2-yl)-1,3-thiazole-4-carboxamide **(Example Compound No. 177)** (120 mg, 0.27 mmol), and palladium on carbon (10%, 28 mg, 0.027 mmol) were combined in EtOH (10 ml) and the mixture stirred under an atmosphere of hydrogen for 1.5 h. The reaction mixture was filtered through a plug of Celite and the residue rinsed with MeOH. The combined filtrates were evaporated *in vacuo* and purified by basic prep-HPLC to afford the title compound (68 mg, 56%) as a white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.20 (s, 1H), 8.60 (t, J = 5.6 Hz, 1H), 8.38 - 8.34 (m, 1H), 7.70 (m, 1H), 7.58 - 7.43 (m, 2H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.16 - 7.09 (m, 2H), 4.63 (dd, J = 5.6, 1.4 Hz, 2H), 4.24 (hept, J = 6.8 Hz, 1H), 3.96 (s, 2H), 3.11 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H), 1.21 (d, J = 6.8 Hz, 6H)

HPLCMS (Method C): [*m/z*]: 453.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(trifluoromethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 186)

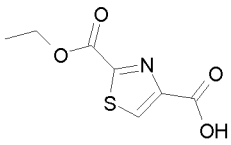


In a similar fashion using general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-(trifluoromethyl)-1,3-thiazole-4-carboxamide dihydrochloride **(207)** (242 mg, 0.57 mmol), N-(2-nitrophenyl)prop-2-enamide (110.4 mg, 0.57 mmol) and DBU (0.301 ml, 2 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (56 mg, 1 mmol) in AcOH (3 ml) to give the title compound (4 mg, 2%) after two purifications by basic prep-HPLC and a final purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.14 (s, 1H), 8.94 (t, J = 5.5 Hz, 1H), 8.39 (dt, J = 4.5, 1.4 Hz, 1H), 7.71 (ddd, J = 9.9, 8.3, 1.4 Hz, 1H), 7.41 (m, 2H), 7.10 (m, 2H), 4.64 (dd, J = 5.7, 1.4 Hz, 2H), 3.18 (t, J = 6.1 Hz, 2H), 3.06 (t, J = 6.1 Hz, 2H), 3.02 - 2.92 (m, 4H)

HPLCMS (Method C): [*m/z*]: 493.1 $[M+H]^+$

2-(Ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid (216)

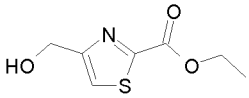


3-Bromo-2-oxopropanoic acid and ethyl amino(thioxo)acetate in THF (100 ml) were stirred at 60°C for 16 h. The reaction mixture was reduced *in vacuo* to give an orange solid. The solid was triturated with Et_2O, filtered and dried *in vacuo* to give the titled compound (4.54 g, 62.8%) as a colourless solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 13.40 (s, 1H), 8.77 (s, 1H), 4.40 (q, J = 7.1 Hz,2H), 1.35 (t, J = 7.1 Hz, 3H)

HPLCMS (ESI+): [*m/z*]: 201.90 $[M+H]^+$

Ethyl 4-(hydroxymethyl)-1,3-thiazole-2-carboxylate (217)

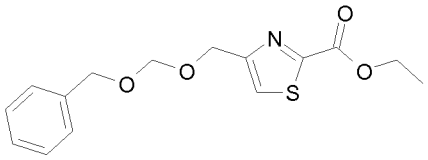


Isobutyl chloroformate (1.16 ml, 8.95 mmol) was added to an ice-cooled (0°C) suspension of 2-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid **(216)** (1.5 g, 7.46 mmol) and TEA (1.25 ml, 8.95 mmol) in THF (60 ml). The reaction was stirred at 0°C for 1 h. The reaction was filtered through a plug of Celite and $NaBH_4$ (0.705 g, 18.64 mmol) was added to the filtrate and stirred for 2h. The reaction was diluted with sat. aq. Na_2CO_3 solution and stirred for 10 mins, then extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and the solvent evaporated. Purification by flash column chromatography (eluting with a gradient of 40-50% EtOAc-Heptane) gave the titled compound (0.734 g, 52.6%) as a crystalline solid.

1H-NMR (DMSO-d6, 500 MHz) d[ppm]= 7.85 (s, 1H), 5.50 (t, *J* = 5.8 Hz, 1H), 4.63 (dd, *J* = 5.8, 0.8 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.33 (d, *J* = 7.1 Hz, 3H)

HPLCMS (ESI+): [*m/z*]: 187.90 $[M+H]^+$

Ethyl 4-{[(benzyloxy)methoxy]methyl}-1,3-thiazole-2-carboxylate (218)

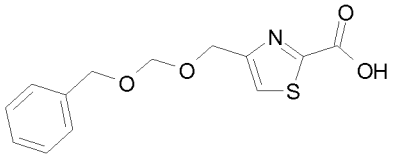


NaH (60%, 0.106 g, 2.66 mmol) was added to an ice-cooled (0°C) solution of ethyl 4-(hydroxymethyl)-1,3-thiazole-2-carboxylate **(217)** (0.415 g, 2.22 mmol) in THF (20 ml) and the reaction stirred at 0°C for 30 mins. [(Chloromethoxy)methyl]benzene (0.416 g, 2.66 mmol) was added and the reaction allowed to warm to room temperature over 3h. The reaction was quenched by addition of sat.aq. NH_4Cl and extracted with EtOAc. The combined organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and the solvent evaporated. Purification by flash column chromatography (eluting with 30-50% EtOAc-Heptane) gave the title compound (0.392 g, 48.9%) as a colourless oil.

1H-NMR ($CDCl_3$, 500 MHz) d[ppm]= 7.52 - 7.50 (m, 1H), 7.36 - 7.33 (m, 5H), 4.90 (s, 2H), 4.86 (d, *J* = 0.8 Hz, 2H), 4.66 (s, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1, 3H).

HPLCMS (ESI+): [*m/z*]: 307.95 $[M+H]^+$

4-{[(Benzyloxy)methoxy]methyl}-1,3-thiazole-2-carboxylic acid (219)

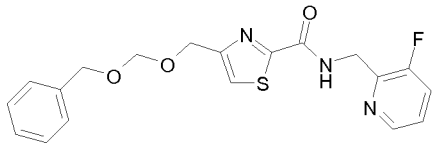


In a similar fashion to general procedure 5, LiOH (64 mg, 1.53 mmol) was added to a solution of ethyl 4-{[(benzyloxy)methoxy]methyl}-1,3-thiazole-2-carboxylate **(218)** (85%, 0.39 g, 1.28 mmol) in THF (5 ml), MeOH (5 ml) and water (5 ml) at room temperature for 4 h, gave the title compound (0.35 g, 88.4%) as a colourless oil.

1H-NMR (DMSO-d6, 500 MHz) d[ppm]= 7.95 (s, 1H), 7.36 - 7.33 (m, 5H), 4.84 (s, 2H), 4.74 (s, 2H), 4.60 (s, 2H), 4.49 (s, 1H).

HPLCMS (ESI+): [*m/z*]: 279.95 $[M+H]^+$

4-{[(Benzyloxy)methoxy]methyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-2-carboxamide (220)

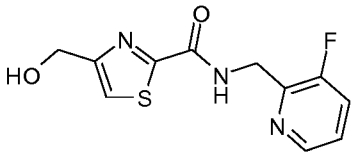


In a similar fashion to general procedure 6, 4-{[(benzyloxy)methoxy]methyl}-1,3-thiazole-2-carboxylic acid **(219)** (0.350 g, 1.25 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.374 g, 1.88 mmol), DIPEA (0.89 ml, 5.01 mmol) and HATU (0.714 g, 1.88 mmol) in DMF (10 ml) at room temperature for 16 h, gave the title compound (0.381 g, 76.1%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-5% MeOH-DCM).

1H-NMR ($CDCl_3$, 250 MHz) d[ppm]= 8.42 - 8.38 (m, 1H), 7.40 - 7.27 (m, 7H), 4.90 (s, 2H), 4.86 - 4.82 (m, 2H), 4.80 (d, *J* = 0.6 Hz, 2H), 4.68 (s, 2H)

HPLCMS (ESI+): [*m/z*]: 388.05 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-4-(hydroxymethyl)-1,3-thiazole-2-carboxamide (221)

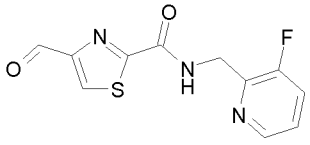


TFA (1 ml, 13.06 mmol) was added to an ice-cooled (0°C) solution of 4-{[(benzyloxy)methoxy]methyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-2-carboxamide **(220)** (0.185 g, 0.48 mmol) in DCM (4 ml). The reaction allowed to warm to room temperature and stirred for 16 h. The solvent evaporated and the resulting residue dissolved in EtOAc (5 ml) and washed with sat. aq. $NaHCO_3$ (20 ml), brine (10 ml), dried (Na_2SO_4), filtered and the solvent evaporated. Purification by flash column chromatography (eluting with a gradient of 5% MeOH-DCM) gave the titled compound (0.085 g, 73.2%) as a colourless powder.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.45 - 8.41 (m, 1H), 8.36 (br s, 1H), 7.45 (s, 1H), 7.44 - 7.40 (m, 1H), 7.31 - 7.26 (m, 1H), 4.85 (dd, *J* = 5.1, 1.6 Hz, 2H), 4.83 (d, *J* = 5.6 Hz, 2H), 2.20 (t, *J* = 6.0 Hz, 1H)

HPLCMS (ESI+): [*m/z*]: 267.95 $[M+H]^+$

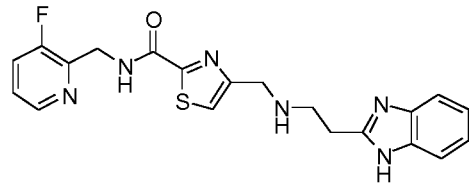
N-[(3-Fluoropyridin-2-yl)methyl]-4-formyl-1,3-thiazole-2-carboxamide (222)



IBX (189 mg, 0.70 mmol) was added to a solution of N-[(3-fluoropyridin-2-yl)methyl]-4-(hydroxymethyl)-1,3-thiazole-2-carboxamide (221) (60 mg, 0.22 mmol) in MeCN (5 ml) and the reaction heated at 80°C for 3 h. The reaction was cooled to room temperature and filtered through Celite. The solution was directly absorbed onto silica and purified by flash column chromatography (eluting with a gradient of 5% MeOH-DCM). The product was re-purified by flash column chromatography (eluting with a gradient of 30-50% EtOAc-Heptane) to give titled compound (56 mg, 94%) as a colourless solid.

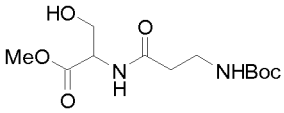
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 10.10 (s, 1H), 8.46 (br s, 1H), 8.46 - 8.44 (m, 1H), 8.37 (s, 1H), 7.46 - 7.42 (m, 1H), 7.33 - 7.28 (m, 1H), 4.88 (dd, *J* = 5.1, 1.7 Hz, 2H)
HPLCMS (ESI+): [*m/z*]: 265.95 $[M+H]^+$

4-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-2-carboxamide (Example Compound No. 205)



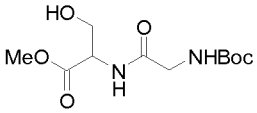
A solution of N-[(3-fluoropyridin-2-yl)methyl]-4-formyl-1,3-thiazole-2-carboxamide **(222)** (56 mg, 0.21 mmol) in DCE (1mL) was added to a suspension of 2-(1H-1,3-benzodiazol-2-yl)ethan-1-amine dihydrochloride (50 mg, 0.21 mmol) and DIPEA (147 µl, 0.84 mmol) in DCE (2 ml). 4Å activated molecular sieves were added and the solution stirred at room temperature for 2 h, then filtered and the filtrates concentrated *in vacuo*. The residue was dissolved in MeOH (10 ml) and cooled to 0°C. $NaBH_4$ (12 mg, 0.32 mmol) was added, the mixture was warmed to room temperature and stirred for 1 h, then quenched with sat. Na_2CO_3(aq) and extracted with EtOAc (2 x 10 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by basic prep-HPLC afforded the title compound (44 mg, 51%) as a colourless foam.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.31 (dt, *J* = 4.5, 1.2 Hz, 1H), 7.62 (s, 1H), 7.57 (ddd, *J* = 9.8, 8.5, 1.2 Hz, 1H), 7.46 (dt, *J* = 6.6, 3.3 Hz, 2H), 7.36 (dt, *J* = 8.5, 4.5 Hz, 1H), 7.18 – 7.14 (m, 2H), 4.75 (d, *J* = 1.6 Hz, 2H), 3.96 (s, 2H), 3.13 – 3.07 (m, 4H).
HPLCMS (Method C): [*m/z*]: 411.1 $[M+H]^+$

General Scheme 12 above
General procedure 13: methyl 2-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-3-hydroxypropanoate (223)



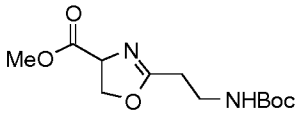
TEA (8.38 ml, 60.1 mmol) was added to a cooled (0°C) solution of methyl serinate hydrochloride (1:1) (8.5 g, 54.6 mmol) in DCM (250 ml) under nitrogen. N-(tert-butoxycarbonyl)-beta-alanine (10.3 g, 54.6 mmol) and DCC (12.4 g, 60.1 mmol) were added portionwise. The reaction mixture was allowed to warm to room temperature and stirred for 19 h. The solvent was evaporated and EtOAc (250 ml) was added. The mixture was heated to 50°C and stirred for 20 min, cooled to room temperature and filtered. The filtrate was evaporated to give a waxy off-white solid (21.7 g). The solid was dissolved in MeOH (200 ml) and silica (300 ml volume) was added. The solvent was evaporated under reduced pressure to give the compound dry loaded onto silica. Purification by flash column chromatography (eluting with a gradient of 20% EtOAc / heptane (2 L), 40% EtOAc / heptane (4 L), 80% EtOAc / heptane (2 L) followed by EtOAc (8 L) gave the title compound (10.4 g, 64.4%) as an off-white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 6.62 (s, 1H), 5.12 (s, 1H), 4.65 (dt, J = 7.1, 3.4 Hz, 1H), 3.96 (t, J = 3.2 Hz, 2H), 3.80 (s, 3H), 3.55 - 3.33 (m, 2H), 2.95 (s, 1H), 2.48 (td, J = 5.8, 2.6 Hz, 2H), 1.43 (s, 9H)
HPLCMS (Method A): [*m/z*]: 291 $[M+H]^+$

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}acetamido)-3-hydroxypropanoate (224)



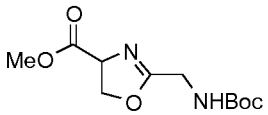
In a similar fashion to general procedure 13, methyl serinate hydrochloride (3 g, 19.28 mmol), TEA (2.96 ml, 21.21 mmol), N-(tert-butoxycarbonyl)glycine (3.38 g, 19.28 mmol) and DCC (4.38 g, 21.21 mmol) in DCM (100ml) afforded the title compound (4.5 g, 69%) as a pale yellow oil after purification by flash chromatography using an elution gradient 20-100% EtOAc / heptane.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.07 (d, J = 7.4 Hz, 1H), 5.32 (s, 1H), 4.77 - 4.60 (m, 1H), 3.99 (m, 2H), 3.87 (m, 2H), 3.81 (s, 3H), 3.04 (s, 1H), 1.48 (s, 9H)
HPLCMS (Method A): [*m/z*]: 298.95 $[M+Na]^+$

General procedure 14: methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (225)



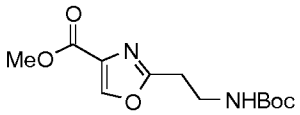
Methyl 2-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-3-hydroxypropanoate **(223)** (98%, 10.42 g, 35.17 mmol) was dissolved in anhydrous DCM (280 ml) under nitrogen. The reaction mixture was cooled in a CO_2 / MeCN bath (approx. -50°C) and stirred for 30 min. DAST (5.58 ml, 42.21 mmol) was added dropwise and the mixture was stirred at -50°C for 2.25 h. K_2CO_3 (4.86 g, 35.17 mmol) was added in one portion and the reaction mixture was allowed to stir for 20 min, before it was warmed up to room temperature. The reaction mixture was then immersed in a water bath and water (60 ml) was added cautiously (effervescence occurred) to the reaction followed by 2 M NaOH (5 ml). The reaction mixture was stirred for further 10 min and the layers were then separated. The aqueous layer was extracted with DCM (2 x 50 ml). The combined organic layers were dried (MgSO4), filtered and evaporated to give the title compound (10.3 g) as an orange oil. The crude product was carried through the next step without further purification.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 5.14 (s, 1H), 4.72 (ddt, J = 10.3, 7.6, 1.2 Hz, 1H), 4.47 (dd, J = 8.7, 7.7 Hz, 1H), 4.39 (dd, J = 10.6, 8.8 Hz, 1H), 3.78 (s, 3H), 3.49 - 3.36 (m, 2H), 2.48 (td, J = 6.2, 1.2 Hz, 2H), 1.42 (s, 9H)
HPLCMS (Method A): [*m/z*]: 273 $[M+H]^+$

Methyl 2-({[(tert-butoxy)carbonyl]amino}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (226)



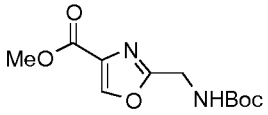
In a similar fashion to general procedure 14, methyl 2-(2-{[(tert-butoxy)carbonyl]amino}acetamido)-3-hydroxypropanoate **(224)** (2.5 g, 7.42 mmol) and DAST (1.18 ml, 8.9 mmol) in DCM (70 ml) afforded the title compound (2.02 g, quant.) as a yellow oil.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.12 (s, 1H), 4.86 - 4.68 (m, 1H), 4.62 - 4.42 (m, 2H), 4.11 - 3.89 (m, 2H), 3.82 (s, 3H), 1.44 (s, 9H)
HPLCMS (Method A): [*m/z*]: 258.95 $[M+H]^+$

General procedure 15: methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylate (227)



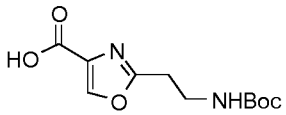
Bromo(trichloro)methane (10.4 ml, 105.56 mmol) was added to a solution of methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **(225)** (93.2%, 10.28 g, 35.19 mmol) in anhydrous DCM (300 ml) under nitrogen cooled to 0°C. DBU (15.75 ml, 105.56 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 2.5 h. Saturated aqueous citric acid (25 ml) was added followed by water (100 ml). The reaction mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with DCM (3 x 100 ml). The organic layer was dried (MgSO4), filtered and evaporated to give a dark brown oil (14.6 g). The crude oil was dry loaded onto silica with MeOH (200 ml). The crude material was filtered through a silica plug [gradient elution with heptane (2 x 500 ml), 25% EtOAc / heptane (2 x 500 ml) and 50% EtOAc / heptane (11 x 500 ml)] to give the title compound (8.63g) as a yellow oil which solidified on standing.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.16 (s, 1H), 4.99 (s, 1H), 3.90 (s, 3H), 3.57 (q, J = 6.0 Hz, 2H), 2.99 (t, J = 6.3 Hz, 2H), 1.40 (s, 9H)
HPLCMS (Method A): [*m/z*]: 293.0 $[M+Na]^+$

Methyl 2-({[(tert-butoxy)carbonyl]amino}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate (228)



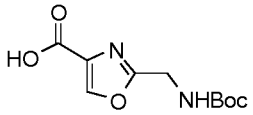
In a similar fashion to general procedure 15, methyl 2-({[(tert-butoxy)carbonyl]amino}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **(226)** (2.02 g, 7.43 mmol), DBU (3.33 ml, 22.29 mmol) and bromo(trichloro)methane (2.2 ml, 22.29 mmol) in DCM (75 ml) afforded the title compound (1.04 g, 55%) as a colourless oil after purification by flash column chromatography using an elution gradient 0-100% TBME / heptane.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.19 (s, 1H), 5.19 (br. s, 1H), 4.49 (d, J = 5.5 Hz, 2H), 3.92 (s, 3H), 1.45 (s, 9H)
HPLCMS (Method A): [*m/z*]: 278.95 $[M+Na]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylic acid (229)



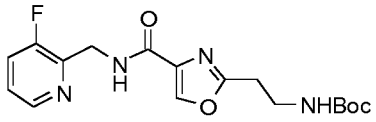
In a similar fashion using general procedure 5, LiOH (1.02 g, 42.76 mmol) and methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylate **(227)** (97%, 6.62 g, 23.76 mmol) in THF (100 ml), and water (25 ml) gave the title compound (4.8 g, 79%) as an off white powder.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.62 (s, 1H), 6.94 (t, J = 5.4 Hz, 1H), 3.31 - 3.26 (m, 2H, partially obscured by HOD peak), 2.87 (t, J = 6.8 Hz, 2H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 278.9 $[M+Na]^+$

2-({[(Tert-butoxy)carbonyl]amino}methyl)-1,3-oxazole-4-carboxylic acid (230)



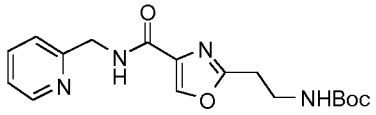
In a similar fashion to general procedure 5, methyl 2-({[(tert-butoxy)carbonyl]amino}methyl)-4,5-dihydro-1,3-oxazole-4-carboxylate **(228)** (1.04 g, 4.06 mmol) and LiOH (0.15 g, 6.09 mmol) in THF / water (20 ml / 5 ml) afforded the title compound (1.07 g, quant.) as an off-white solid.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.29 (s, 1H), 5.39 (br. s, 1H), 4.54 (d, J = 4.9 Hz, 2H), 1.47 (s, 9H)
HPLCMS (Method A): [*m/z*]: 265 $[M+Na]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate (231)



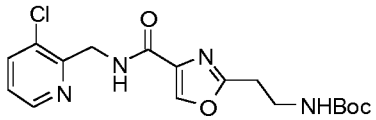
In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylic acid **(229)** (3.78 g, 14.75 mmol), HATU (6.17 g, 16.23 mmol), (DIPEA) (8.48 ml, 48.68 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (2.94 g, 14.75 mmol) in THF / water (100 ml / 40 ml) gave the title compound (4.83 g, 87%) as a yellow glassy solid after purification by flash column chromatography (eluting with a gradient 0-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.51 (s, 2H), 8.40 (d, J = 4.4 Hz, 1H), 7.70 (t, J = 9.3 Hz, 1H), 7.45 - 7.37 (m, 1H), 6.98 (t, J = 5.5 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 3.32 - 3.28 (m, 2H, signal partially obscured by HOD peak), 2.90 (t, J = 6.7 Hz, 2H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 365.0 $[M+H]^+$

Tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}ethyl)carbamate (232)



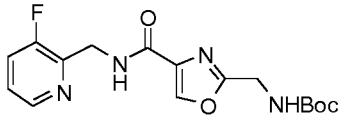
In a similar fashion using general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylic acid **(229)** (4 g, 15.61 mmol), DIPEA (5.44 ml, 31.22 mmol), HATU (8.9 g, 23.41 mmol), pyridin-2-ylmethanamine (2.41 ml, 23.41 mmol) in DMF (65 ml) gave the title compound (6.03 g) as a yellow viscous oil after purification by flash column chromatography (eluting with a gradient 0-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.74 (t, J = 5.9 Hz, 1H), 8.54 - 8.48 (m, 2H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.32 - 7.22 (m, 2H), 6.98 (s, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.29 (d, J = 6.5 Hz, 2H), 2.90 (t, J = 6.7 Hz, 2H), 1.34 (s, 9H)
HPLCMS (Method A): [*m/z*]: 347.1 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate (233)



In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1,3-oxazole-4-carboxylic acid **(229)** (295 mg, 0.76 mmol, 66%), (3-chloropyridin-2-yl)methanamine dihydrochloride (246 mg, 1.14 mmol), TEA (0.1 ml, 0.76 mmol) and HATU (0.43 g, 1.14 mmol) in DMF (10 ml) afforded the title compound (202 mg, 59%, 85% purity) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.58 – 8.45 (m, 2H), 7.96 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.40 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.00 (t, *J* = 6.2 Hz, 1H), 4.65 (d, *J* = 5.4 Hz, 2H), 2.97 – 2.86 (m, 4H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 381.05 $[M+H]^+$

Tert-butyl N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)methyl]carbamate (234)



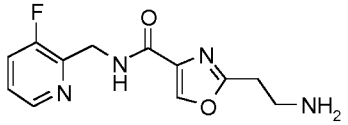
In a similar fashion to general procedure 6, 2-({[(tert-butoxy)carbonyl]amino}methyl)-1,3-oxazole-4-carboxylic acid **(230)** (0.5 g, 2.06 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.41 g, 2.06 mmol), DIPEA (1.19 ml, 6.81 mmol) and HATU (0.86 g, 2.27 mmol) in THF (15 ml) and DMF (6 ml)

gave the title compound (0.744 g, 98%) as a colourless oil after purification by flash chromatography using an elution gradient 0-100% EtOAc / heptane.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.56 (s, 1H), 8.51 (t, J = 5.2 Hz, 1H), 8.38 (d, J = 4.6 Hz, 1H), 7.73 - 7.65 (m, 1H), 7.55 (t, J = 5.8 Hz, 1H), 7.44 - 7.37 (m, 1H), 4.65 - 4.59 (m, 2H), 4.29 (d, J = 5.9 Hz, 2H), 1.39 (s, 9H)

HPLCMS (Method A): [*m/z*]: 351.0 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride (235)



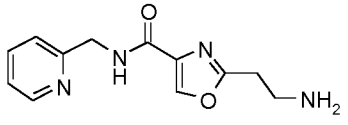
2HCl

In a similar fashion using general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate **(231)** (4.83 g, 12.86 mmol), 4 M HCl in 1,4-dioxane (50 ml) and DCM (80 ml) gave the title compound (4.61 g) as an off-white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.71 (t, J = 5.8 Hz, 1H), 8.59 (s, 1H), 8.42 - 8.36 (m, 1H), 8.13 (br. s, 3H), 7.76 - 7.68 (m, 1H), 7.46 - 7.39 (m, 1H), 4.64 (dd, J = 5.8, 1.4 Hz, 2H), 3.25 (app. q, J = 6.1 Hz, 2H), 3.20 - 3.14 (m, 2H)

HPLCMS (Method F): [*m/z*]: 265.1 $[M+H]^+$

2-(2-Aminoethyl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide dihydrochloride (236)



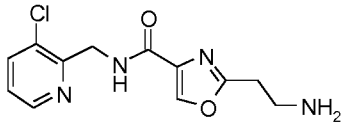
2HCl

In a similar fashion using general procedure 2, tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}ethyl)carbamate **(232)** (90%, 6.03 g, 15.68 mmol), 12 M HCl (26.13 ml) in MeOH gave the title compound (5.78 g) as a cream foam.

1H-NMR (Methanol-d4, 250 MHz): d[ppm]= 8.80 (dd, J = 5.9, 0.8 Hz, 1H), 8.62 (td, J = 8.0, 1.6 Hz, 1H), 8.44 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.01 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H), 3.51- 3.43 (m, 2H), 3.26 (t, J = 6.4 Hz, 2H).

HPLCMS (Method A): [*m/z*]: 246.9 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride (237)



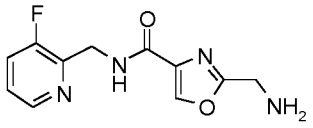
2HCl

In a similar fashion using general procedure 2, tert-butyl N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)ethyl]carbamate **(233)** (85%, 202 mg, 0.45 mmol), MeOH (5 ml) and 4 M HCl in dioxane (1.65 ml) gave the title compound (125 mg, 62%) as a brown solid.

^{1}H NMR (DMSO-d6, 500 MHz): d[ppm]= 8.67 (t, J = 5.6 Hz, 1H), 8.61 (s, 1H), 8.52 (dd, J = 4.7, 1.4 Hz, 1H), 8.15 (s, 3H), 7.96 (dd, J = 8.1, 1.4 Hz, 1H), 7.40 (dd, J = 8.1, 4.7 Hz, 1H), 4.67 (d, J = 5.6 Hz, 2H), 3.29 – 3.23 (m, 2H), 3.21 – 3.16 (m, 2H).

HPLCMS (Method A): [*m/z*]: 281.1 $[M+H]^+$

2-(Aminomethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride (238)



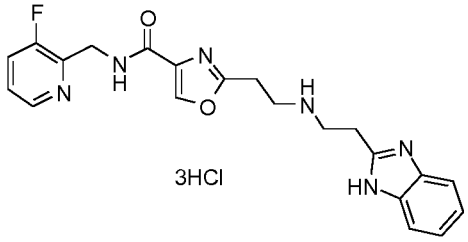
2HCl

In a similar fashion to general procedure 2, tert-butyl N-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)methyl]carbamate **(234)** (744 mg, 2.02 mmol) and 4 M HCl in 1,4-dioxane (15 ml) in DCM (20 ml) afforded the title compound (668 mg, quant.) as a white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.79 (s, 1H), 8.73 (br. s, 3H), 8.54 (t, J = 5.6 Hz, 1H), 8.39 (d, J = 4.7 Hz, 1H), 7.80 - 7.68 (m, 1H), 7.49 - 7.38 (m, 1H), 4.66 (d, J = 4.6 Hz, 2H), 4.32 (t, J = 5.5 Hz, 2H)

HPLCMS (Method F): [*m/z*]: 251.1 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride (Example Compound No. 127)



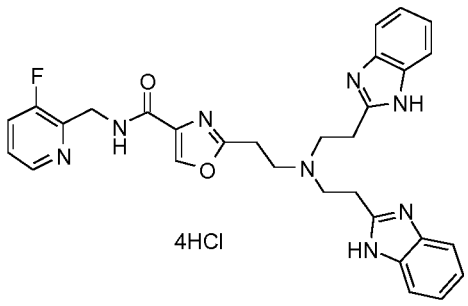
3HCl

In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (1 g, 2.97 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (0.63 g, 3.26 mmol) and DBU (1.5 ml, 10.08 mmol) in MeCN (30 ml) at room temperature overnight gave the crude intermediate which was further reacted with iron powder (0.5 g) in AcOH (10 ml) under nitrogen at 80°C for 3 h. the crude material was purified by basic prep-HPLC followed by further purification by flash column chromatography (eluting with gradient 0-30% MeOH in DCM) gave 2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide. The free base was dissolved in MeOH (10 ml) and treated with 12 M hydrogen chloride (1.5 ml). The solvent was then rigorously evaporated under vacuum to give the title compound (333 mg, 22%) as a white solid.

1H-NMR (D_2O, 500 MHz): d[ppm]= 8.34 - 8.30 (m, 2H), 7.86 (ddd, J = 9.6, 8.7, 1.2 Hz, 1H), 7.74 - 7.69 (m, 2H), 7.62 - 7.57 (m, 1H), 7.57 - 7.52 (m, 2H), 3.74 - 3.66 (m, J = 4.3 Hz,4H), 3.64 (t, J = 6.7 Hz, 2H), 3.33 (t, J = 6.7 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 409.1 $[M+H]^+$

2-(2-{bis[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide tetrahydrochloride (Example Compound No. 128)



4HCl

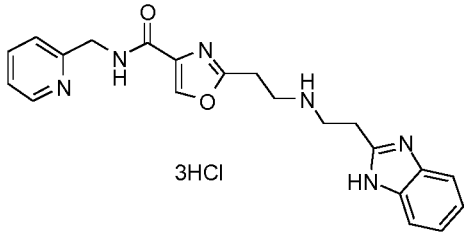
In a similar fashion to general procedure 7, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(Example Compound No. 127)** (305 mg, 0.9 mmol), 2-(2-chloroethyl)-1H-1,3-benzodiazole hydrochloride (216 mg, 1 mmol) and DIPEA (3.15 ml, 18mmol) in DMF (5ml) afforded the title compound freebase after purification by basic prep-HPLC. The freebase was treated with 12 M HCl

(0.5 ml) in MeOH (5 ml) to afford the title compound as tetrahydrochloride sal (5 mg, 0.8%) as a brown residue.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.56 - 8.52 (m, 1H), 8.45 (s, 1H), 8.21 - 8.15 (m, 1H), 7.90 - 7.84 (m, 2H), 7.84 - 7.77 (m, 3H), 7.69 - 7.60 (m, 3H), 7.58 (ddd, J = 8.2, 7.4, 0.6 Hz, 1H), 5.32 - 5.22 (m, 2H), 4.90 (s, 2H), 4.17 - 4.11 (m, 2H), 4.02 - 3.94 (m, 2H), 3.93 - 3.86 (m, 2H), 3.78 (t, J = 6.3 Hz, 2H), 3.48 (t, J = 6.3 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 553.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide trihydrochloride (Example Compound No. 171)

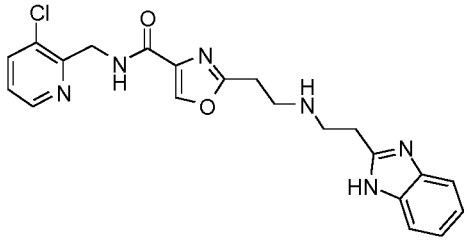


In a similar fashion using general procedure 8, 2-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide dihydrochloride **(236)** (86%, 1.2 g, 3.25 mmol), DBU (1.46 ml, 9.76 mmol) and *N*-(2-nitrophenyl)prop-2-enamide **(D)** (0.69 g, 3.58 mmol) in MeCN (30 ml) gave the crude intermediate, which was further reacted with iron powder (0.52 g) in AcOH (10 ml) to give the title compound (0.22 g, 12%) as a pale brown solid.

1H-NMR (D_2O), 500 MHz): d[ppm]= 8.72 (d, J = 5.8 Hz, 1H), 8.54 (td, J = 8.0, 1.5 Hz, 1H), 8.46 (s, 1H), 8.00 - 7.94 (m, 2H), 7.81 (dt, J = 6.2, 3.2 Hz, 2H), 7.63 (dt, J = 6.2, 3.3 Hz, 2H), 4.88 (s, 2H), 3.83- 3.70 (m, 6H), 3.43 (t, J = 6.9 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 391.2 $[M+H]^+$

2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 173)

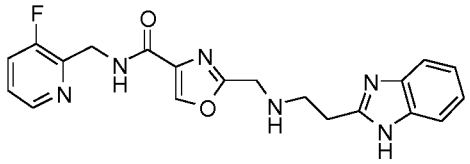


In a similar fashion using general procedure 8, 2-(2-aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(237)** (75%, 120 mg, 0.25 mmol), DBU (76 µl, 0.51 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (48 mg, 0.25 mmol) in MeCN (5ml) gave the crude intermediate, which was further reacted with iron powder (36.9 mg) in AcOH (2 ml) to give the title compound (4.6mg, 3%) as a clear film after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.44 (dd, J = 4.7, 1.4 Hz, 1H), 8.28 (s, 1H), 7.86 (dd, J = 8.1, 1.4 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.33 (dd, J = 8.1, 4.8 Hz, 1H), 7.19 - 7.14 (m, 2H), 4.70 (s, 2H), 3.18 - 3.04 (m, 8H)

HPLCMS (Method C): [*m/z*]: 425.2 $[M+H]^+$

2-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 206)

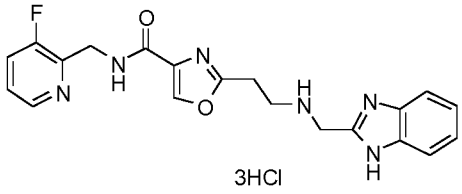


In a similar fashion to general procedure 8, 2-(aminomethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(238)** (300 mg, 0.93 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (196 mg, 1.02 mmol) and DBU (471.1 µl, 3.16 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (156 mg, 2.79 mmol) in AcOH (5 ml) to afford the title compound (20 mg, 27%) as a white solid after purification by basic prep-HPLC followed by flash chromatography using an elution gradient 2-20% MeOH / DCM.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.57 (s, 1H), 8.53 (t, J = 5.6 Hz, 1H), 8.38 (dt, J = 4.6, 1.3 Hz, 1H), 7.70 (m, 1H), 7.51 (d, J = 6.9 Hz, 1H), 7.41 (m, 2H), 7.15- 7.07 (m, 2H), 4.62 (dd, J = 5.6, 1.3 Hz, 2H), 3.92 (s, 2H), 3.04 - 2.99 (m, 2H), 2.98 - 2.94 (m, 2H)

HPLCMS (Method C): [*m/z*]: 395.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide trihydrochloride (Example Compound No. 126)

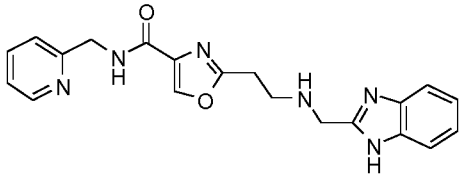


In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (100 mg, 0.3 mmol), 1H-benzimidazole-2-carbaldehyde (43.3 mg, 0.3 mmol), DIPEA (0.207 ml, 1.19 mmol) and anhydrous $MgSO_4$ (200 mg) in DCM (10 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (17 mg, 0.45 mmol) afforded the free base compound after purification by basic prep-HPLC. The residue was re-dissolved in MeOH (5 ml) and treated with 12M HCl (1 ml) for 30 min to give the title compound (64 mg, 42%) as a white hygroscopic solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.57 (dd, J = 5.4, 0.9 Hz, 1H), 8.46 (s, 1H), 8.26 - 8.19 (m, 1H), 7.88 (ddt, J = 13.4, 8.9, 4.1 Hz, 3H), 7.68 (td, J = 6.3, 5.5, 2.1 Hz, 2H), 5.02 (s, 2H), 4.94 (s, 2H), 3.83 (t, J = 6.3 Hz, 2H), 3.47 (t, J = 6.3 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 395.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridine-2-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 137)

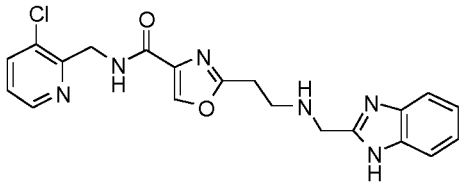


In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-(pyridine-2-ylmethyl)-1,3-oxazole-4-carboxamide dihydrochloride **(236)** (430 mg, 1.31 mmol), 1H-benzimidazole-2-carbaldehyde (229 mg, 1.57 mmol) and DIPEA (0.91 ml, 5.23 mmol) in MeOH (20 ml) at room temperature for 17 h, followed by addition of $NaBH_4$ (74 mg, 1.96 mmol) afforded the title compound (380 mg, 77%) as a yellow solid after purification by flash chromatography using a gradient elution of 0-20% MeOH / DCM.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.72 (t, J = 5.9 Hz, 1H), 8.53 - 8.46 (m, 2H), 7.74 (td, J = 7.7, 1.7 Hz, 1H), 7.48 (m, 2H), 7.31 - 7.22 (m, 2H), 7.12 (m, 2H), 4.52 (d, J = 6.0 Hz, 2H), 3.95 (s, 2H), 3.03 - 2.93 (m, 4H)

HPLCMS (Method C): [*m/z*]: 377.2 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-chloropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 141)

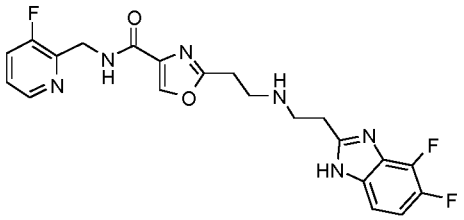


In a similar fashion using general procedure 3, 2-(2-aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(237)** (118 mg, 0.31 mmol), 1H-benzimidazole-2-carbaldehyde (54 mg, 0.37 mmol) and DIPEA (0.216 ml, 1.24 mmol) in MeOH (4 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (18 mg, 0.46 mmol) gave the title compound (51 mg, 40%) as a brown solid after purification by basic prep-HPLC.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.41 (dd, J = 4.8, 1.4 Hz, 1H), 8.29 (s, 1H), 7.86 (dd, J = 8.1, 1.4 Hz, 1H), 7.53 - 7.49 (m, 2H), 7.34 - 7.30 (m, 1H), 7.21 - 7.18 (m, 2H), 4.76 (s, 2H), 4.08 (s, 2H), 3.14 - 3.09 (m, 2H), 3.07 - 3.03 (m, 2H)

HPLCMS (Method D): [*m/z*]: 411.2 $[M+H]^+$

2-(2-{[2-(4,5-Difluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 257)

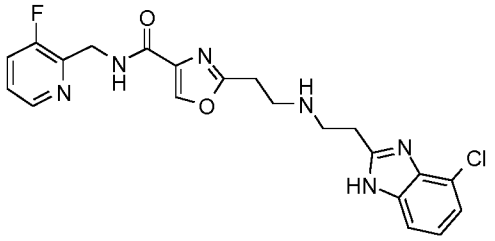


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (350 mg, 1.04 mmol), N-(2,3-difluoro-6-nitrophenyl)prop-2-enamide **(K10)** (250 mg, 1.10 mmol) and DBU (465 µl, 3.11 mmol) in MeCN (10 ml) gave an intermediate (193 mg) after purification by flash column chromatography (eluting with a gradient 0-20% MeOH / DCM). The intermediate was further reacted with iron powder (88 mg, 1.57 mmol) in AcOH (2 ml) to give the title compound (14 mg, 8%) as a pale yellow solid after purification by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.55 - 8.47 (m, 2H), 8.38 (d, J = 4.6 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.44 - 7.36 (m, 1H), 7.23 (dd, J = 8.8, 3.6 Hz, 1H), 7.17 - 7.09 (m, 1H), 4.61 (d, J = 4.8 Hz, 2H), 3.02 - 2.91 (m, 8H)

HPLCMS (Method G): [*m/z*]: 445.2 $[M+H]^+$

2-(2-{[2-(4-Chloro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 226)

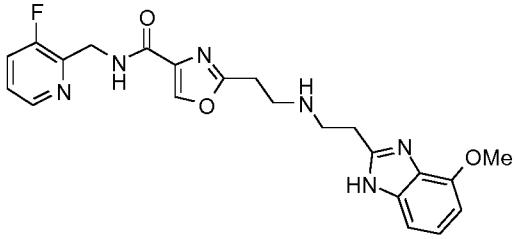


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (340 mg, 1.01 mmol), N-(3-chloro-2-nitrophenyl)prop-2-enamide **(H)** (245 mg, 1.08 mmol) and DBU (147 µl, 0.98 mmol) in MeCN (10 ml) gave a crude intermediate which was further reacted with iron powder (81 mg, 1.45 mmol) in AcOH (4 ml) to give the title compound (31 mg, 19%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.51 (m, 2H), 8.38 (dt, J = 4.6, 1.2 Hz, 1H), 7.70 (ddd, J = 10.0, 8.3, 1.2 Hz, 1H), 7.41 (m, 2H), 7.19 (dd, J = 7.7, 0.8 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 4.62 (dd, J = 5.6, 1.3 Hz, 2H), 3.09 - 2.95 (m, 8H)

HPLCMS (Method C): [*m/z*]: 443.1 $[M+H]^+$

N-[(3-fluoropyridin-2-yl)methyl]-2-(2-{[2-(4-methoxy-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 227)

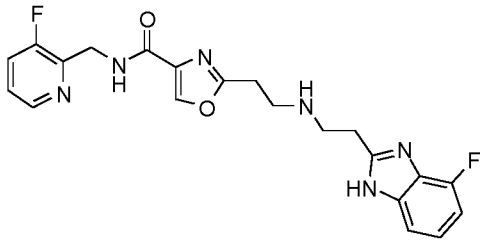


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (301 mg, 0.89 mmol), N-(2-methoxy-6-nitrophenyl)prop-2-enamide **(I)** (198 mg, 0.89 mmol) and DBU (0.4 ml, 2.68 mmol) in MeCN (10 ml) gave a crude intermediate which was partially purified by flash column chromatography using a gradient elution of 0-10% MeOH in DCM. The intermediate was further reacted with iron powder (86 mg) in AcOH (3 ml) to give the title compound (2 mg, 1%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.30 (d, J = 4.7 Hz, 1H), 8.26 (s, 1H), 7.60 - 7.54 (m, 1H), 7.39 - 7.32 (m, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.03 (d, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.65 (d, J = 1.4 Hz, 2H), 3.93 (s, 3H), 3.22 - 3.16 (m, 4H), 3.14 - 3.05 (m, 4H)

HPLCMS (Method G): [*m/z*]: 439.2 $[M+H]^+$

2-(2-{[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 228)

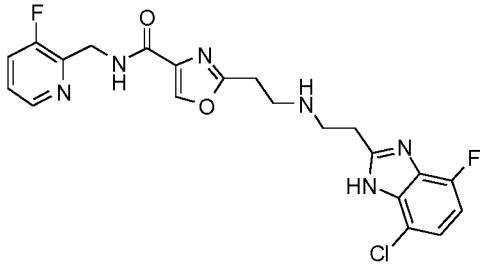


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (200 mg, 0.59 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (198 mg, 0.89 mmol) and DBU (266 µl, 1.78 mmol) in MeCN (10 ml) gave an intermediate which was partially purified by flash column chromatography with a gradient elution of 0-10% MeOH in DCM. The intermediate was further reacted with iron powder (114 mg) in AcOH (2 ml) to afford the title compound (10 mg, 5%) as an off-white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM) and kp-NH flash chromatography (eluting with a gradient of 0-4% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.53 - 8.45 (m, 2H), 8.39 - 8.35 (m, 1H), 7.72 - 7.67 (m, 1H), 7.42 - 7.37 (m, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.11 - 7.05 (m, 1H), 6.93 - 6.88 (m, 1H), 4.61 (d, J = 4.4 Hz, 2H), 3.01 - 2.91 (m, 8H)

HPLCMS (Method G): [*m/z*]: 427.1 $[M+H]^+$

2-(2-{[2-(7-Chloro-4-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 247)

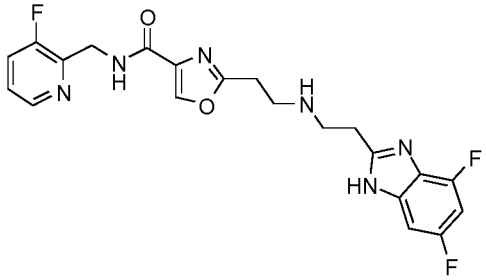


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (300 mg, 0.89 mmol), N-(6-chloro-3-fluoro-2-nitrophenyl)prop-2-enamide **(K2)** (272 mg, 0.89 mmol) and DBU (0.398 ml, 2.67 mmol) in MeCN (15 ml) gave a crude intermediate which was purified by flash column chromatography using an elution gradiant 0-15% MeOH in DCM. The intermediated was further reacted with iron powder (145 mg) in AcOH(3 ml) to give the title compound (7 mg, 2%) as a beige solid after purification by flash column chromatography (eluting with a gradient of 0-35% MeOH / DCM) followed by kp-NH column chromatography (eluting with a gradient of 0-15% MeOH / DCM) and basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.34 (d, J = 4.7 Hz, 1H), 8.27 (s, 1H), 7.63- 7.56 (m, 1H), 7.42 - 7.36 (m, 1H), 7.16 (dd, J = 8.6, 3.9 Hz, 1H), 6.93 (dd, J = 10.2, 8.6 Hz, 1H), 4.71 (d, J = 1.6 Hz, 2H), 3.16- 3.11 (m, 6H), 3.07 - 3.03 (m, 2H)

HPLCMS (Method D): [m/z]: 461.1 [M+H]+

2-(2-{[2-(4,6-Difluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 249)

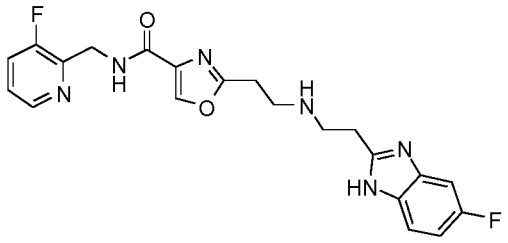


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (500 mg, 1.48 mmol), N-(2,4-difluoro-6-nitrophenyl)prop-2-enamide **(K4)** (338 mg, 1.48 mmol) and DBU (0.664 ml, 4.45 mmol) in MeCN (15 ml) gave a crude intermediate which was partially purified by flash column chromatography using a gradient of 0-20% MeOH in DCM. The intermediate was further reacted with iron powder (145 mg) in AcOH (4ml) to give the title compound (23 mg, 8%) as an off-white solid after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM) followed by kp-NH flash chromatography (eluting with a gradient of 0-5% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.53 - 8.46 (m, 2H), 8.41 - 8.36 (m, 1H), 7.73 - 7.67 (m, 1H), 7.43 - 7.37 (m, 1H), 7.14 (dd, J = 8.9, 2.2 Hz, 1H), 6.96 (td, J = 10.7, 2.2 Hz, 1H), 4.62 (dd, J = 5.7, 1.4 Hz, 2H), 3.02 - 2.90 (m, 8H)

HPLCMS (Method G): [*m/z*]: 445.2 $[M+H]^+$

2-(2-{[2-(5-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 250)

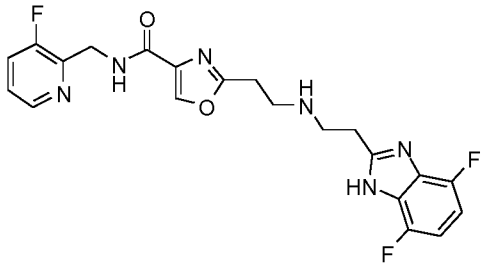


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (1.07 g, 2.59 mmol, 82% purity), N-(5-fluoro-2-nitrophenyl)prop-2-enamide **(J)** (0.54 g, 2.59 mmol) and DBU (1.28 ml, 8.54 mmol) in MeCN (30 ml) at room temperature for 20 h gave a crude mixture of mono : bis-alkylated (1:1.4) adducts (1.1 g) which was further reacted with iron powder (0.52 g) in AcOH (8 ml) to give the title compound (90 mg, 9%) as a brown solid after purification by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM), followed by kp-NH flash column chromatography (eluting with a gradient of 0-2% MeOH / DCM), then by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) and basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.52 - 8.47 (m, 2H), 8.39 - 8.36 (m, 1H), 7.72 - 7.66 (m, 1H), 7.46 - 7.36 (m, 2H), 7.24 (dd, J = 9.6, 2.3 Hz, 1H), 6.99 - 6.89 (m, 1H), 4.61 (dd, J = 5.7, 1.3 Hz, 2H), 3.02 - 2.89 (m, 8H)

HPLCMS (Method C): [*m/z*]: 427.2 $[M+H]^+$

2-(2-{[2-(4,7-Difluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 251)

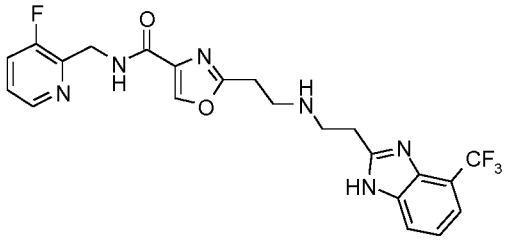


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (400 mg, 1.19 mmol), N-(3,6-difluoro-2-nitrophenyl)prop-2-enamide **(K6)** (316 mg, 1.20 mmol) and DBU (0.53 ml, 3.56 mmol) in MeCN (15 ml) gave a crude intermediate which was partially purified by flash column chromatography using a gradient elution of 0-20% MeOH in DCM. This intermediate was further reacted with iron powder (230 mg) in AcOH (4 ml) to give the title compound (63 mg, 14%) as an off-white solid after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM) followed by kp-NH flash chromatography (eluting with a gradient of 0-5% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.52 - 8.46 (m, 2H), 8.38 (m, 1H), 7.74 - 7.66 (m, 1H), 7.44 - 7.37 (m, 1H), 6.95 - 6.91 (m, 2H), 4.62 (dd, J = 5.6, 1.4 Hz, 2H), 3.03 - 2.90 (m, 8H).

HPLCMS (Method G): [*m/z*]: 445.2 $[M+H]^+$

N-[(3-fluoropyridin-2-yl)methyl]-2-[2-({2-[4-(trifluoromethyl)-1H-1,3-benzodiazol-2-yl]ethyl}amino)ethyl]-1,3-oxazole-4-carboxamide (Example Compound No. 256)

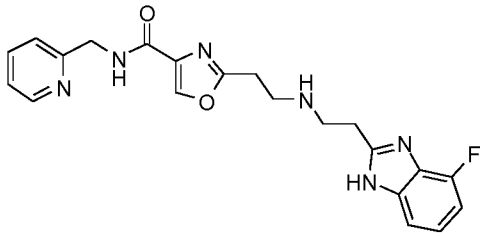


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (300 mg, 0.89 mmol), N-[2-nitro-6-(trifluoromethyl)phenyl]prop-2-enamide **(K8)** (272 mg, 0.90 mmol) and DBU (398 µl, 2.67 mmol) in MeCN (10 ml) gave a crude intermediate which was partially purified by flash column chromatography using a gradient of 0-10% MeOH in DCM. The intermediate was further reacted with iron powder (177 mg) in AcOH (3 ml) to give the title compound (99 mg, 26%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 0-25% MeOH / DCM) followed by kp-NH flash chromatography (eluting with a gradient of 0-6% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.53 - 8.47 (m, 2H), 8.40 - 8.37 (m, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.28 (t, J = 7.8 Hz, 1H), 4.62 (d, J = 4.7 Hz, 2H), 3.01 (s, 4H), 3.00 - 2.93 (m, 4H)

HPLCMS (Method G): [*m/z*]: 477.4 $[M+H]^+$

2-(2-{[2-(4-fluoro-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 236)

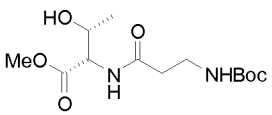


In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide dihydrochloride **(236)** (350 mg, 0.95 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (206 mg, 0.95 mmol), DBU (1.0 ml, 2.85 mmol) in MeCN (15 ml) gave a crude mixture which was partially purified by flash column chromatography (eluting with a gradient of 0-15% MeOH / DCM). The mixture was further reacted with iron powder (136 mg) in AcOH (4 ml) to afford the title compound (9 mg, 4%) as a pale brown solid after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM), kp-NH flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM) and basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.52 - 8.47 (m, 1H), 8.28 (s, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.34 - 7.30 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.19 - 7.10 (m, 1H), 6.96 - 6.88 (m, 1H), 4.65 (s, 2H), 3.17 - 3.08 (m, 6H), 3.08 - 3.02 (m, 2H)

HPLCMS (Method D): [*m/z*]: 409.1 $[M+H]^+$

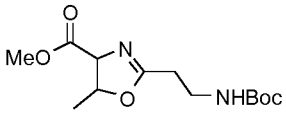
Methyl 2-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-3-hydroxybutanoate (315)



In a similar fashion to general procedure 13, methyl L-threoninate hydrochloride (1:1) (11 g, 64.9 mmol), N-(tert-butoxycarbonyl)-beta-alanine (12.3 g, 64.9 mmol), TEA (9.94 ml, 71.3 mmol) and DCC (14.7 g, 71.3

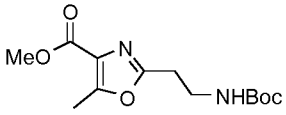
mmol) in DCM (250 ml) afforded the title compound (16.4 g, 72.4%, 87% purity) as a viscous yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc/ heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 6.35 (s, 1H), 5.12 (s, 1H), 4.59 (dd, J = 8.8, 2.5 Hz, 1H), 4.36 (qd, J = 6.4, 2.5 Hz, 1H), 3.78 (s, 3H), 3.45 (q, J = 5.9 Hz, 2H), 2.57 - 2.46 (m, 2H), 1.43 (s, 9H), 1.23 (d, J = 6.4 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 291.05 $[M+H]^+$

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate (316)



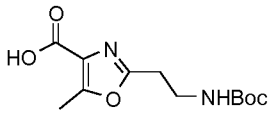
In a similar fashion to general procedure 14, methyl 2-(3-{[(tert-butoxy)carbonyl]amino}propanamido)-3-hydroxybutanoate **(315)** (1 g, 2.87 mmol, 87% purity), DAST (0.45 ml, 3.44 mmol) and K_2CO_3 (0.79 g, 5.73 mmol) in anhydrous DCM (25 ml) gave the title compound (0.61 g, 67%) as a pale yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.22 (br s, 1H), 4.87 (dq, J = 9.9, 6.3 Hz, 1H), 4.76 (dt, J = 10.1, 1.2 Hz, 1H), 3.76 (s, 3H), 3.52 - 3.37 (m, 2H), 2.53 - 2.44 (m, 2H), 1.44 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H)

Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-oxazole-4-carboxylate (317)



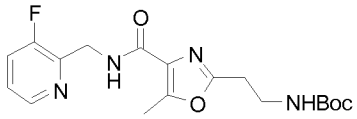
In a similar fashion to general procedure 15, methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-4,5-dihydro-1,3-oxazole-4-carboxylate **(316)** (0.61 g, 1.98 mmol), bromo(trichloro)methane (0.59 ml, 5.95 mmol) and DBU (0.89 ml, 5.95 mmol) in DCM (15 ml) gave the title compound (0.42 g, 71%) as a dark orange oil which solidified on standing after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 4.94 (s, 1H), 3.90 (s, 3H), 3.55 (q, J = 6.2 Hz, 2H), 2.93 (t, J = 6.3 Hz, 2H), 2.59 (s, 3H), 1.42 (s, 9H)
HPLCMS (Method A): [*m/z*]: 284.95 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-oxazole-4-carboxylic acid (318)



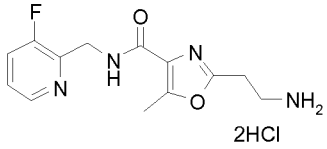
In a similar fashion to general procedure 5, methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-oxazole-4-carboxylate **(317)** (0.42 g, 1.42 mmol), LiOH (0.067 g, 2.84 mmol) in THF (8 ml) and water (2 ml) gave the title compound (0.4 g, 98%) as a pale orange oil which solidified on standing.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 12.72 (s, 1H), 6.90 (t, J = 5.5 Hz, 1H), 3.25 (d, J = 6.2 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.34 (s, 9H) [CH_3 peak obscured by DMSO peak]
HPLCMS (Method A): [*m/z*]: 293.00 $[M+Na]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1,3-oxazol-2-yl)ethyl]carbamate (319)



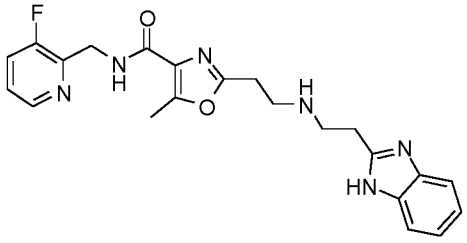
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1,3-oxazole-4-carboxylic acid **(318)** (0.4 g, 1.39 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.415 g, 2.09 mmol), DIPEA (0.8 ml, 4.59 mmol) and HATU (0.79 g, 2.09 mmol) in DMF (6 ml) gave the title compound (0.653 g, 79%, 64% purity) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.44 - 8.30 (m, 2H), 7.75 - 7.64 (m, 1H), 7.46 - 7.34 (m, 1H), 6.97 (br s, 1H), 4.60 (d, J = 4.2 Hz, 2H), 3.34 - 3.24 (m, 2H), 2.83 (t, J = 6.8 Hz, 2H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 379.05 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-oxazole-4-carboxamide dihydrochloride (320)



In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1,3-oxazol-2-yl)ethyl]carbamate **(319)** (0.65 g, 1.10 mmol, 64% purity) and 12M HCl (1.16 ml, 11.04 mmol) in MeOH (10 ml) gave the title compound (0.51 g, 76% purity) as a hygroscopic off-white solid. The compound was used in the next step without further purification.
1H-NMR (MeOD, 250 MHz): d[ppm]= 8.55 (dd, J = 5.3, 1.0 Hz, 1H), 8.22- 8.10 (m, 1H), 7.86 - 7.75 (m, 1H), 3.70 (dd, J = 11.2, 7.3 Hz, 3H), 3.43 (t, J = 6.5 Hz, 2H), 3.17 (t, J = 6.5 Hz, 2H), 2.58 (s, 3H) [CH_2 peak obscured by the H_2O]
HPLCMS (Method A): [*m/z*]: 279.2 $[M+H]^+$

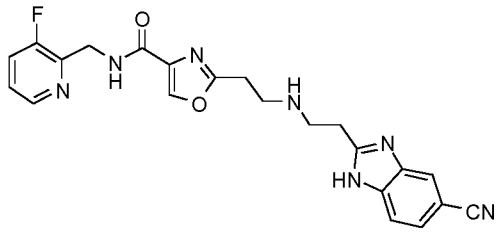
N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-2-[2-({2-[(2-nitrophenyl)carbamoyl]ethyl}amino)ethyl]-1,3-oxazole-4-carboxamide (Example Compound No. 230)



In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1,3-oxazole-4-carboxamide dihydrochloride **(320)** (0.51 g, 1.11 mmol, 76% purity), N-(2-nitrophenyl)prop-2-enamide **(D)** (0.4 g, 2.09 mmol) and DBU (0.69 ml, 4.59 mmol) in MeCN (15 ml) at room temperature for 20 h gave a mixture of mono : bis-alkylated (1:3.6) adducts which was further reacted with iron powder (0.31 g) in AcOH (3.5 ml) to give the title compound (0.12 g, 20%) as a pale green solid after purification by flash column chromatography (eluting with a gradient of 0-30% MeOH / DCM), followed by flash column chromatography (KP-NH, eluting with a gradient of 0-5% MeOH / DCM) and a final purification by flash column chromatography (eluting with a slow gradient of 0-30% MeOH / DCM).
1H-NMR (MeOD, 250 MHz): d[ppm]= 8.33 - 8.30 (d, J = 4.7 Hz, 1H), 7.60 - 7.54 (m, 1H), 7.48 - 7.40 (m, 2H), 7.38 - 7.33 (m, 1H), 7.18 - 7.14 (m, 2H), 4.65 (d, J = 1.6 Hz, 2H), 3.15 - 3.07 (m, 6H), 2.97 (t, J = 6.6 Hz, 2H), 2.52 (s, 3H)
HPLCMS (Method C): [*m/z*]: 423.1 $[M+H]^+$

General Scheme 12 above:

2-(2-{[2-(5-cyano-1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 265)



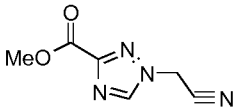
In a similar fashion to general procedure 8, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(235)** (400 mg, 1.19 mmol) and N-(4-cyano-2-nitrophenyl)prop-2-enamide **(K12)** (325 mg, 1.49 mmol) and DBU (0.53 ml, 3.56 mmol) in MeCN (12 ml) gave a crude intermediate which was further reacted with iron powder (239 mg, 4.28 mmol) in AcOH (4 ml) to afford the title compound (24 mg, 5%) as a brown solid after purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.51 - 8.46 (m, 2H), 8.39 - 8.36 (m, 1H), 8.01 - 7.95 (m, 1H), 7.72 - 7.67 (m, 1H), 7.63 - 7.59 (m, 1H), 7.50 (dd, J = 8.3, 1.5 Hz, 1H), 7.42 - 7.38 (m, 1H), 4.63 - 4.59 (m, 2H), 3.02 - 2.91 (m, 8H)

HPLCMS (Method B): [*m/z*]: 434.2 $[M+H]^+$

General Scheme 13 above:

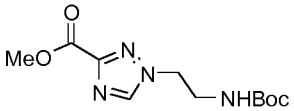
Methyl 1-(cyanomethyl)-1H-1,2,4-triazole-3-carboxylate (239)



Methyl 1H-1,2,4-triazole-3-carboxylate (5 g, 39.34 mmol) and 2-bromoacetonitrile (2.7 ml, 39.34 mmol) in DMF (45 ml) were stirred for 5 min. K_2CO_3 (5.44 g, 39.34 mmol) was added and the reaction stirred at room temperature for 23 h. The solvent was evaporated under vacuum, water (20 ml) added and the aqueous layer extracted with EtOAc (8 x 50 ml). The combined organic layers were washed with 5% aqueous LiCl (2 x 20 ml), brine (2 x 20 ml), dried (MgSO4), filtered and evaporated to give a mixture of regioisomers (1.5:1) as a dark brown oil (5.27 g). The crude material was purified by flash column chromatography (eluting with a gradient of 10 to 100% EtOAc / heptane) to give the title compound (3.5g, 45%) as a pale brown oil which solidified on standing.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.30 (s, 1H), 5.79 (s, 2H), 3.94 (s, 3H)

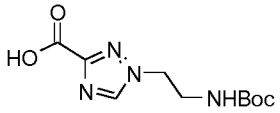
Methyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,2,4-triazole-3-carboxylate (240)



Methyl 1-(cyanomethyl)-1H-1,2,4-triazole-3-carboxylate **(239)** (1 g, 6.02 mmol), di-tert-butyl dicarbonate (2.63 g, 12.04 mmol) and TEA (1.7 ml, 12.04 mmol) in EtOH (30 ml) were stirred for 5 min before 10% palladium on carbon (128 mg, 0.602 mmol) was added. The reaction was stirred under a hydrogen atmosphere for 18 h. The reaction mixture was filtered through celite and the residue washed with EtOH (30 ml). The filtrate was evaporated to give a brown oil which began crystallising on standing (1.95 g).

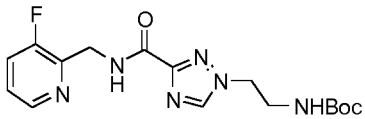
Purification by flash column chromatography (eluting with a gradient of 0 to 100% EtOAc / heptane) gave the title compound (1.35 g, 69.7%) as a pale brown solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.13 (s, 1H), 4.69 (br s, 1H), 4.40 (t, J = 5.6 Hz, 2H), 4.00 (s, 3H), 3.60 (app q, J = 5.9 Hz, 2H), 1.42 (s, 9H)
HPLCMS (Method A): [*m/z*]: 271.1 $[M+H]^+$

1-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1H-1,2,4-triazole-3-carboxylic acid (241)



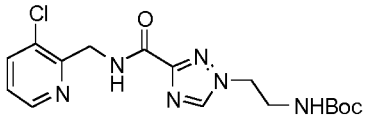
In a similar fashion using general procedure 5, LiOH (0.11 g, 4.72 mmol) and methyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,2,4-triazole-3-carboxylate **(240)** (0.87 g, 2.69 mmol) in THF (20 ml) / water (5 ml) gave the title compound (0.71 g, 100%) as a cream solid. The compound was used in the next step without further purification.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.54 (s, 1H), 6.97 (br s, 1H), 4.26 (t, J = 5.9 Hz, 2H), 3.34 (app q, J = 5.8 Hz, 2H) obscured by H_2O peak, 1.34 (s, 9H)
HPLCMS (Method A): [*m/z*]: 257.05 $[M+H]^+$

Tert-butyl N-[2-(3-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-1,2,4-triazol-1-yl)ethyl]carbamate (242)



In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,2,4-triazole-3-carboxylic acid **(241)** (0.5 g, 1.95 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.58 g, 2.93 mmol), DIPEA (1.7 ml, 9.76 mmol), HATU (1.11 g, 2.93 mmol) in DMF (10 ml) gave the title compound (0.55 g, 76%) as an off-white solid after purification by flash column chromatography (eluting with a gradient 0 to 10% MeOH / DCM) followed by a second flash column chromatography (eluting with a gradient 0 to 10% MeOH / EtOAc).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.74 (t, J = 5.6 Hz, 1H), 8.57 (s, 1H), 8.39 (d, J = 4.6 Hz, 1H), 7.78 - 7.63 (m, 1H), 7.42 (dt, J = 8.6, 4.4 Hz, 1H), 7.00 (s, 1H), 4.64 (d, J = 4.7 Hz, 2H), 4.28 (t, J =5.9 Hz, 2H), 3.36 (app q, J = 5.9 Hz, 2H), 1.35 (s, 9H)
HPLCMS (Method A): [*m/z*]: 365.15 $[M+H]^+$

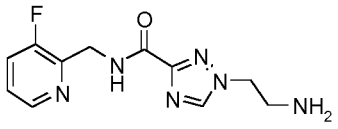
Tert-butyl N-[2-(3-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1H-1,2,4-triazol-1-yl)ethyl]carbamate (243)



In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,2,4-triazole-3-carboxylic acid **(241)** (0.58 g, 2.26 mmol), (3-chloropyridin-2-yl)methanamine dihydrochloride (0.732 g, 3.4mmol), HATU (1.29 g, 3.4 mmol), DIPEA (1971 µl, 11.32 mmol) in DMF (11 ml) gave the titlecompound (0.87 g, 96%) as a brown foam after purification by flash column chromatography eluting with a gradient of 0 to 10% MeOH / DCM.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.73 (t, J = 5.3 Hz, 1H), 8.57 (s, 1H), 8.52 (d, J = 4.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.0, 4.7 Hz, 1H), 7.00 (s, 1H), 4.67 (d, J = 5.4 Hz, 2H), 4.28 (t, J = 5.9 Hz, 2H), 3.36 (app q, J = 6.1 Hz, 2H), 1.35 (s, 9H)

HPLCMS (Method A): [*m/z*]: 381.05 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide dihydrochloride (244)



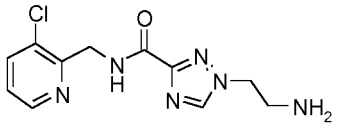
2HCl

In a similar fashion using general procedure 2, 12 M HCl (2.48 ml) and tert-butyl N-[2-(3-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-1,2,4-triazol-1-yl)ethyl]carbamate **(242)** (0.54 g, 1.49 mmol) in MeOH (10 ml) at 40°C for 2 h gave the title compound (0.52 g, 100%) as an off-white foam. The compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.89 (t, J = 5.6 Hz, 1H), 8.70 (s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 8.25 (s, 3H), 7.80 - 7.67 (m, 1H), 7.43 (dt, J = 8.6, 4.5 Hz, 1H), 4.66 (d, J = 4.4 Hz, 2H), 4.55 (t, J = 5.9 Hz, 2H), 3.32 (q, J = 5.6 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 265.05 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide dihydrochloride (245)



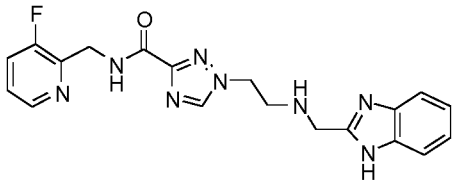
2HCl

In a similar fashion using general procedure 2, 12 M HCl (3.6ml) and tert-butyl N-[2-(3-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1H-1,2,4-triazol-1-yl)ethyl]carbamate **(243)** (0.87g, 2.17mmol) in MeOH (15 ml) at 40°C for 3h gave the title compound (0.84g, 99%) as a pale orange foam.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.89 (t, J = 5.5 Hz, 1H), 8.74 (s, 1H), 8.53 (dd, J = 4.7, 1.3 Hz, 1H), 8.35 (s, 3H), 7.99 (dd, J = 8.1, 1.4 Hz, 1H), 7.42 (dd, J = 8.1, 4.7 Hz, 1H), 4.69 (d, J = 5.5 Hz, 2H), 4.58 (t, J = 5.9 Hz, 2H), 3.33 (q, J = 5.8 Hz, 2H), 3.17 (s, 1H), 2.69 (s, 1H)

HPLCMS (Method A): [*m/z*]: 280.95 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide (Example Compound No. 169)

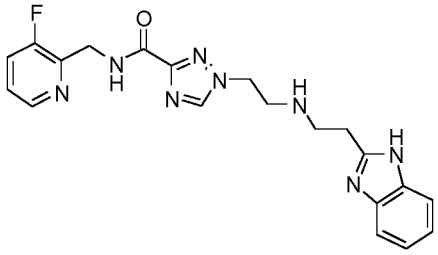


In a similar fashion using general procedure 3, 1H-1,3-Benzodiazole-2-carbaldehyde (104 mg, 0.71 mmol), 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide dihydrochloride **(244)** (200 mg, 0.59 mmol) and DIPEA (0.41 ml, 2.37 mmol) in MeOH (8 ml) at room temperature for 17 h, followed by addition of $NaBH_4$ (32 mg, 0.86 mmol) gave the title compound (79 mg, 34%) as a beige solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.16 (s, 1H), 8.76 (t, J = 5.6 Hz, 1H), 8.65 (s, 1H), 8.38 (d, J = 4.7 Hz, 1H), 7.70 (app t, J = 9.3 Hz, 1H), 7.49 (br d, J = 38.6 Hz, 2H), 7.40- 7.43 (m, 1H), 7.12 (d, J = 3.7 Hz, 2H), 4.64 (d, J = 5.5 Hz, 2H), 4.34 (t, J = 6.0 Hz, 2H), 3.92 (s, 2H), 3.02 (t, J = 5.9Hz, 2H)

HPLCMS (Method C): [*m/z*]: 395.2 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide (Example Compound No. 181)

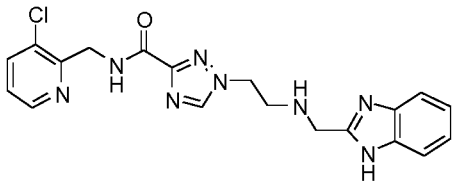


In a similar fashion using general procedure 8, DBU (0.39 ml, 2.58 mmol), 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide dihydrochloride **(244)** (300 mg, 0.86 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (165 mg, 0.86 mmol) in MeCN (14 ml) at room temperature for 16 h, gave the crude intermediate (0.364 g) as a mixture of mono:bis-alkylated (2:1) adducts. The mixture was dissolved in AcOH (5 ml), iron (112 mg) was added and the reaction heated to 80°C for 4 h to give the title compound (20 mg, 11%) as an off-white solid after purification by basic prep-HPLC followed by flash column chromatography (x 2) (KP-NH, eluting with a gradient 0-30% MeOH / DCM and 5-20% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz) d[ppm]= 12.14 (s, 1H), 8.75 (t, J = 5.6 Hz, 1H), 8.59 (s, 1H), 8.41 - 8.35 (m, 1H), 7.73 - 7.67 (m, 1H), 7.45 (br s, 2H), 7.43 - 7.38 (m, 1H), 7.13 - 7.07 (m, 2H), 4.64 (dd, J = 5.6, 1.3 Hz, 2H), 4.31 (t, J = 6.0 Hz, 2H), 2.99 (dt, J = 12.3, 6.0 Hz, 4H), 2.94 - 2.89 (m, 2H)

HPLCMS (Method C): [*m/z*]: 409.3 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-chloropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide (Example Compound No. 170)



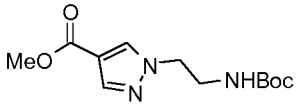
In a similar fashion using general procedure 3, 1H-1,3-Benzodiazole-2-carbaldehyde (156 mg, 1.07 mmol), 1-(2-aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-1,2,4-triazole-3-carboxamide dihydrochloride **(245)** (350 mg, 0.89 mmol) and DIPEA (0.62 ml, 3.56 mmol) in MeOH (10 ml) at 40°C for 2 h, followed by addition of $NaBH_4$ (50.5 mg, 1.34 mmol) added gave the title compound (190 mg, 52%) as a cream solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.16 (s, 1H), 8.75 (t, J = 5.4 Hz, 1H), 8.66 (s, 1H), 8.51 (dd, J = 4.7, 1.1 Hz, 1H), 7.95 (dd, J = 8.1, 1.2 Hz, 1H), 7.49 (br d, J = 37.6 Hz, 2H), 7.39 (dd, J = 8.0, 47 Hz, 1H), 7.12 (s, 2H), 4.67 (d, J = 5.4 Hz, 2H), 4.35 (t, J = 6.0 Hz, 2H), 3.93 (s, 2H), 3.03 (t, J = 5.9 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 411.3 $[M+H]^+$

General Scheme 14 above

Methyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylate (246)



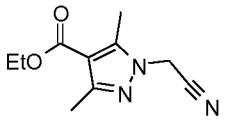
DIAD (9.39 ml, 43.61 mmol) was added dropwise to an ice-cooled solution of methyl 1H-pyrazole-4-carboxylate (5 g, 39.65 mmol), tert-butyl (2-hydroxyethyl)carbamate (6.13 ml, 39.65 mmol) and PPh_3 (11.44 g, 43.61 mmol) in THF (300 ml). The reaction was then allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with water (150 ml) and the layers separated. The

aqueous layer was extracted using EtOAc (3 x 150 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated to give the crude product. Purification by flash column chromatography (eluting with a gradient of 15-100% EtOAc / heptane) gave the title compound (11.3 g, 68%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.93 (s, 1H), 7.87 (s, 1H), 4.25 (t, J = 5.3 Hz, 2H), 3.83 (s, 3H), 3.61-3.54 (m, 2H), 1.44 (s, 9H)

HPLCMS (Method A): [m/z]: 270.1 $[M+H]^+$

Ethyl 1-(cyanomethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate (247)

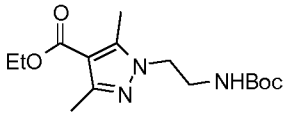


A mixture of ethyl 3,5-dimethyl-1H-pyrazole-4-carboxylate (2 g, 11.89 mmol), bromoacetonitrile (1.24 ml, 17.84 mmol), K_2CO_3 (3.29 g, 23.78 mmol) and acetone (6 ml) was heated at 100°C under microwave irradiation for 1 h. Further bromoacetonitrile (0.828 ml, 11.89 mmol) was added and the mixture was heated at 100°C under microwave irradiation for a further 1 h. The reaction mixture was concentrated *in vacuo*, the residue was taken up in water (100 ml) and extracted with EtOAc (5 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash column chromatography using an elution gradient 0-20% MeOH / DCM afforded the title compound (2.22 g, 71%) as an orange solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 5.42 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.30 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 207.95 $[M+H]^+$

Ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate (248)

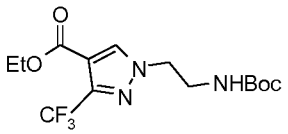


A suspension of ethyl 1-(cyanomethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate **(247)** (2.22 g, 9.64 mmol), BOC anhydride (4.21 g, 19.27 mmol), TEA (2.69 ml, 19.27 mmol) and palladium on carbon (10% wt, 0.103 g, 0.964 mmol) in EtOH (100 ml) was stirred under an atmosphere of hydrogen for 28 h. The reaction mixture was filtered and the residue rinsed with MeOH. The combined filtrates were evaporated *in vacuo* and the residue partitioned between water (100 ml) and EtOAc (50 ml). The phases were separated and the aqueous phase extracted with EtOAc (3 x 50 ml). The combined organiclayers were dried ($MgSO_4$), filtered and evaporated in vacuo. Purification by flash column chromatography using an elution gradient 70-100% EtOAc / heptane afforded the title compound (1.52 g, 51%) as a yellow-brown solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 6.90 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.02 (t, J = 6.1 Hz, 2H), 3.21 (q, J = 6.1 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H), 1.38- 1.28 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 312.45 $[M+H]^+$

Ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (248)



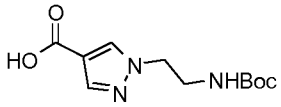
A solution of ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (3 g, 14.41 mmol), tert-butyl (2-hydroxyethyl)carbamate (2.45 ml, 15.85 mmol) and PPh_3 (4.16 g, 15.85 mmol) in THF (50 ml) was stirred

at room temperature for 16 h. Additional (2-hydroxyethyl)carbamate (2.45 ml, 15.85 mmol) was added and the reaction stirred at room temperature for a further 48 h. The reaction was quenched with water (30 ml) and extracted into EtOAc (3 x 50 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$), filtered and evaporated gave a yellow oil. Purification by flash column chromatography (eluting with a gradient of 5-80% TBME / heptane) gave a residue which was re-purified by flash column chromatography (eluting with a gradient of 5-60% TBME / heptane) providing the title compound (1.19 g, 21%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.97 (s, 1H), 4.72 (br s, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.32 - 4.27 (m , 2H), 3.59 (app q, *J* = 5.9 Hz, 2H), 1.44 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 374 $[M+Na]^+$

1-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylic acid (249)

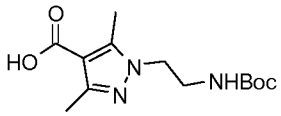


In a similar fashion to general procedure 5, LiOH (0.72 g, 30.08 mmol) and 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylate **(246)** (54%, 5 g, 10.03 mmol) in THF (80 ml) and water (30 ml) at room temperature for 24 h gave the title compound (2.6 g, 96.5%). Compound was used without purification.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.06 (s, 1H), 7.87 (s, 1H), 4.23 (t, J = 5.8 Hz, 2H), 3.46 (app q, J = 5.5 Hz, 2H), 1.42 (d, J = 19.0 Hz, 9H)

HPLCMS (Method A): [*m/z*]: 255.95 $[M+H]^+$

1-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylic acid (250)

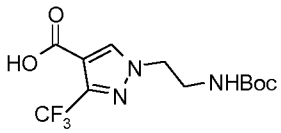


In a similar fashion to general procedure 5, ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate **(247)** (1 g, 2.58 mmol, 80% purity) and LiOH (0.37 g, 15.49 mmol) in THF (60 ml) and water (30 ml) at 70°C afforded the title compound (0.417 g, 52%, 90% purity) as a yellow solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.02 (s, 1H), 6.91 (t, J = 5.6 Hz, 1H), 4.00 (t, J = 6.0 Hz, 2H), 3.21 (q, J = 6.0 Hz, 2H), 2.40 (s, 3H), 2.26 (s, 3H), 1.37 (s, 9H)

HPLCMS (Method A): [*m/z*]: 284.05 $[M+H]^+$

1-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (251)

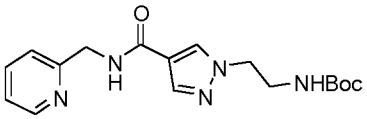


In a similar fashion to general procedure 5, LiOH (0.241 g, 10.08 mmol) and ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate **(248)** (89%, 1.18 g, 2.99 mmol) in THF / water (25 ml / 8 ml) at room temperature for 16 h gave the title compound (0.54 g, 45%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.03 (s, 1H), 4.80 (br s, 1H), 4.36 - 4.18 (br m, 2H), 3.71 - 3.54 (m, 2H), 1.45 (s, 9H)

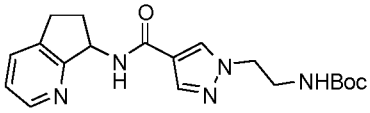
HPLCMS (Method A): [*m/z*]: 346.1 $[M+Na]^+$

Tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1H-pyrazol-1-yl}ethyl)carbamate (252)



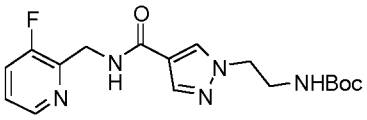
In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylic acid **(249)** (0.50 g, 1.96 mmol), 1-(pyridin-2-yl)methanamine (0.30 ml, 2.94 mmol), DIPEA (1.0 ml, 5.88 mmol) and HATU (1.12 g, 2.94 mmol) in DCM (30 ml) gave the title compound (0.647 g, 56%, 59% purity) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 3:2 EtOAc / heptane and 100% EtOAc). The compound was used in the next step without further purification.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.56 (d, J = 4.4 Hz, 1H), 7.87 (d, J = 3.8 Hz, 2H) 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.24 - 7.20 (m, 1H), 7.14 (s, 1H), 4.84 (s, 1H), 4.71 (d, J = 4.8 Hz, 2H), 4.25 (t, J = 5.4 Hz, 2H), 3.58 (q, J = 5.4 Hz, 2H), 1.43 (s, 9H)
HPLCMS (Method A): [*m/z*]: 346.3 $[M+H]^+$

Tert-butyl N-{2-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1H-pyrazol-1-yl]ethyl}carbamate (253)



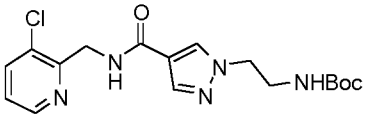
In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylic acid **(249)** (0.7 g, 2.74 mmol), 5H,6H,7H-cyclopenta[b]pyridin-7-amine hydrochloride (0.7 g, 4.11 mmol), DIPEA (1.4 ml, 8.23 mmol) and HATU (1.56 g, 4.11 mmol) in DMF (15 ml) gave the title compound (0.709 g, 70%) as an off-white solid after purification by flash column chromatography (eluting with a gradient of 80-100 % EtOAc / heptane).
1H-NMR (MeOD-d6, 500 MHz): d[ppm]= 8.35 (d, J = 4.6 Hz, 1H), 8.07 (s, 1H), 7.94 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.6, 5.0 Hz, 1H), 5.53 (t, J = 8.1 Hz, 1H), 4.23 (t, J = 5.7 Hz, 2H), 3.49- 3.43 (m, 2H), 3.13 - 3.03 (m, 1H), 2.95 (dt, J = 16.8, 8.5 Hz, 1H), 2.66 (ddt, J = 11.3, 8.1, 3.9 Hz, 1H), 2.07- 1.95 (m, 1H), 1.40 (s, 9H)
HPLCMS (Method A): [*m/z*]: 372.1 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)ethyl]carbamate (254)



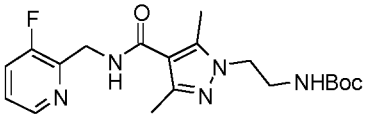
In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylic acid **(249)** (0.35 g, 1.3 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.46 g, 1.95 mmol), DIPEA (1.13 ml, 6.51 mmol) and HATU (0.74 g, 1.95 mmol) in DMF (7 ml) gave the title compound (0.4 g, 82%) as an orange foam after purification by flash column chromatography (eluting with a gradient of 0-50% MeOH / EtOAc).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.40 - 8.37 (m, 1H), 7.89 (s, 2H), 7.46 - 7.38 (m, 1H), 7.30 - 7.24 (m, 1H), 4.86 (br s, 1H), 4.78 (dd, J = 4.4 and 1.2 Hz, 2H), 4.26 (t, J = 5.3 Hz, 2H), 3.64- 3.50 (m, 2H), 1.43 (s, 9H)
HPLCMS (Method A): [*m/z*]: 364.40 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)ethyl]carbamate (255)



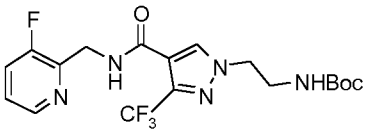
In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-pyrazole-4-carboxylic acid **(249)** (0.7 g, 2.74 mmol), (3-chloropyridin-2-yl)methanamine dihydrochloride (0.89 g, 4.11 mmol), DIPEA (2.39 ml, 13.71 mmol) and HATU (1.56 g, 4.11 mmol) in DMF (15 ml) at room temperature for 24 h, gave the title compound (0.79 g, 76%) as a viscous brown oil after purification by flash column chromatography (eluting with a gradient of 0-50% MeOH / EtOAc). The oil solidified on standing.
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.48 (dd, J = 4.7, 1.0 Hz, 1H), 7.91 (s, 1H), 7.91 (s, 1H), 7.72 (dd, J = 8.0, 1.2 Hz, 1H), 7.50 (br s, 1H), 7.23 (dd, J = 8.0, 4.8 Hz, 1H), 4.87 (br s, 1H), 4.78 (d, J = 4.2 Hz, 2H), 4.26 (t, J = 5.3 Hz, 2H), 3.59 (app q, J = 5.6 Hz, 2H), 1.44 (s, 9H)
HPLCMS (Method A): [*m/z*]: 380.4 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-3,5-dimethyl-1H-pyrazol-1-yl)ethyl]carbamate (256)



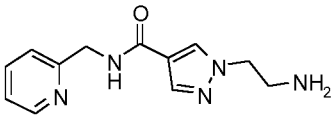
In a similar fashion to general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3,5-dimethyl-1H-pyrazole-4-carboxylic acid **(250)** (0.42 g, 1.33 mmol, 90% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.47 g, 2.0 mmol), DIPEA (1.16 ml, 6.67 mmol) and HATU (0.76 g, 2.0 mmol) in THF (15 ml) and DMF (3 ml) afforded the title compound (0.40 g, 77%) as a colourless glassy solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 60-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 500MHz): d[ppm]= 8.38 (d, J = 4.7 Hz, 1H), 7.81 - 7.77 (m, 1H), 7.71 - 7.65 (m, 1H), 7.39 (dt, J = 8.6, 4.4 Hz, 1H), 6.94 - 6.89 (m, 1H), 4.59 (d, J = 4.3 Hz, 2H), 3.99 (t, J = 6.5 Hz, 2H), 3.20 (q, J = 6.5 Hz, 2H), 2.34 (s, 3H), 2.25 (s, 3H), 1.37 (s, 9H)
HPLCMS (Method A): [*m/z*]: 392.1 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethyl]carbamate (257)



In a similar fashion using general procedure 6, 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid **(251)** (90%, 0.54 g, 1.53 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.23 g, 1.8 mmol), DIPEA (0.87 ml, 5.01 mmol) and HATU (0.57 g, 1.5 mmol) in DMF (3 ml) and THF (15 ml) at room temperature for 72 h, gave the gave the title compound (0.646 g, 65%) after purification by flash column chromatography (eluting with a gradient of 5-100% EtOAc / heptane).
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.40 - 8.35 (m, 1H), 7.98 (s, 1H), 7.56 (s, 1H), 7.46 - 7.37 (m, 1H), 7.31 - 7.23 (m, 4H), 4.80 (dd, *J* = 4.3, 1.2 Hz, 2H), 4.30 (t, *J* = 5.4 Hz, 2H), 3.60 (app q, *J* = 6.0 Hz, 2H), 1.44 (s, 9H)
HPLCMS (Method A): [*m/z*]: 432.1 $[M+H]^+$

1-(2-Aminoethyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide dihydrochloride (258)



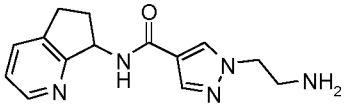
2HCl

In a similar fashion using general procedure 2, 12 M HCl (6.5 ml) and tert-butyl N-(2-{4-[(pyridin-2-ylmethyl)carbamoyl]-1H-pyrazol-1-yl}ethyl)carbamate **(252)** (0.647 g, 1.11 mmol, 59% pure) in MeOH (6.5 ml) at room temperature for 2.5 h, gave the title compound (0.513 g, quant.) as a pale yellow oil. The compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 9.16 (s, 1H), 8.77 (s, 1H), 8.33 (s, 1H), 8.13 (s, 2H), 8.05 (s, 1H), 7.80 (s, 2H), 4.72 (s, 2H), 4.42 (s, 2H), 3.27 (d, J = 5.9 Hz, 2H), 3.05 - 2.78 (m, 3H)

HPLCMS (Method A): [*m/z*]: 246 $[M+H]^+$

1-(2-Aminoethyl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide dihydrochloride (259)

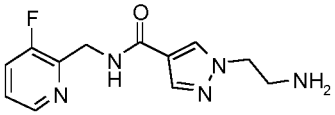


2HCl

In a similar fashion using general procedure 2, 12 M HCl (3.2 ml) and tert-butyl N-{2-[4-({5H,6H,7H-cyclopenta[b]pyridin-7-yl}carbamoyl)-1H-pyrazol-1-yl]ethyl}carbamate **(253)** (0.709 g, 1.909 mmol) in MeOH (20 ml) at room temperature for 20 h, gave the title compound (0.745 g, quant.) as a grey solid.^{1}H NMR (500 MHz, Methanol-d4): d[ppm]= 8.60 (d, J = 5.8 Hz, 1H), 8.51 (d, J = 7.8 Hz, 1H), 8.29 (s, 1H), 8.05 (s, 1H), 7.93 (dd, J = 7.7, 6.0 Hz, 1H), 5.80 (t, J = 8.4 Hz, 1H), 4.53- 4.49 (m, 2H), 3.46 (t, J = 5.7 Hz, 2H), 3.39 - 3.35 (m, 1H), 3.18 (dt, J = 17.0, 8.5 Hz, 1H), 2.83 - 2.74 (m, 1H), 2.41 - 2.31 (m, 1H)

HPLCMS (Method A): [*m/z*]: 272.05 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride (260)



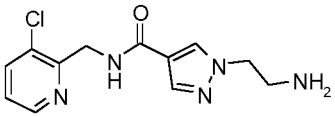
2HCl

In a similar fashion using general procedure 2, 12 M HCl (3.67 ml) and tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)ethyl]carbamate **(254)** (0.4 g, 1.1 mmol) in MeOH (5 ml) at room temperature for 16 h, gave the title compound (0.38 g, quant.) as a cream foam. The compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.65 (t, J = 5.7 Hz, 1H), 8.38 (dt, J = 4.6, 1.4 Hz, 1H), 8.25 (s, 1H), 8.12 (br s, 3H), 8.00 - 7.97 (m, 1H), 7.73 - 7.68 (m, 1H), 7.43 - 7.39 (m, 1H), 4.59 (dd, J = 5.6, 1.5 Hz, 2H), 4.40 (t, J = 6.1 Hz, 2H), 3.25 (app h, J = 5.7 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 264.05 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride (261)



2HCl

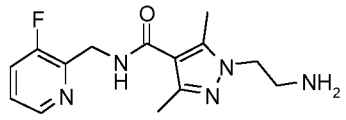
In a similar fashion using general procedure 2, 12 M HCl (6.5 ml) and tert-butyl N-[2-(4-{[(3-chloropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)ethyl]carbamate **(255)** (0.79 g, 1.97 mmol) in MeOH (10 ml) at room

temperature for 25 h, gave the title compound (0.7 g, 95%) as a beige solid. The compound was used in the next step without further purification.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.69 (dd, J = 5.5, 1.2 Hz, 1H), 8.51 (dd, J = 8.3, 1.2 Hz, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.86 (dd, J = 8.3, 5.5 Hz, 1H), 4.88 (s, 2H), 4.51 (t, J = 5.6 Hz, 2H), 3.46(t, J = 5.6 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 279.9 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3,5-dimethyl-1H-pyrazole-4-carboxamide dihydrochloride (262)



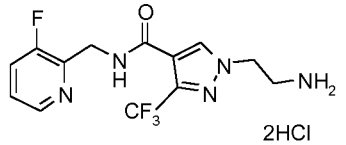
2HCl

In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-3,5-dimethyl-1H-pyrazol-1-yl)ethyl]carbamate **(256)** (0.4 g, 1.02 mmol) and 12 M HCl (1.7 ml) in MeOH (5 ml) afforded the title compound (0.399 g, 93% purity) as a white solid.

1H-NMR (Methanol-d4, 500MHz): d[ppm]= 8.64 (dd, J = 5.5, 1.2 Hz, 1H), 8.33 (t, J = 8.9 Hz, 1H), 7.97 - 7.92 (m, 1H), 4.86 - 4.85 (m, 2H), 4.34 – 4.29 (m, 2H), 3.40 (t, J = 5.8 Hz, 2H), 2.46 (s, 3H), 2.38 (s, 3H)

HPLCMS (Method A): [*m/z*]: 292 $[M+H]^+$

1-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide dihydrochloride (263)



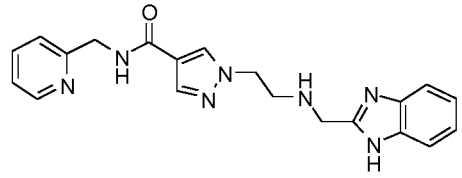
2HCl

In a similar fashion using general procedure 2, 12 M HCl (2.1 ml) and tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-3-(trifluoromethyl)-1H-pyrazol-1-yl)ethyl]carbamate **(257)** (80%, 0.68 g, 1.26 mmol) in MeOH (10 ml) at room temperature for 17 h, gave the title compound (0.588 g, 93.4%) as a pink solid. The compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.80 (t, J = 5.7 Hz, 1H), 8.52 (s, 1H), 8.42 - 8.36 (m, 1H), 8.23 (s, 3H), 7.78 - 7.68 (m, 1H), 7.48 - 7.39 (m, 1H), 4.59 (dd, J = 5.5, 1.3 Hz, 2H), 4.50 (t, J = 6.0 Hz, 2H), 3.29 (q, J = 5.7 Hz, 2H), 2.89 (s, 1H), 2.69 (s, 7H)

HPLCMS (Method A): [*m/z*]: 332.2 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide (Example Compound No. 92)

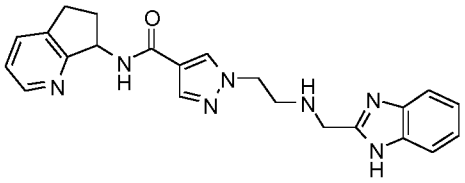


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide dihydrochloride **(258)** (256 mg, 0.805 mmol), 1H-benzimidazole-2-carbaldehyde (129 mg, 0.885 mmol) and DIPEA (0.70 ml, 4.02 mmol) in MeOH (7 ml) at room temperature for 65 h, followed by addition of $NaBH_4$ (46 mg, 1.21 mmol) gave the title compound (58 mg, 19%) as a pale yellow solid after purification by prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.68 (t, J = 6.0 Hz, 1H), 8.49 (d, J = 4.2 Hz, 1H), 8.23 (s, 1H), 7.91 (s, 1H), 7.74 (td, J = 7.7, 1.8 Hz, 1H), 7.51 (s, 1H), 7.45 (s, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 7.1, 5.1 Hz, 1H), 7.18 - 7.05 (m, 2H), 4.49 (d, J = 6.0 Hz, 2H), 4.22 (t, J = 6.2 Hz, 2H), 3.91 (s, 2H), 2.97 (t, J = 6.1 Hz, 2H), 2.45 (s, 1H)

HPLCMS (Method B): [*m/z*]: 376.2 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide (Example Compound No. 132)

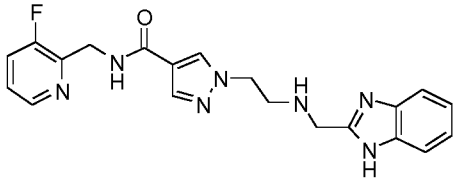


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide dihydrochloride **(259)** (150 mg, 0.38 mmol), 1H-benzimidazole-2-carbaldehyde (67 mg, 0.46 mmol) and DIPEA (0.267 ml, 1.53 mmol) in MeOH (6 ml) at room temperature for 24 h, followed by addition of $NaBH_4$ (22 mg, 0.57 mmol) gave the title compound (23 mg, 15%) as a yellow solid after purification by basic prep-HPLC followed by flash column chromatography (kp-NH, eluting with a gradient of 0-20% MeOH / EtOAc).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.35 (d, J = 4.9 Hz, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.51 (s, 2H), 7.28 (dd, J = 7.6, 4.9 Hz, 1H), 7.20 (dd, J = 6.0, 3.2 Hz, 2H), 5.54 (t, J = 8.2 Hz, 1H), 4.29 (t, J = 5.9 Hz, 2H), 4.01 (s, 2H), 3.09 (t, J = 5.9 Hz, 2H), 3.08- 3.04 (m, 1H), 2.99 - 2.91 (m, 1H), 2.71 - 2.63 (m, 1H), 2.06 - 1.97 (m, 1H)

HPLCMS (Method B): [*m/z*]: 402.1 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 145)

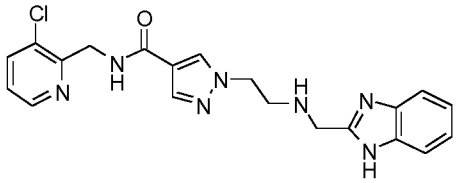


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride **(260)** (200 mg, 0.59 mmol), 1H-benzimidazole-2-carbaldehyde (104 mg, 0.71 mmol) and DIPEA (0.41 ml, 2.38 mmol) in MeOH (8 ml) at room temperature for 18 h, followed by addition of $NaBH_4$ (32.7 mg, 0.87 mmol) gave the title compound (91 mg, 40%) as a colourless film after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (br s, 1H), 8.53 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.4 Hz, 1H), 8.21 (s, 1H), 7.88 (s, 1H), 7.70 - 7.65 (m, 1H), 7.59 - 7.41 (m, 2H), 7.41 - 7.37 (m, 1H), 7.12 (d, J = 4.7 Hz, 2H), 4.57 (dd, J = 5.7, 1.6 Hz, 2H), 4.21 (t, J = 6.2 Hz, 2H), 3.90 (br s, 2H), 2.96 (app br s, 2H)

HPLCMS (Method C): [*m/z*]: 394.1 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-chloropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 138)

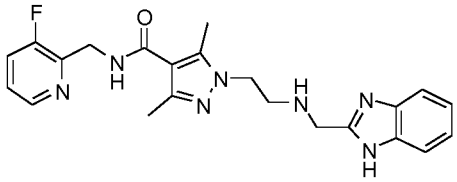


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride **(261)** (200 mg, 0.54 mmol), 1H-benzimidazole-2-carbaldehyde (94.5 mg, 0.65 mmol) and DIPEA (0.38 ml, 2.16 mmol) in MeOH (8 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (30.6 mg, 0.81 mmol) gave the title compound (127 mg, 56%) as a pale green foam after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.51 - 8.46 (m, 2H), 8.23 (s, 1H), 7.92 (dd, J = 8.1, 1.4 Hz, 1H), 7.90 (s, 1H), 7.58 - 7.41 (br m, 2H), 7.37 (dd, J = 8.1, 4.7 Hz, 1H), 7.17 - 7.08 (m, 2H), 4.62 (d, J = 5.6 Hz, 2H), 4.23 (t, J = 6.2 Hz, 2H), 3.92 (br s, 2H), 2.98 (br s, 2H)

HPLCMS (Method C): [*m/z*]: 410.2 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-3,5-dimethyl-1H-pyrazole-4-carboxamide (Example Compound No. 142)

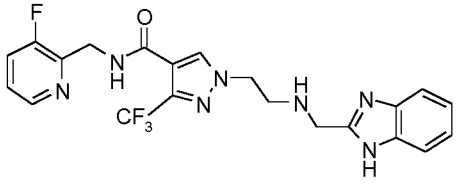


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3,5-dimethyl-1H-pyrazole-4-carboxamide dihydrochloride **(262)** (150 mg, 0.384 mmol), 1H-benzimidazole-2-carbaldehyde (73 mg, 0.499 mmol), DIPEA (0.268 ml, 1.537 mmol) and $MgSO_4$ (100 mg) in MeOH (7 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (22 mg, 0.576 mmol) gave the title compound (14 mg, 9%) as a yellow solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.16 (s, 1H), 8.40 - 8.37 (m, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.72 - 7.66 (m, 1H), 7.56 - 7.50 (m, 1H), 7.46 - 7.42 (m, 1H), 7.40 (dt, J = 8.4, 4.4 Hz, 1H), 7.17 - 7.09 (m, 2H), 4.59 (d, J = 4.3 Hz, 2H), 4.05 (t, J = 6.4 Hz, 2H), 3.92 (s, 2H), 2.90 (t, J = 6.4 Hz, 2H), 2.38 (s, 3H), 2.24 (s, 3H)

HPLCMS (Method D): [*m/z*]: 422.3 $[M+H]^+$

1-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (Example Compound No. 156)

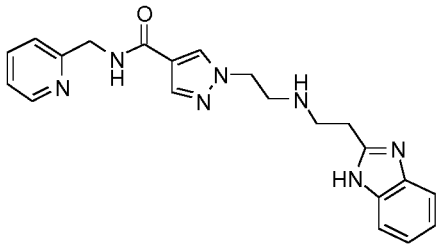


In a similar fashion using general procedure 3, 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide dihydrochloride **(263)** (81%, 100 mg, 0.20 mmol), 1H-benzimidazole-2-carbaldehyde (35 mg, 0.24 mmol) and DIPEA (0.14 ml, 0.8 mmol) in MeOH (5 ml) at room temperature for 16 h, followed by addition of $NaBH_4$ (22 mg, 0.6 mmol) gave the title compound (12 mg, 13%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.69 (t, 1H), 8.45 (s, 1H), 8.37 (d, 1H), 7.72 - 7.66 (m, 1H), 7.53 (d, 1H), 7.45 - 7.38 (m, 2H), 7.12 (t, 2H), 4.71 - 4.45 (m, 2H), 4.29 (t, 2H), 3.92 (s, 2H), 2.99 (s, 2H)

HPLCMS (Method C): [*m/z*]: 462.1 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide (Example Compound No. 109)

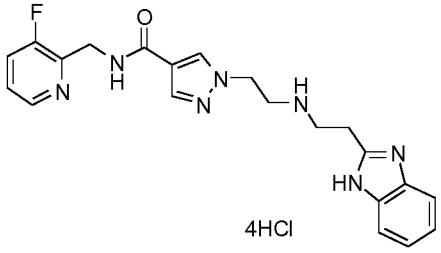


In a similar fashion using general procedure 7, 1-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide dihydrochloride **(258)** (250 mg, 0.79 mmol), 2-(2-chloroethyl)-1H-benzimidazole hydrochloride (340 mg, 1.58 mmol) and DIPEA (2.1 ml, 11.8 mmol) in DMF (7.5 ml) at room temperature for 6 d to give the title compound (17 mg, 5%) as a pale yellow solid after purification by prep-HPLC, followed by (KP-NH) flash column chromatography using 4:6 EtOAc / heptane to 100% EtOAc then 20% MeOH: 80% DCM followed by prep-HPLC (MeCN / Water, 2 mM NH_4HCO_3).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.10 (s, 1H), 8.68 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 4.1 Hz, 1H), 8.21 (s, 1H), 7.90 (s, 1H), 7.74 (td, J = 7.7, 1.8 Hz, 1H), 7.58- 7.33 (m, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.25 (dd, J = 7.4, 4.9 Hz, 1H), 7.09 (dd, J = 6.0, 2.8 Hz, 2H), 4.49 (d, J = 6.0 Hz, 2H), 4.19 (t, J = 6.2 Hz, 2H), 3.00 - 2.93 (m, 4H), 2.91 (t, J = 6.2 Hz, 2H), 2.05 (s, 1H)

HPLCMS (Method B): [*m/z*]: 390.2 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide tetrahydrochloride (Example Compound No. 111)

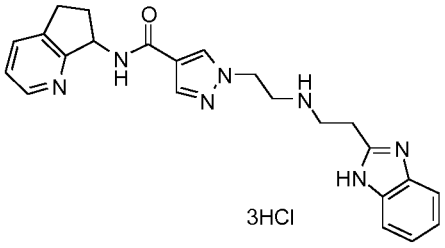


In a similar fashion using general procedure 7, 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride **(260)** (0.7 g, 2.08 mmol), 2-(2-chloroethyl)-1H-benzimidazole (0.451 g, 2.499 mmol) and DIPEA (5.4 ml, 31.23 mmol) in DMF (15 ml) at 30°C for 6 d gave the product as the free base (63 mg) after purification by silica column chromatography (kp-NH, eluting with a gradient of 0-40% MeOH / EtOAc) followed by basic prep-HPLC. The freebase product was dissolved in MeOH (3 ml) and 12 M HCl (2 ml) at room temperature for 2 h to give the title compound (65 mg, 5.6%) as a brown solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.46 (s, 1H), 8.25 (s, 1H), 8.01 (s, 1H),7.81 (dd, J = 6.2, 3.2 Hz, 3H), 7.63 (dd, J = 6.2, 3.1 Hz, 3H), 4.78 (s, 2H), 4.64 (s, 2H), 3.72 (d, J = 7.6 Hz, 6H)

HPLCMS (Method B): [*m/z*]: 408.2 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide trihydrochloride (Example Compound No. 131)

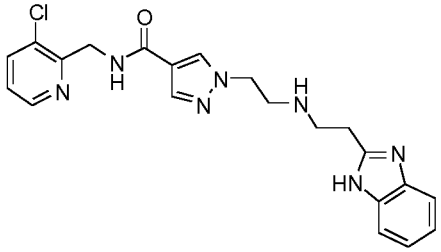


In a similar fashion using general procedure 7, 1-(2-aminoethyl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide dihydrochloride **(259)** (0.2 g, 0.51 mmol), 2-(2-chloroethyl)-1H-benzimidazole hydrochloride (0.13 g, 0.61 mmol) and DIPEA (0.44 ml, 2.55 mmol) in DMF (3 ml) at room temperature for 72 h then heated to 40°C for 21 h gave the free base product (55 mg) after purification basic prep-HPLC. The free base product was then dissolved in MeOH (3 ml) and 12 M HCl (0.5 ml) at room temperature for 2 h to give the title compound (0.049 g, 18%) as a brown solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.60 (d, J = 5.2 Hz, 1H), 8.51 (d, J = 6.8 Hz, 1H), 8.31 (s, 1H), 8.03 (s, 1H), 7.95 - 7.91 (m, 1H), 7.83 - 7.79 (m, 2H), 7.65 - 7.62 (m, 2H), 5.80 (t, J = 8.5 Hz, 1H), 4.68 - 4.64 (m, 2H), 3.77 - 3.70 (m, 6H), 3.34 (d, J = 3.3 Hz, 1H), 3.23 - 3.17 (m, 1H), 2.83 - 2.75 (m, 1H), 2.39 - 2.30 (m, 1H)

HPLCMS (Method B): [*m/z*]: 416.1 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 144)

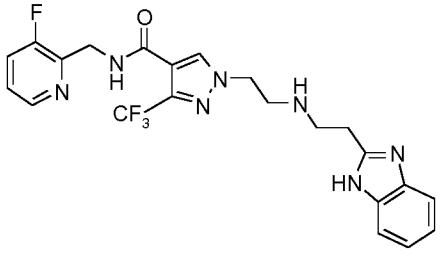


In a similar fashion using general procedure 7, 1-(2-aminoethyl)-N-[(3-chloropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride **(261)** (0.45 g, 1.28 mmol), 2-(2-chloroethyl)-1H-benzimidazole (0.28 g, 1.53 mmol) and DIPEA (3.3 ml, 19.14 mmol) in DMF (7 ml) at room temperature for 66 h, then heated to 40°C for 90 h, gave the title compound (112 mg, 21%) as a colourless film after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.10 (s, 1H), 8.52 - 8.44 (m, 2H), 8.22 (s, 1H), 7.92 (dd, J = 8.1, 1.4 Hz, 1H), 7.90 (s, 1H), 7.55 - 7.38 (br m, 2H), 7.37 (dd, J = 8.1, 4.7 Hz, 1H), 7.13 - 7.07 (m, 2H), 4.63 (d, J = 5.7 Hz, 2H), 4.20 (t, J = 6.2 Hz, 2H), 2.99 - 2.93 (m, 4H), 2.93 - 2.89 (m, 2H)

HPLCMS (Method C): [*m/z*]: 424.1 $[M+H]^+$

1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (Example Compound No. 162)

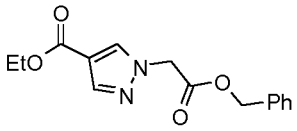


In a similar fashion using general procedure 8, DBU (62.94 µl, 0.42 mmol), 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide dihydrochloride **(263)** (81%, 140 mg, 0.28 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (52.84 mg, 0.27 mmol) in MeCN (5 ml) at room temperature for 16 h gave a residue (0.160 g) as a mixture of mono:bis-alkylated (1:1) adducts. The residue was dissolved in AcOH (4 ml). Iron (0.03 g) was added and the reaction heated to 80°C for 1 h. The reaction was cooled and diluted with water (5 ml). The mixture was cooled in an ice-bath and basified to pH 12 using 10 M NaOH. Water (10 ml) was added and the mixture extracted with $CHCl_3$:IPA (4:1, 4 x 30 ml). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. Purification by flash column chromatography (eluting with a gradient 5-10% MeOH / DCM followed by 0-10% 7 N NH_3 in MeOH / DCM) followed by purification by basic prep-HPLC gave the title compound (19 mg, 13.9%) as a colourless oil.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.11 (br s, 1H), 8.69 (t, *J* = 5.6 Hz, 1H), 8.43 (s, 1H), 8.42 - 8.35 (m, 1H), 7.74 - 7.65 (m, 1H), 7.52 - 7.36 (br m, 2H), 7.43 - 7.37 (m, 1H), 7.15 - 7.06 (br m, 2H), 4.59 - 4.55 (m, 2H), 4.26 (t, *J* = 6.1 Hz, 2H), 3.02 - 2.94 (m, 4H), 2.94 - 2.89 (m, 2H)

HPLCMS (Method C): [*m/z*]: 476.2 $[M+H]^+$

Ethyl 1-[2-(benzyloxy)-2-oxoethyl]-1H-pyrazole-4-carboxylate (268)

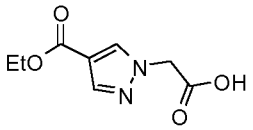


Benzyl bromoacetate (2.82 ml, 18 mmol) was added dropwise to an ice-cold suspension of ethyl 1H-pyrazole-4-carboxylate (2.3 g, 16 mmol) and K_2CO_3 (3.4 g, 25 mmol) in DMF (20 ml). The mixture was warmed to room temperature and stirred for 2 h. The mixture was diluted with diethyl ether (100 ml) and washed with water (2 x 40 ml) and brine (5 x 20 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash chromatography using an elution gradient 0-100% DCM / heptane afforded the title compound (1.57 g, 33%) as a colourless oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.01 (s, 1H), 7.98 (s, 1H), 7.44 - 7.32 (m, 5H), 5.24 (s, 2H), 4.98 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 288.95 $[M+H]^+$

2-[4-(Ethoxycarbonyl)-1H-pyrazol-1-yl]acetic acid (269)

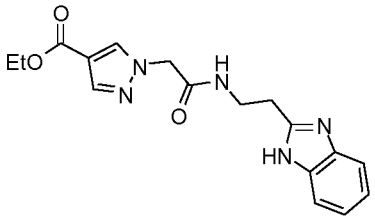


A suspension of ethyl 1-[2-(benzyloxy)-2-oxoethyl]-1H-pyrazole-4-carboxylate **(268)** (1.57 g, 5.44 mmol) and palladium on carbon (10% wt, 0.590 g, 0.55 mol) in EtOH (50 ml) was stirred under an atmosphere of hydrogen for 2.5 h. The mixture was filtered through a plug of Celite and the residue rinsed with MeOH. The combined filtrates were evaporated *in vacuo* to give the title compound (0.99 mg, 92%) as a yellow solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.07 (s, 1H), 8.03 (s, 1H), 5.07 (s, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 198.9 $[M+H]^+$

Ethyl 1-({[2-(1H-1,3-benzodiazol-2-yl)ethyl]carbamoyl}methyl)-1H-pyrazole-4-carboxylate (270)

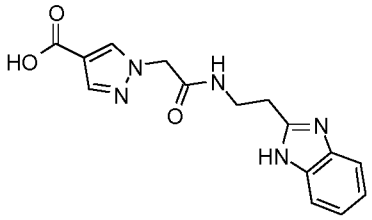


In a similar fashion to general procedure 6, HATU (1.1 g, 2.88 mmol), 2-[4-(ethoxycarbonyl)-1H-pyrazol-1-yl]acetic acid **(269)** (0.476 g, 2.4 mmol), 2-(1H-1,3-benzodiazol-2-yl)ethan-1-amine dihydrochloride (0.62 g, 2.64 mmol) and DIPEA (1.67 ml, 9.61 mmol) in THF (30 ml) at room temperature for 2 h afforded the title compound (0.676 g, 82%) as a white solid after purification by flash chromatography (eluting with a gradient elution 0-8% MeOH / DCM).

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.01 (s, 1H), 7.87 (s, 1H), 7.62 (m, 2H), 7.36 (m, 3H), 4.90 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.80 (q, J = 5.9 Hz, 3H), 3.39 (t, J = 5.9 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 342.1 $[M+H]^+$

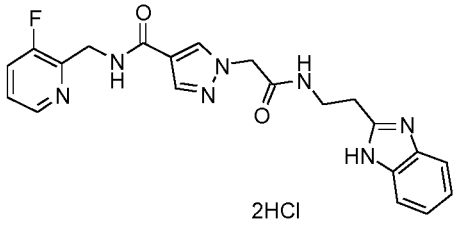
1-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]carbamoyl}methyl)-1H-pyrazole-4-carboxylic acid (271)



In a similar fashion to general procedure 5, ethyl 1-({[2-(1H-1,3-benzodiazol-2-yl)ethyl]carbamoyl}methyl)-1H-pyrazole-4-carboxylate **(270)** (667 mg, 1.95 mmol) and LiOH (140 mg, 5.85 mmol) in THF / water (30 ml / 4 ml) at room temperature for 16 h, gave the crude title compound (420 mg) as a white residue.

HPLCMS (Method A): [*m/z*]: 314 $[M+H]^+$

1-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]carbamoyl}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide dihydrochloride (Example Compound No. 117)



2HCl

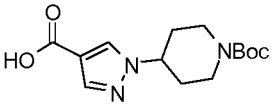
In a similar fashion to general procedure 6, crude 1-({[2-(1H-1,3-benzodiazol-2-yl)ethyl]carbamoyl}methyl)-1H-pyrazole-4-carboxylic acid **(271)** (200 mg), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (140 mg, 0.7 mmol), DIPEA (0.44 ml, 2.55 mmol) and HATU (290 mg, 0.76 mmol) in THF (10 ml) and DMF (2 ml) afforded the title compound as the freebase after purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) followed by basic prep-HPLC. The freebase was converted to the di HCl salt (28 mg, 9%) after treatment with 12M HCl (1 ml) in MeOH (5 ml).

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.49 (d, J = 5.2 Hz, 1H), 8.13 (s, 1H), 8.00 - 7.92 (m, 2H), 7.76 (dt, J = 6.7, 3.4 Hz, 2H), 7.67 (dt, J = 8.8, 4.8 Hz, 1H), 7.59 (dt, J = 6.2, 3.4 Hz, 2H), 4.88 (s, 2H), 4.79 (d, J = 1.4 Hz, 2H), 3.77 (t, J = 6.4 Hz, 2H), 3.39 (t, J = 6.4 Hz, 2H)

HPLCMS (Method C): [*m/z*]: 422.2 $[M+H]^+$

General Scheme 15 above:

1-{1-[(Tert-butoxy)carbonyl]piperidin-4-yl}-1H-pyrazole-4-carboxylic acid (272)

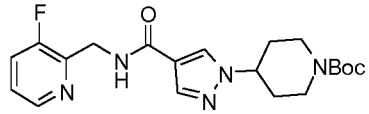


Ethyl 1H-pyrazole-4-carboxylate (0.2 g, 1.427 mmol), tert-butyl 4-[(methylsulfonyl)oxy]piperidine-1-carboxylate (0.362 g, 1.296 mmol) in DMF (5 ml) were stirred for 5 min. The reaction was cooled to 0°C and NaH (0.234 g, 5.85 mmol) added portion wise. Once gas evolution ceased, the reaction was heated to 50°C for 26 h. The reaction was cooled, quenched with water (15 ml) and evaporated to dryness. Water (40 ml) was added and the aqueous layer extracted with EtOAc (3 x 15 ml). The aqueous layer was acidified with saturated $KHSO_4$ to pH 3 and extracted with EtOAc (4 x 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give the title compound (0.331 g, 79%) as a pale yellow solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.29 (s, 1H), 7.81 (s, 1H), 4.44 - 4.36 (m, 1H), 4.08 - 3.97 (m, 2H), 2.89 (s, 2H), 2.01 - 1.95 (m, 2H), 1.79 (qd, J = 12.4, 4.4 Hz, 2H), 1.41 (s, 9H)

HPLCMS (Method A): [*m/z*]: 318.0 $[M+Na]^+$

Tert-butyl 4-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate (273)

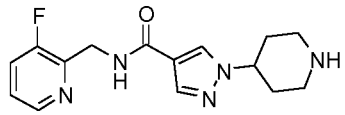


In a similar fashion using general procedure 6, 1-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}-1H-pyrazole-4-carboxylic acid **(272)** (301 mg, 1.02 mmol), 3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (358 mg, 1.53 mmol), DIPEA (0.8 ml), HATU (581 mg, 1.53 mmol) in THF (15 ml) and DMF (3 ml) gave the title compounds (315 mg, 65%) as a glassy solid after purification by flash column chromatography (eluting with a gradient of 20-100% EtOAc / heptane).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.51 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6 and 1.5 Hz, 1H), 8.25 (s, 1H), 7.89 (s, 1H), 7.71 - 7.64 (m, 1H), 7.42 - 7.36 (m, 1H), 4.57 (dd, J = 5.7, 1.5 Hz, 2H), 4.44 - 4.32 (m, 1H), 4.04 - 3.96 (m, 2H), 2.89 (br s, 2H), 2.01 (s, 2H), 1.74 (qd, J = 12.4, 4.4 Hz, 2H), 1.41 (s, 9H)

HPLCMS (Method A): [*m/z*]: 404.1 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide dihydrochloride (274)



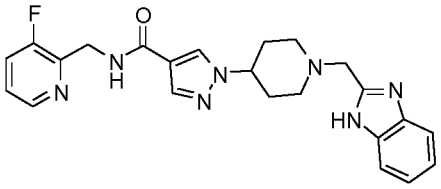
2HCl

In a similar fashion using general procedure 2, 12M HCl (1.1ml) and tert-butyl 4-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate **(273)** (315 mg, 0.664 mmol) in MeOH (4 ml) at 35°C for 16 h gave the title compound (277 mg) as an off-white solid. The compound was used in the next step without further purification.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.54 - 8.47 (m, 1H), 8.22 (d, J = 2.4 Hz, 1H), 8.00 – 8.11 (m, 1H), 7.98 (s, 1H), 7.69 – 7.78 (m, 1H), 4.80 (s, 2H), 4.66 - 4.56 (m, 1H), 3.56 (dt, *J* = 13.1, 3.4 Hz, 2H), 3.22 (td, J = 12.8, 3.4 Hz, 2H), 2.38 - 2.19 (m, 4H)

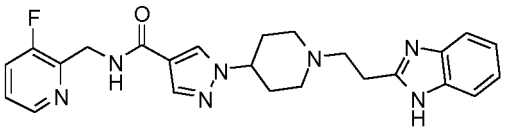
HPLCMS (Method A): [*m/z*]: 304 $[M+H]^+$

1-[1-(1H-1,3-Benzodiazol-2-ylmethyl)piperidin-4-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 150)



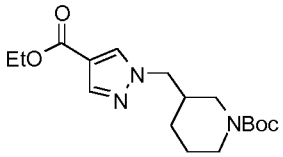
In a similar fashion to general procedure 7, 2-(Chloromethyl)-1H-benzimidazole (71 mg, 0.424 mmol), N-[(3-fluoropyridin-2-yl)methyl]-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide **(274)** (99 mg, 0.326 mmol) and DIPEA (0.171 ml, 0.98 mmol) in DMF (2 ml) at 30°C for 16 h, gave the title compound (21 mg, 15%) as a white solid after purification by basic prep-HPLC followed by further purification by flash column chromatography (kp-NH, eluting with a gradient of 0-20% MeOH / EtOAc).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.28 (s, 1H), 8.52 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.5 Hz, 1H), 8.22 (s, 1H), 7.89 (s, 1H), 7.71 - 7.65 (m, 1H), 7.54 (br s, 1H), 7.44 (br s, 1H), 7.42 - 7.36 (m, 1H), 7.14 (br s, 2H), 4.58 (dd, J = 5.7, 1.6 Hz, 2H), 4.26 - 4.12 (m, 1H), 3.77 (s, 2H), 2.95 (d, J = 12.0 Hz, 2H), 2.32 - 2.23 (m, 2H), 2.05 - 1.94 (m, 4H)
HPLCMS (Method D): [*m/z*]: 434.3 $[M+H]^+$

1-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]piperidin-4-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 198)



In a similar fashion to general procedure 8, DBU (0.28 ml, 1.89 mmol), N-[(3-fluoropyridin-2-yl)methyl]-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide dihydrochloride **(274)** (248 mg, 0.47 mmol) and N-(2-nitrophenyl)prop-2-enamide **(D)** (154 mg, 0.8 mmol) in MeCN (10 ml) at room temperature for 17 h gave the required intermediate (200 mg, 82%) after purified by flash column chromatography (eluting with a gradient of 0-25% MeOH / EtOAc) to give the title compound as a yellow solid.
HPLCMS (Method A): [*m/z*]: 496.1 $[M+H]^+$
The intermediate was further treated with iron powder (87 mg, 1.56 mmol) in AcOH (3 ml) at 80°C for 1.5 h, to give the title compound (72 mg, 33%) as an off-white solid after purification by flash column chromatography eluting with 0 to 20% MeOH / DCM.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.14 (s, 1H), 8.51 (t, J = 5.7 Hz, 1H), 8.38 (dt, J = 4.6, 1.5 Hz, 1H), 8.24 (s, 1H), 7.89 (s, 1H), 7.72 - 7.65 (m, 1H), 7.51 (s, 1H), 7.46 - 7.37 (m, 2H), 7.11 (d, J = 5.1 Hz, 2H), 4.58 (dd, J = 5.7, 1.6 Hz, 2H), 4.22 - 4.12 (m, 1H), 3.07 - 2.96 (m, 4H), 2.82 (t, J = 7.5 Hz, 2H), 2.23 - 2.14 (m, 2H), 2.05 - 1.97 (m, 2H), 1.95 - 1.86 (m, 2H)
HPLCMS (Method C): [*m/z*]: 448.3 $[M+H]^+$

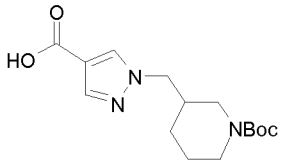
Tert-butyl 3-{[4-(ethoxycarbonyl)-1H-pyrazol-1-yl]methyl}piperidine-1-carboxylate (275)



Ethyl 1H-pyrazole-4-carboxylate (334 mg, 2.38 mmol), tert-butyl 3-(hydroxymethyl)piperidine-1-carboxylate (667 mg, 3.1 mmol) and triphenylphosphine (1.25 g, 4.8 mmol) were dissolved in THF (30 ml) and cooled in an ice-water bath. DIAD (0.94 ml, 4.8 mmol) was added dropwise. The mixture was stirred whilst warming to room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (80 ml) and washed with sat.$NaHCO_3$ (aq) (50 ml) and brine (50 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash chromatography using a gradient elution of 0-40% EtOAc /

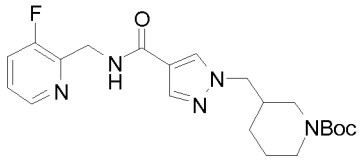
heptane gave the crude title compound (2.23 g) as a colourless oil. The crude product was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 338.15 $[M+H]^+$

1-({1-[(Tert-butoxy)carbonyl]piperidin-3-yl}methyl)-1H-pyrazole-4-carboxylic acid (276)



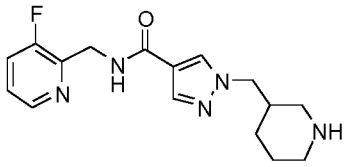
In a similar fashion using general procedure 5, tert-butyl 3-{[4-(ethoxycarbonyl)-1H-pyrazol-1-yl]methyl}piperidine-1-carboxylate **(275)** (2.23 g, 4.69 mmol, 71% purity) and LiOH (1.12 g, 0.05 mol) in THF / water (20 ml / 20 ml) gave the crude product (638 mg, 16%, 38% purity) as a colourless oil.
HPLCMS (Method A): [*m/z*]: 310.05 $[M+H]^+$

Tert-butyl 3-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)methyl]piperidine-1-carboxylate (277)



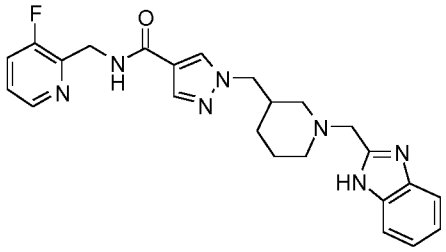
In a similar fashion using general procedure 6, 1-({1-[(tert-butoxy)carbonyl]piperidin-3-yl}methyl)-1H-pyrazole-4-carboxylic acid **(276)** (0.638 g, 2.06 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.451 g, 2.27 mmol), DIPEA (1.26 ml, 7.2 mmol) and HATU (1.18 g, 3.1 mmol) in THF (40 ml) and DMF (5 ml) gave the crude title compound (0.348 g, 32%, 79%purity) as a hygroscopic yellow solid after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane followed by 4-8% MeOH / EtOAc).
HPLCMS (Method A): [*m/z*]: 418.15 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-1-(piperidin-3-ylmethyl)-1H-pyrazole-4-carboxamide (278)



In a similar fashion using general procedure 2, tert-butyl 3-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)methyl]piperidine-1-carboxylate **(277)** (348 mg, 0.83 mmol) and 12 M HCl (0.69 ml) gave the title compound (182 mg, 64%) as the free base after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.36 (dt, J = 4.7, 1.1 Hz, 1H), 8.18 (s, 1H), 7.97 (s, 1H), 7.60 (ddd, J = 9.8, 8.4, 1.2 Hz, 1H), 7.39 (dt, J = 8.6, 4.4 Hz, 1H), 4.73 (d, J = 1.5 Hz, 2H), 4.18 (td, J = 7.1, 2.6 Hz, 2H), 3.29 - 3.22 (m, 1H), 3.19 - 3.13 (m, 1H), 2.81 (td, J = 12.5, 3.1 Hz, 1H), 2.70 (t, J = 12.1 Hz, 1H), 2.42 - 2.30 (m, 1H), 1.94 - 1.85 (m, 1H), 1.83 - 1.66 (m, 2H), 1.35 - 1.22 (m, 1H)
HPLCMS (Method A): [*m/z*]: 318.10 $[M+H]^+$

1-{[1-(1H-1,3-Benzodiazol-2-ylmethyl)piperidin-3-yl]methyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 153)

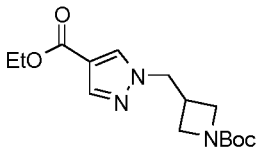


In a similar fashion using general procedure 7, N-[(3-fluoropyridin-2-yl)methyl]-1-(piperidin-3-ylmethyl)-1H-pyrazole-4-carboxamide **(278)** (180 mg, 0.57 mmol), 2-(chloromethyl)-1H-1,3-benzodiazole (189 mg, 1.13 mmol) and DIPEA (180 mg, 1.4 mmol) in DMF (8 ml) gave the title compound (66 mg, 25%) after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.20 (s, 1H), 8.54 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.2 Hz, 1H), 8.16 (s, 1H), 7.88 (s, 1H), 7.71 - 7.65 (m, 1H), 7.53 (d, J = 7.4 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.18 - 7.07 (m, 2H), 5.75 (s, 0H), 4.60 - 4.54 (m, 2H), 4.12 - 3.99 (m, 2H), 3.67 (q, J = 14.0 Hz, 2H), 2.71 - 2.62 (m, 3H), 2.17 - 2.04 (m, 2H), 1.96 (t, J = 10.4 Hz, 1H), 1.67 - 1.58 (m, 1H), 1.54 - 1.38 (m, 2H), 1.05 - 0.91 (m, 1H)

HPLCMS (Method C): [*m/z*]: 448.3 $[M+H]^+$

Ethyl 1-({1-[(tert-butoxy)carbonyl]azetidin-3-yl}methyl)-1H-pyrazole-4-carboxylate (279)

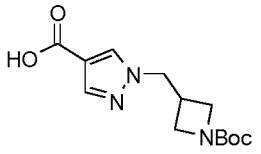


Ethyl 1H-pyrazole-4-carboxylate (0.55 g, 3.92 mmol), tert-butyl 3-(bromomethyl)azetidine-1-carboxylate (0.982 g, 3.92 mmol) and potassium carbonate (1.08 g, 8 mmol) in DMF (10 ml) were stirred at room temperature for 16 h. The mixture was diluted with water and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (4 x 50 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo* to yield the title compound (1.33 g) as a pale yellow oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.92 (s, 1H), 7.90 (s, 1H), 4.38 - 4.26 (m, 4H), 4.06 (t, *J* = 9.0 Hz, 2H), 3.74 (dd, *J* = 9.0, 5.1 Hz, 2H), 3.17 - 3.01 (m, 1H), 1.46 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 310.15 $[M+H]^+$

1-({1-[(Tert-butoxy)carbonyl]azetidin-3-yl}methyl)-1H-pyrazole-4-carboxylic acid (280)

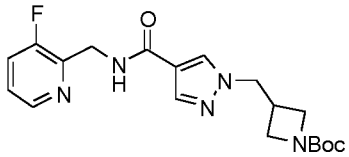


In a similar fashion using general procedure 5, LiOH (2.06 g, 86 mmol) and ethyl 1-({1-[(tert-butoxy)carbonyl]azetidin-3-yl}methyl)-1H-pyrazole-4-carboxylate **(279)** (1.33 g, 4.3 mmol) in THF (30 ml) and water (30 ml) gave the title compound (1.02 g, 83%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 12.31 (s, 1H), 8.31 (s, 1H), 7.81 (s, 1H), 4.36 (d, *J* = 7.3 Hz, 2H), 3.94 - 3.81 (m, 2H), 3.72 - 3.61 (m, 2H), 3.07 - 2.89 (m, 1H), 1.37 (s, 9H)

HPLCMS (Method A): [*m/z*]: 304.05 $[M+Na]^+$

Tert-butyl 3-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)methyl]azetidine-1-carboxylate (281)

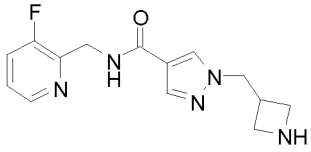


In a similar fashion using general procedure 6, 1-({1-[(tert-butoxy)carbonyl]azetidin-3-yl}methyl)-1H-pyrazole-4-carboxylic acid **(280)** (500 mg, 1.78 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (389 mg, 1.96 mmol), DIPEA (1.1 ml, 6 mmol) and HATU (740 mg, 2 mmol) in DCM (30 ml) gavethe title compound (624 mg, 89%) as a colourless oil after purification by flash column chromatography using a gradient elution of 50 to 100% EtOAc / heptane followed by 0 to 10% MeOH / EtOAc.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.32 (dt, J = 4.7, 1.1 Hz, 1H), 7.84 (s, 1H), 7.79 (s, 1H), 7.35 (m, 1H), 7.24 - 7.20 (m, 1H), 4.71 (dd, J = 4.5, 1.3 Hz, 2H), 4.27 (d, J = 7.6 Hz, 2H), 3.97 (t, J = 8.6 Hz, 2H), 3.66 (dt, J = 7.6, 3.9 Hz, 2H), 3.02 - 2.98 (m, 1H), 1.36 (s, 9H)

HPLCMS (Method A): [*m/z*]: 390.1 $[M+H]^+$

1-(Azetidin-3-ylmethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (282)

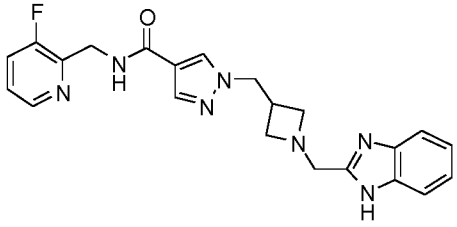


In a similar fashion using general procedure 2, tert-butyl 3-[(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1H-pyrazol-1-yl)methyl]azetidine-1-carboxylate **(281)** (624 mg, 1.6 mmol) and 12 M HCl (2 ml) in MeOH (20 ml) gave the free base title compound (248 mg, 54%) as a white solid after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.42 (d, J = 4.6 Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.44 (t, J = 9.3 Hz, 1H), 7.34 - 7.25 (m, 1H), 4.81 (d, J = 4.2 Hz, 2H), 4.42 (d, J = 7.4 Hz, 2H), 3.82 (t, J = 8.2 Hz, 2H), 3.55-3.47 (m, 2H), 3.28 (m,1H)

HPLCMS (Method A): [*m/z*]: 290 $[M+H]^+$

1-{[1-(1H-1,3-Benzodiazol-2-ylmethyl)azetidin-3-yl]methyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 187)

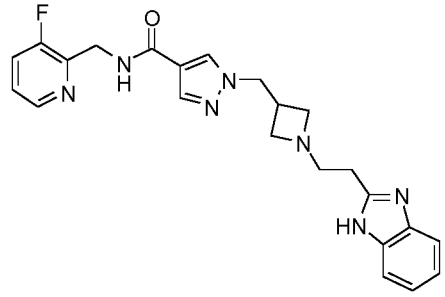


In a similar fashion using general procedure 3, 1-(azetidin-3-ylmethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide **(281)** (50 mg, 0.17 mmol), 1H-benzimidazole-2-carbaldehyde (37.9 mg, 0.26 mmol), DIPEA (0.06 ml, 0.34 mmol) and $MgSO_4$ (300 mg) in MeOH (5 ml) at room temperature for 18 h, followed by addition of $NaBH_4$ (7 mg, 0.17 mmol) afforded the title compound (32 mg, 43%) as pale yellow solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.08 (s, 1H), 8.54 (t, J = 5.7 Hz, 1H), 8.37 (dt, J = 4.6, 1.4 Hz, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.68 (ddd, J = 10.1, 8.3, 1.3 Hz, 1H), 7.47 (s, 2H), 7.40 (dt, J = 8.6, 4.4 Hz, 1H), 7.15 - 7.10 (m, 2H), 4.57 (dd, J = 5.6, 1.5 Hz, 2H), 4.35 (d, J = 7.5 Hz, 2H), 3.77 (s, 2H), 3.38 (t, J = 7.5 Hz, 2H), 3.12 - 3.05 (m, 2H), 2.89 - 2.79 (m, 1H)

HPLCMS (Method C): [*m/z*]: 420.1 $[M+H]^+$

1-({1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide [Example Compound No. 192]



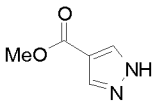
In a similar fashion using general procedure 8, 1-(azetidin-3-ylmethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide **(281)** (200 mg, 0.69 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (139.5 mg, 0.73 mmol) and DBU (0.12 ml, 0.83 mmol) in MeCN (10 ml) gave the crude intermediate which was further reacted with iron powder (130 mg) in AcOH (3 ml). Purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) gave the title compound (67mg, 25%) as a white solid.

1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.36 (dt, J = 4.5, 1.3 Hz, 1H), 8.12 (s, 1H), 7.93 (s, 1H), 7.61 (ddd, J = 9.8, 8.5, 1.3 Hz, 1H), 7.52 (td, J = 6.1, 3.1 Hz, 2H), 7.40 (dt, J = 8.5, 4.5 Hz, 1H), 7.24- 7.17 (m, 2H), 4.73 (d, J = 1.6 Hz, 2H), 4.37 (d, J = 7.2 Hz, 2H), 3.45 (t, J = 7.9 Hz, 2H), 3.14- 3.07 (m, 2H), 3.00 (dq, J = 13.8, 7.0 Hz, 1H), 2.94 (s, 4H)

HPLCMS (Method C): [*m/z*]: 434.2 $[M+H]^+$

General Scheme 16 above

Methyl 1H-pyrazole-4-carboxylate (282)

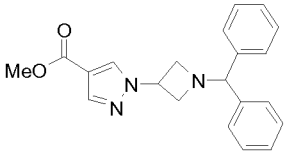


1H-pyrazole-4-carboxylic acid (20 g, 178.4 mmol) and sulfuric acid (39.65 ml) in MeOH (200 ml) were heated at 70°C for 20 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Aqueous NaOH solution was added to adjust the pH to ~6. The aqueous layer was extracted with EtOAc (3 x 200 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to afford the title compound (18.5 g, 78%) as a white solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.10 (s, 2H), 3.87 (s, 3H)

HPLCMS (Method A): [*m/z*]: 126.85 $[M+H]^+$

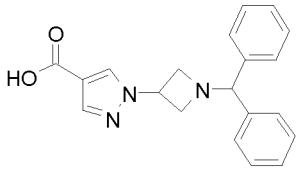
Methyl 1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxylate (283)



A suspension of methyl 1H-pyrazole-4-carboxylate **(282)** (3.34 g, 26.48 mmol), 1-(diphenylmethyl)azetidin-3-yl methanesulfonate (10.93 g, 34.43 mmol) and potassium carbonate (10.98 g, 79 mmol) in DMF (70 ml) was heated at 100°C for 3 h. The reaction mixture was cooled to room temperature and diluted with water (150 ml). The mixture was extracted with EtOAc (3 x 150 ml), the combined organic extracts were washed with brine (5 x 100 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was flushed through

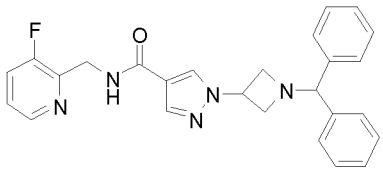
a plug of silica (~15 g) (eluting with 10-20% EtOAc / heptane), the eluent was evaporated in vacuo and the title compound (4.03 g, 44%) obtained as a white solid after precipitation from EtOAc / heptane.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.14 (s, 1H), 7.96 (s, 1H), 7.49 – 7.42 (m, 4H), 7.36 - 7.17 (m, 6H), 4.98 (m, 1H), 4.54 (s, 1H), 3.86 (s, 3H), 3.75– 3.69 (td, J = 7.2, 1.5 Hz, 2H), 3.54 - 3.45 (m, 2H)
HPLCMS (Method A): [*m/z*]: 348.10 $[M+H]^+$

1-[1-(Diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxylic acid (284)



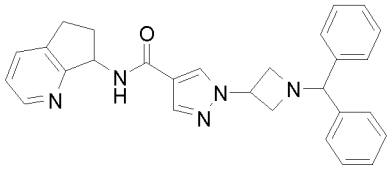
In a similar fashion to general procedure 5, methyl 1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxylate **(283)** (2.1 g, 6.04 mmol) and LiOH (1.45 g, 60 mmol) in THF / water (20 ml / 20 ml) afforded the title compound (1.95 g, 93%) as a white solid.
1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.15 (s, 1H), 8.04 (s, 1H), 7.82 - 7.70 (m, 4H), 7.51 – 7.37 (m, 6H), 5.65 - 5.55 (m, 1H), 5.55 - 5.42 (m, 1H), 4.84 - 4.69 (m, 2H), 4.39 - 4.25 (m, 2H)
HPLCMS (Method A): [*m/z*]: 334.1 $[M+H]^+$

1-[1-(Diphenylmethyl)azetidin-3-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (285)



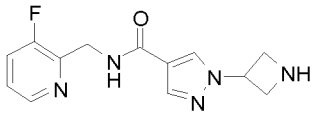
In a similar fashion to general procedure 6, 1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxylic acid **(284)** (1.18 g, 2.46 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.587 g, 2.95 mmol), DIPEA (1.71 ml, 9.82 mmol) and HATU (1.21 g, 3.19 mmol) in THF (50 ml) and DMF (10 ml) afforded the title compound (1.06 g, 82%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 60-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.59 (t, J = 5.7 Hz, 1H), 8.40 (s, 1H), 8.37 (d, J = 4.6 Hz, 1H), 7.93 (s, 1H), 7.68 (t, J = 9.3 Hz, 1H), 7.47 (m, 4H), 7.39 (m, 1H), 7.29 (t, J = 7.6 Hz, 4H), 7.19 (t, J = 7.3 Hz, 2H), 5.04 (p, J = 6.8 Hz, 1H), 4.62 - 4.56 (m, 3H), 3.59 (t, J = 7.7 Hz, 2H), 3.35 (s, 2H)
HPLCMS (Method A): [*m/z*]: 442.15 $[M+H]^+$

N-{5H,6H,7H-Cyclopenta[b]pyridin-7-yl}-1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxamide (286)



In a similar fashion to general procedure 6 1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxylic acid **(284)** (500 mg, 1.5 mmol), 5H,6H,7H-cyclopenta[b]pyridin-7-amine dihydrochloride (404 mg, 1.95 mmol), DIPEA (0.86 ml, 5 mmol) and HATU (0.74 g, 2 mmol) in DCM(20 ml) afforded the crude title compound (949 mg) as a white residue which was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 450.15 $[M+H]^+$

1-(Azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (287)

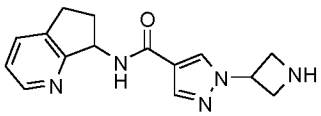


1-[1-(diphenylmethyl)azetidin-3-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide **(285)** (1.06 g, 2.01 mmol) and Pd/C (10%) (0.20 g, 0.201 mmol) were suspended in EtOH (11 ml). A solution of TEA (0.849 ml, 6.04 mmol) and formic acid (0.228 ml, 6.04 mmol) in EtOH (11 ml) was added and the reaction mixture was stirred at reflux for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite and the residue rinsed with MeOH (10 ml). The filtrate was evaporated *in vacuo* to afford the crude material. Purification using a SCX-2 cartridge, washing with DCM and MeOH and eluting with 7 N ammonia / MeOH gave the title compound (0.354 g, 56%) as a colourless oil.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.57 (t, J = 5.6 Hz, 1H), 8.37 (d, J = 4.6 Hz, 1H), 8.34 (s, 1H), 7.93 (s, 1H), 7.72 - 7.65 (m, 1H), 7.40 (dd, J = 8.5, 4.3 Hz, 1H), 5.18 (p, J = 7.3 Hz, 1H), 4.58 (dd, J = 5.6, 1.4 Hz, 2H), 3.84 (t, J = 7.7 Hz, 2H), 3.73 (t, J = 8.1 Hz, 2H)

HPLCMS (Method A): [*m/z*]: 276.1 $[M+H]^+$

1-(Azetidin-3-yl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide (288)

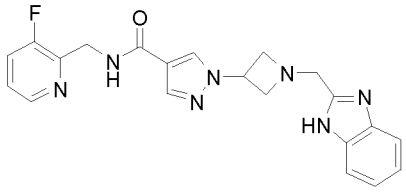


Crude N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1-[1-(diphenylmethyl)azetidin-3-yl]-1H-pyrazole-4-carboxamide (286) (949 mg) and palladium (10% wt. on carbon, 0.12g, 0.11mmol)were suspended in EtOH (20 ml). TEA (454 µL, 3 mmol) and formic acid (125 µL, 3 mmol) in EtOH (20 ml) were added and the mixture heated at reflux for 1 h. The reaction mixture was cooled to room temperature and filtered through a plug of Celite. The residue was rinsed with MeOH and the combined filtrates evaporated *in vacuo*. The residue was dissolved in a minimum amount of MeOH and purified by passage through an SCX-2 cartridge, rinsing with DCM and MeOH and elution with 7 N ammonia in MeOH. Evaporation of the basic eluent afforded the title compound (342 mg, quant) as a white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.40 – 8.34 (m, 3H), 7.94 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 7.6, 4.9 Hz, 1H), 5.48 – 5.40 (m, 1H), 5.18 (m, 1H), 3.88 – 3.81 (m, 2H), 3.78 – 3.71 (m, 2H), 2.98 (ddd, J = 16.0, 8.9, 3.0 Hz, 1H), 2.86 (dt, J = 16.0, 8.3 Hz, 2H), 2.47 (dd, J = 6.5, 4.8 Hz, 1H), 1.95– 1.84 (m, 1H)

HPLCMS (Method A): [*m/z*]: 284.05 $[M+H]^+$

1-[1-(1H-1,3-Benzodiazol-2-ylmethyl)azetidin-3-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide [Example Compound No. 136]

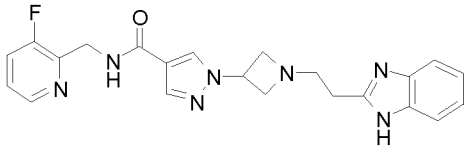


In a similar fashion using general procedure 3, 1-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide **(287)** (196 mg, 0.71 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (125 mg, 0.85 mmol) and $MgSO_4$ (100 mg) in MeOH (8 ml) at room temperature for 3 d, followed by addition of $NaBH_4$ (81 mg, 2.1 mmol) afforded the title compound (82 mg, 28%) as a white solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.32 (s, 1H), 8.58 (t, J = 5.7 Hz, 1H), 8.43 (s, 1H), 8.39 - 8.37 (m, 1H), 7.96 (s, 1H), 7.69 (ddd, J = 10.0, 8.3, 1.2 Hz, 1H), 7.61 - 7.45 (m, 2H), 7.40 (dt, J = 8.6, 4.4 Hz,

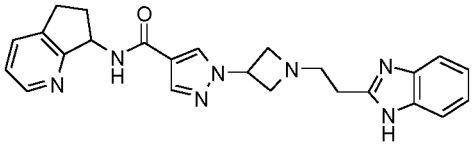
1H), 7.17 - 7.10 (m, 2H), 5.06 (m, 1H), 4.59 (dd, J = 5.7, 1.5 Hz, 2H), 3.92 (s, 2H), 3.85 - 3.81 (m, 2H), 3.61 - 3.57 (m, 2H)
HPLCMS (Method C): [*m/z*]: 406.2 $[M+H]^+$

1-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide (Example Compound No. 167)



In a similar fashion to general procedure 8, 1-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1H-pyrazole-4-carboxamide **(287)** (364 mg, 1.32 mmol), *N*-(2-nitrophenyl)prop-2-enamide **(D)** (254 mg, 1.32 mmol) and DBU (0.197 ml, 1.32 mmol) in MeCN (12 ml) gave the crude intermediate which was following treatment with AcOH (8 ml) and iron powder (62 mg) gave the title compound (104 mg, 43 %) as a white solid after purification by basic prep-HPLC.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.15 (s, 1H), 8.56 (t, J = 5.7 Hz, 1H), 8.37 (d, J = 4.6 Hz, 1H), 8.34 (s, 1H), 7.93 (s, 1H), 7.71 - 7.65 (m, 1H), 7.49 (br s, 1H), 7.45 - 7.37 (m, 2H), 7.14 - 7.07 (m, 2H), 4.98 (p, J = 6.8 Hz, 1H), 4.59 - 4.56 (m, 2H), 3.69 (t, J = 7.6 Hz, 2H), 3.38 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 7.1 Hz, 2H), 2.85 (t, J = 7.0 Hz, 2H)
HPLCMS (Method D): [*m/z*]: 420.3 $[M+H]^+$

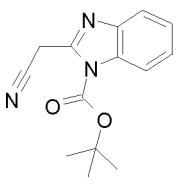
1-{1-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide (Example Compound No. 191)



In a similar fashion to general procedure 8, 1-(azetidin-3-yl)-N-{5H,6H,7H-cyclopenta[b]pyridin-7-yl}-1H-pyrazole-4-carboxamide **(288)** (342 mg, 1.21 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (244 mg, 1.27 mmol) and DBU (0.22 ml, 1.5 mmol) in MeCN (10 ml) afforded a crude intermediate which wasfurther reacted with iron powder (170 mg, 3 mmol) in AcOH (4 ml) to afford the title compound (145 mg, 44%) as a white solid after purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 8.37 (d, J = 5.0 Hz, 1H), 8.26 (s, 1H), 8.01 (s, 1H), 7.78 - 7.73 (m, 1H), 7.52 (dd, J = 5.4, 3.0 Hz, 2H), 7.30 (dd, J = 7.6, 5.0 Hz, 1H), 7.24 - 7.18 (m, 2H), 5.56 (t, J = 8.2 Hz, 1H), 5.06 (m, 1H), 3.86 (td, J = 7.3, 1.6 Hz, 2H), 3.64 - 3.58 (m, 2H), 3.11 - 3.07 (m, 3H), 3.03 - 2.92 (m, 3H), 2.69 (m, 1H), 2.02 (m, 1H)
HPLCMS (Method C): [*m/z*]: 428.2 $[M+H]^+$

General Scheme 18 above:

Tert-butyl 2-(cyanomethyl)-1H-1,3-benzodiazole-1-carboxylate (296)



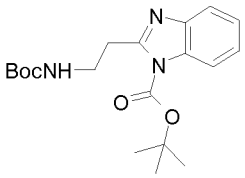
2-(1H-1,3-benzodiazol-2-yl)acetonitrile (1 g, 6.36 mmol) and TEA (887 µl, 6.36 mmol) were dissolved in THF (20 ml) and BOC anhydride (1.64 g, 7.51 mmol) was added. The mixture was stirred at room

temperature for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in chloroform and washed with 1 M HCl (aq) (50 ml), sat. $NaHCO_3$ (aq) (50 ml) and brine (50 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash chromatography using an elution gradient 10-30% EtOAc / heptane afforded the title compound (923 mg, 56%) as an orange solid following trituration with DCM / heptane.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 8.00 - 7.91 (m, 1H), 7.84 - 7.74 (m, 1H), 7.48 - 7.36 (m, 2H), 4.37 (s, 2H), 1.77 (s, 9H)

HPLCMS (Method A): [*m/z*]: 158.35 $[M+H\text{-}Boc]^+$

Tert-butyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate (297)

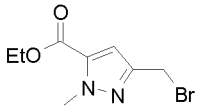


A suspension of tert-butyl 2-(cyanomethyl)-1H-1,3-benzodiazole-1-carboxylate **(296)** (597 mg, 2.32 mmol), TEA (258 mg, 2.55 mmol), Boc_2O (557 mg, 2.55 mmol) and Pd (10% wt on carbon, 247 mg, 0.23 mmol) in EtOH (20 ml) was stirred under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through a plug of Celite and the residue rinsed with MeOH and 7 N ammonia in MeOH. The combined filtrates were evaporated *in vacuo*. Purification by flash chromatography using an elution gradient 0-60% EtOAc / heptane afforded the title compound (748 mg, 89%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.99 - 7.90 (m, 1H), 7.75 - 7.67 (m, 1H), 7.39 - 7.31 (m, 2H), 5.50 (s, 1H), 3.76 (q, J = 5.7 Hz, 2H), 3.36 (t, J = 5.7 Hz, 2H), 1.73 (s, 9H), 1.43 (s, 9H)

HPLCMS (Method A): [*m/z*]: 362.1 $[M+H]^+$

Ethyl 3-(bromomethyl)-1-methyl-1H-pyrazole-5-carboxylate (298)

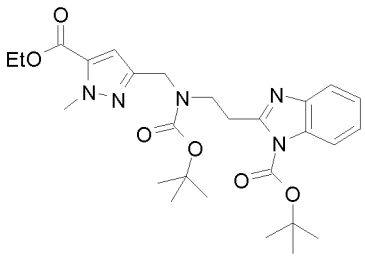


Ethyl 1,3-dimethyl-1H-pyrazole-5-carboxylate (433 mg, 2.57 mmol), NBS (0.623 g, 3.5 mmol) and AIBN (40 mg) in DCE (10 ml) was heated at 80°C for 1.5 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo*. Purification by flash chromatography using an elution gradient 0-10% Et_2O / heptane afforded the title compound (419mg, 66%) as a white waxy solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 6.90 (s, 1H), 4.48 (s, 2H), 4.36 (q, J = 7.1 Hz, 3H), 4.18 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 246.75 /248.75 $[M+H]^+$

Tert-butyl 2-(2-{[(tert-butoxy)carbonyl]({[5-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]methyl})amino}ethyl)-1H-1,3-benzodiazale-1-carboxylate (299)



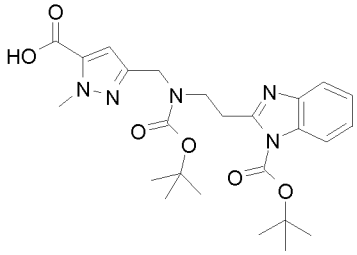
Tert-butyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate **(298)** (263 mg, 0.73 mmol) in THF (5 ml) was cooled in an ice/water bath. $NaBH_4$ (60% in mineral oil, 60 mg, 1.5 mmol) was

added and the mixture stirred for 5 min. Ethyl 3-(bromomethyl)-1-methyl-1H-pyrazole-5-carboxylate **(297)** (90 mg, 0.36 mmol) in THF (2 ml) was added, the mixture allowed to warm to room temperature and stirred for 10 min. The reaction mixture was quenched by dropwise addition of water, then further diluted with water and extracted with DCM (3 x 20 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash chromatography using an elution gradient 0-80% EtOAc / heptane afforded the title compound (126 mg, 66%) as a colourless oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 7.68 - 7.62 (m, 1H), 7.32 - 7.27 (m, 1H), 7.18 - 7.13 (m, 2H), 6.43 (s, 1H), 5.26 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 4.09 - 4.06 (m, 2H), 4.05 (s, 3H), 3.18 (dd, J = 8.4, 6.8 Hz, 2H), 1.39 (s, 18H), 1.23 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 528.2 $[M+H]^+$

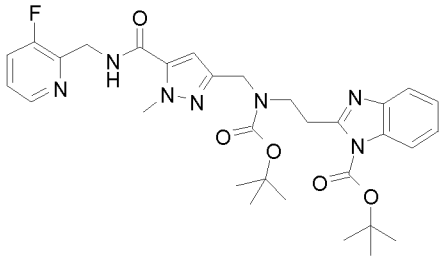
3-({[(Tert-butoxy)carbonyl](2-{1-[(tert-butoxy)carbonyl]-1H-1,3-benzodiazol-2-yl}ethyl)amino}methyl)-1-methyl-1H-pyrazole-5-carboxylic acid (300)



In a similar fashion to general procedure 5, tert-butyl 2-(2-{[(tert-butoxy)carbonyl]({[5-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]methyl})amino}ethyl)-1H-1,3-benzodiazale-1-carboxylate **(299)** (126 mg, 0.24 mmol) and LiOH (17 mg, 0.72 mmol) in THF (5 ml) and water (5 ml) afforded the title compound (152 mg) as a pale yellow oil.

HPLCMS (Method A): [*m/z*]: 500.15 $[M+H]^+$

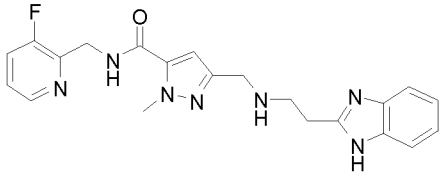
Tert-butyl 2-(2-{[(tert-butoxy)carbonyl][(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1-methyl-1H-pyrazol-3-yl)methyl]amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate (301)



In a similar fashion to general procedure 6, tert-butyl 2-(2-{[(tert-butoxy)carbonyl]({[5-(ethoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]methyl})amino}ethyl)-1H-1,3-benzodiazale-1-carboxylate **(300)** (130 mg, 0.26 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (57 mg, 0.29 mmol), DIPEA (150 µl, 0.86 mmol) and HATU (119 mg, 0.31 mmol) in DCM (10 ml) afforded the crude title compound (317 mg, 30% purity) as a white solid which was used in the next step without purification.

HPLCMS (Method A): [*m/z*]: 608.2 $[M+H]^+$

3-({[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}methyl)-N-[(3-fluoropyridin-2-yl)methyl]-1-methyl-1H-pyrazole-5-carboxamide (Example Compound No. 220)



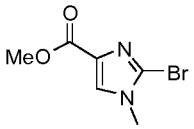
In a similar fashion to general procedure 2, tert-butyl 2-(2-{[(tert-butoxy)carbonyl][(5-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1-methyl-1H-pyrazol-3-yl)methyl]amino}ethyl)-1H-1,3-benzodiazole-1-carboxylate **(301)** (30%, 317 mg, 0.16 mmol) and 12 M HCl (0.63 ml) in MeOH (5 ml) at 60°C for 15 min afforded the title compound (44 mg, 69%) as a white solid after purification by basic prep-HPLC

1H-NMR (DMSO-d6, 500MHz): d[ppm]= 8.93 (m, 1H), 8.34 (dt, J = 4.6, 1.4 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.56 (m, 1H), 7.52 (dd, J = 7.0, 1.4 Hz, 1H), 7.43 - 7.33 (m, 1H), 7.21 - 7.11 (m, 2H), 6.71 (s, 1H), 5.41 (s, 2H), 4.57 - 4.49 (m, 2H), 4.00 (s, 3H), 3.05 - 2.96 (m, 4H)

HPLCMS (Method C): [*m/z*]: 408.1 $[M+H]^+$

General Scheme 19 above

Methyl 2-bromo-1-methyl-1H-imidazole-4-carboxylate (302)

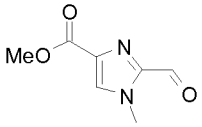


To a stirring solution of methyl 1-methyl-1H-imidazole-4-carboxylate (5 g, 46.38 mmol) in THF (100 ml) was added NBS (8.25 g, 46.38 mmol). The reaction mixture was allowed to stir at room temperature for 72 h. The mixture was concentrated and the crude residue was dissolved in EtOAc (80 ml), washed with sat.$Na_2S_2O_3$ (100 ml) and a ~pH 12 solution of NaOH (50 ml). The NaOH solution was extracted using 1:4 IPA : CHCl3 (5 x 10 ml) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give the crude product. Purification by column chromatography with a gradient of 0-100% EtOAc / heptane gave the purified product which was dissolved in a pH~12 solution of NaOH (50 ml) and extracted using DCM. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give the title compound (5.58 g, 71%) as a white solid.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.08 (s, 1H), 3.74 (s, 3H), 3.63 (s, 3H)

HPLCMS (Method A): [*m/z*]: 218.8, 220.75 $[M+H]^+$

Methyl 2-formyl-1-methyl-1H-imidazole-4-carboxylate (303)

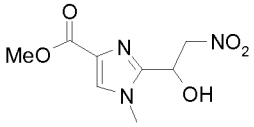


To an N_2 purged stirring solution of methyl 2-bromo-1-methyl-1H-imidazole-4-carboxylate **(302)** (200mg, 0.91 mmol) in THF (1 ml) at -40°C was added dropwise 2 M iPrMgCl in THF (3.31 ml, 6.62 mmol). After 20 min, the reaction was cooled to -78°C and DMF (1.08 ml, 13.96 mmol) added dropwise. The reaction was allowed to warm to room temperature, after 40 min, the reaction was quenched with satNaHCO$_3$ (10 ml) which gave a thick white emulsion. The product was extracted with EtOAc (5 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product. Purification by silica flash column chromatography with a gradient of 0-70% EtOAc / heptane gave the title compound (128 mg, 66%) as a white solid.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 9.74 (d, J = 0.7 Hz, 1H), 8.26 (s, 1H), 3.96 (s, 3H), 3.80 (s, 3H)

HPLCMS (Method A): [*m/z*]: 168.9 $[M+H]^+$

Methyl 2-(1-hydroxy-2-nitroethyl)-1-methyl-1H-imidazole-4-carboxylate (304)

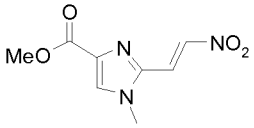


To a stirring solution of methyl 2-formyl-1-methyl-1H-imidazole-4-carboxylate **(303)** (523 mg, 1.47 mmol), MeOH (12 ml) and nitromethane (78.9 µl, 1.47 mmol) followed by dropwise addition of 1 M NaOH solution (12 ml), the reaction was allowed to warm to room temperature over the duration of the experiment. After 1 h, the solution was acidified using 2 M HCl to ~pH 4 and concentrated to remove methanol. The aqueous layer was extracted with 1:4 IPA / $CHCl_3$ (4 x 10 ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by silica flash column chromatography with a gradient of 0-80% EtOAc / heptane to give the final product (165 mg, 36%) as an off-white oil.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 7.94 (s, 1H), 6.35 (d, J = 7.7 Hz, 1H), 5.40 (m, 1H), 5.13 (dd, J = 13.3, 4.0 Hz, 1H), 4.90 (dd, J = 13.3, 9.4 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H)

HPLCMS (Method A): [*m/z*]: 229.9 $[M+H]^+$

Methyl 1-methyl-2-[(E)-2-nitroethenyl]-1H-imidazole-4-carboxylate (305)

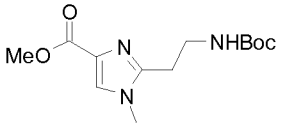


A stirring solution of methyl 2-(1-hydroxy-2-nitroethyl)-1-methyl-1H-imidazole-4-carboxylate **(304)** (197 mg, 0.64 mmol) and acetic anhydride (3.5 ml) was heated to 45°C. After 4 h, the reaction was concentrated to give a yellow residue which was partitioned between sat.$NaHCO_3$ (20 ml) and EtOAc (20 ml). The organic layer was separated and the aqueous extracted using EtOAc (4 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product, purified by silica flash column chromatography with a gradient of 20-100% EtOAc / heptane to give the required product (97 mg, 60%) as a yellow solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.19 (s, 1H), 8.02 - 7.93 (m, 2H), 3.89 (s, 3H), 3.78 (s, 3H)

HPLCMS (Method A): [*m/z*]: 211.9 $[M+H]^+$

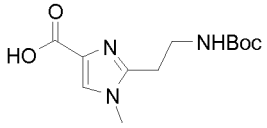
Methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1-methyl-1H-imidazole-4-carboxylate (306)



To an N_2 purged stirring solution of methyl 1-methyl-2-[(E)-2-nitroethenyl]-1H-imidazole-4-carboxylate **(305)** (110 mg, 0.44 mmol), di-tert-butyl dicarbonate (386.5 mg, 1.77 mmol) and EtOH (5 ml) was added Pd/C (10%) (47.1 mg, 0.04 mmol). The reaction was purged (x 3) with N_2 followed by H_2. After 48 h, the reaction was filtered under vacuum through glass fibre paper using methanol (20 ml) to wash the filter cake and the filtrate was concentrated to give the crude product. The crude was purified by flash column chromatography (eluting with a gradient of 0-8% MeOH / DCM) to give the purified product (75 mg, 26%) as a yellow solid.

HPLCMS (Method A): [*m/z*]: 284 $[M+H]^+$

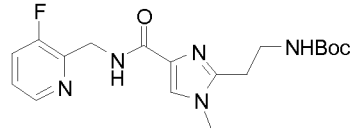
2-(2-{[(Tert-butoxy)carbonyl]amino}ethyl)-1-methyl-1H-imidazole-4-carboxylic acid (307)



In a similar fashion to general procedure 5, methyl 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1-methyl-1H-imidazole-4-carboxylate **(306)** (0.5 g, 0.79 mmol) and LiOH (0.19 g, 7.94 mmol) in THF (20 ml) and water (10 ml) gave the crude product as a yellow solid (0.703 g, quant.)

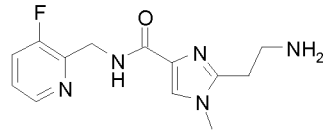
HPLCMS (Method A): [*m/z*]: 270.05 $[M+H]^+$

Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1-methyl-1H-imidazol-2-yl)ethyl]carbamate (308)



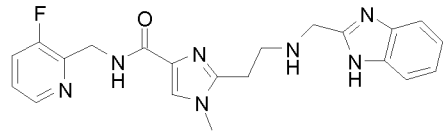
In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-1-methyl-1H-imidazole-4-carboxylic acid **(307)** (0.703 g, 0.79 mmol), HATU (0.604 g, 1.59 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.316 g, 1.58 mmol) and DIPEA (0.968 ml, 5.56 mmol) in THF (20 ml) and DMF (5 ml) at room temperature for 3h gave the title compound (0.092 g, 30%) as a yellow solid after purification by flash column chromatography (eluting with a gradient of 0-9% MeOH / DCM)
HPLCMS (Method A): [*m/z*]: 378.15 $[M+H]^+$

2-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1-methyl-1H-imidazole-4-carboxamide (309)



In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1-methyl-1H-imidazol-2-yl)ethyl]carbamate **(308)** (94 mg, 0.25 mmol) and 12M HCl (0.415 ml, 4.98 mmol) in MeOH (4 ml) at 40°C for 2 h gave the product (9 mg, 13%) as a brown solid after flushing through a the column with 7 M NH_3 / MeOH (x 3).
HPLCMS (Method D): [*m/z*]: 278.05 $[M+H]^+$

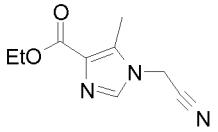
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1-methyl-1H-imidazole-4-carboxamide (Example Compound No. 210)



In a similar fashion to general procedure 3, 2-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1-methyl-1H-imidazole-4-carboxamide **(309)** (9 mg, 0.032 mmol), anhydrous $MgSO_4$ (150 mg), 1H-benzimidazole-2-carbaldehyde (6.2 mg, 0.042 mmol) and DIPEA (11.3 µl, 0.065 mmol) in MeOH (2 ml) for 72 h, followed by the addition of $NaBH_4$ (1.8 mg, 0.049 mmol) gave the title compound (4.1 mg, 30%) as a brown solid after purification by flash column chromatography with a gradient of 0-50% MeOH / DCM.
1H-NMR (MeOD, 500 MHz): d[ppm]= 8.18 (d, J = 4.7 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.44 (s, 1H), 7.42 - 7.37 (m, 2H), 7.28 - 7.22 (m, 1H), 7.11 - 7.06 (m, 2H), 4.63 (s, 2H), 3.97 (s, 2H), 3.53 (s, 3H), 2.97 (t, J = 6.6 Hz, 2H), 2.81 (t, J = 6.6 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 408.1 $[M+H]^+$

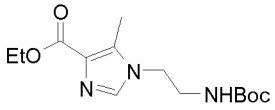
General Scheme 20 above:

Ethyl 1-(cyanomethyl)-5-methyl-1H-imidazole-4-carboxylate (310)



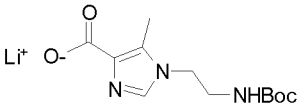
To a N_2 purged, stirring solution of NaH (60% in oil) (0.856 g, 21.41 mmol) in DMF (10 ml) at 0°C was added a solution of ethyl 4-methyl-1H-imidazole-5-carboxylate (3g, 19.46 mmol) in DMF (25 ml) dropwise. After 10 min, bromoacetonitrile (1.63 ml, 23.35 mmol) was added dropwise to the solution giving a red mixture. The reaction was allowed to warm to room temperature. After 16 h, the reaction was concentrated and the residue diluted with sat.$NaHCO_3$ (40 ml). The solution was extracted with EtOAc (6 x 20 ml) and the combined organic layers were washed with brine (4 x 15 ml), dried over $MgSO_4$, filtered and concentrated to give the crude product. Purification by flash column chromatography with a gradient of 0-6% MeOH / DCM gave the title compound (1.3 g, 35%) as an orange solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 7.76 (s, 1H), 5.38 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 2.52 (s,3H), 1.27 (t, J = 7.1 Hz, 3H)
HPLCMS (Method A): [*m/z*]: 194 $[M+H]^+$

Ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-4-methyl-1H-imidazole-4-carboxylate (311)



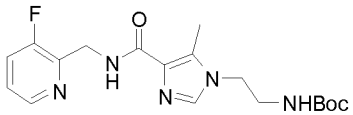
To a N_2 purged stirring solution of ethyl 1-(cyanomethyl)-5-methyl-1H-imidazole-4-carboxylate **(310)** (0.72 g, 3.73 mmol), EtOH (20 ml), TEA (0.675 ml, 4.85 mmol) and di-tert-butyl dicarbonate (1.06 g, 4.85 mmol) at room temperature was added Pd/C (10%) (0.397 g, 0.37 mmol). The reaction was purged with N_2 (x3) followed by H_2. After 16 h, the reaction was filtered through glass fibre paper and the filter cake washed with 7 M NH_3 / MeOH (40 ml). The filtrate was concentrated to give the crude product which was further purified by flash column chromatography using a gradient of 0-10% MeOH / DCM yielding the required product (1.07g, 84%) as an off-white solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 7.53 (s, 1H), 7.01 - 6.93 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.97 (t, J = 5.9 Hz, 2H), 3.19 (q, J = 6.0 Hz, 2H), 2.43 (s, 3H), 1.37 - 1.32 (m, 9H), 1.28 - 1.23 (m, 3H)
HPLCMS (Method A): [*m/z*]: 298.1 $[M+H]^+$

Lithium 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1H-imidazole-4-carboxylate (312)



To a stirring solution of ethyl 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1H-imidazole-4-carboxylate **(311)** (1.07 g, 3.12 mmol), THF (35 ml) and water (10 ml) was added LiOH (0.224 g, 9.36 mmol), the reaction was heated to 50°C. After 24 h, the reaction was concentrated to give the lithium salt of the product (0.670 g) as a yellow solid.
HPLCMS (Method A): [*m/z*]: 270.05 $[M+H]^+$

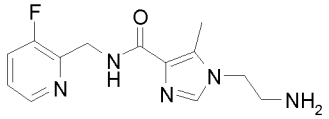
Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1H-imidazol-1-yl)ethyl]carbamate (313)



In a similar fashion to general procedure 6, lithium 1-(2-{[(tert-butoxy)carbonyl]amino}ethyl)-5-methyl-1H-imidazole-4-carboxylate **(312)** (0.670 g, 2.488 mmol), THF (30 ml), DMF (10 ml) and DIPEA (1.733 ml, 9.952 mmol) at room temperature was added HATU (1.419 g, 3.732 mmol) and (3-fluoropyridin-2-yl)methanamine dihydrochloride (0.743 g, 3.732 mmol). After 2 h, the reaction mixturewas concentrated and the residue dissolved in sat.$NaHCO_3$ (100 ml) which was extracted with EtOAc (6 x 20 ml). The combined organic layers were washed with brine (3 x 20 ml), dried over $MgSO_4$, filtered and concentrated

to give the crude product which was further purified by silica column chromatography with a gradient of 0-10 % MeOH in DCM to give an orange oil, further purified using a kp-NH silica column chromatography with a gradient of 0-100 % EtOAc in heptane to give the final product (0.320 g, 31 %) asa yellow oil.
1H-NMR (DMSO-d6, 500 MHz,) d[ppm]= 8.39 (d, J = 4.6 Hz, 1H), 8.22 (t, J = 5.4 Hz, 1H), 7.70 (t, J = 9.3 Hz, 1H), 7.54 (s, 1H), 7.45 - 7.37 (m, 1H), 6.98 (t, J = 5.6 Hz, 1H), 4.60 (d, J = 4.4 Hz, 2H), 3.96 (t, J = 6.0 Hz, 2H), 3.19 (q, J = 5.9 Hz, 2H), 2.44 (s, 3H), 1.39 - 1.20 (m, 9H)
HPLCMS (Method A): [*m/z*]: 378.05 $[M+H]^+$

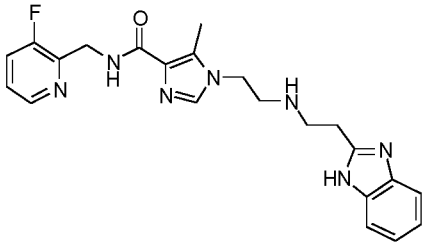
1-(2-Aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1H-imidazole-4-carboxamide dihydrochloride (314)



2HCl

In a similar fashion to general procedure 2, To a stirred sdution of tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-5-methyl-1H-imidazol-1-yl)ethyl]carbamate **(313)** (0.320 g, 0.776 mmol) in MeOH (10 ml) at room temprature was added conc. HCl (1.293 ml, 15.52 mmol), the reaction was heated to 50°C. After 2h, the reaction was concentrated to give the required product (0.294 g, quant) as a yellow solid.
1H-NMR (Methanol-d4, 500 MHz): d[ppm]= 9.03 (s, 1H), 8.54 (s, 1H), 8.06 (s, 1H), 7.75 (s, 1H), 4.89 (s, 2H), 4.58 (t, J = 6.5 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.67 (s, 3H)
HPLCMS (Method A): [*m/z*]: 277.95 $[M+H]^+$

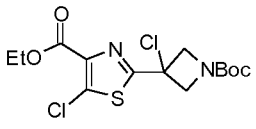
1-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1H-imidazole-4-carboxamide (Example Compound No. 219)



In a similar fashion to general procedure 8, 1-(2-aminoethyl)-N-[(3-fluoropyridin-2-yl)methyl]-5-methyl-1H-imidazole-4-carboxamide dihydrochloride **(314)** (0.294 g, 0.77 mmol), DBU (0.347 ml, 2.33 mmol) and *N*-(2-nitrophenyl)prop-2-enamide **(D)** (0.332 g, 1.73 mmol) in MeCN (20 ml) followed by silica column chromatography (0-3 % MeOH in DCM) followed by reaction with AcOH (2 ml) and iron powder (0.041 g) gave the title compound (0.030 g, 30 %) as an off-white solid after purification by basic prep-HPLC followed by flash column chromatography (kp-NH, eluting with a gradient 0-5% MeOH / DCM).
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.09 (br s, 1H), 8.39 (d, J = 4.7 Hz, 1H), 8.22 (t, J = 5.5 Hz, 1H), 7.75 - 7.66 (m, 1H), 7.61 (s, 1H), 7.53 - 7.35 (m, 3H), 7.13 - 7.06 (m, 2H), 4.60 (d, J = 4.3 Hz, 2H), 3.97 (t, J = 6.3 Hz, 2H), 3.00 - 2.93 (m, 2H), 2.94 - 2.88 (m, 2H), 2.84 (t, J = 6.3 Hz, 2H), 2.47 (s, 3H)
HPLCMS (Method G): [*m/z*]: 422.1 $[M+H]^+$

General Scheme 21 above:

Ethyl 2-{1-[(tert-butoxy)carbonyl]-3-chloroazetidin-3-yl}-5-chloro-1,3-thiazole-4-carboxylate (321)

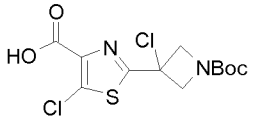


Ethyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-thiazole-4-carboxylate **(161)** (1.15 g, 3.68 mmol) and hexachloroethane (0.83 g, 3 mmol) were dissolved in THF (40 ml) and cooled to-78°C. 2 M NaHMDS (1.75 ml) was added dropwise and the reaction mixture was left stirring at -78°C for 30 min. Further 2M NaHMDS (0.6 ml) were added and the reaction mixture and left stirred at-78°C for further 30 min. The reaction was quenched with sat. NH_4Cl (aq), warmed to room temperature, diluted with water and extracted with DCM (3 x 80 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. Two major components were identified in the crude mixture. Purification by flash column chromatography (eluting with a gradient of 2-15% EtOAc / heptane) gave the title compound (456 mg, 32%) as a pale yellow oil.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 4.72 (d, J = 9.2 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.32 (m, 2H), 1.40 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H)

HPLCMS (Method A): [*m/z*]: 402.9 $[M+Na]^+$

2-{1-[(Tert-butoxy)carbonyl]-3-chloroazetidin-3-yl}-5-chloro-1,3-thiazole-4-carboxylic acid (322)

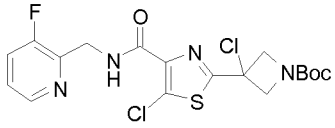


In a similar fashion to general procedure 5, ethyl 2-{1-[(tert-butoxy)carbonyl]-3-chloroazetidin-3-yl}-5-chloro-1,3-thiazole-4-carboxylate **(321)** (450 mg, 1.18 mmol) and LiOH (0.08 g, 4 mmol) in THF (5 ml) and water (5 ml) gave the crude title compound (461 mg) as a colourless oil which crystallised on standing.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 4.76 (dd, J = 9.6, 1.0 Hz, 2H), 4.45 (dd, J = 9.6, 1.0 Hz, 2H), 1.50 (s, 9H)

HPLCMS (Method A): [*m/z*]: 378.85 $[M+Na]^+$

Tert-butyl 3-chloro-3-(5-chloro-4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate (323)

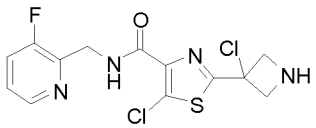


In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]-3-chloroazetidin-3-yl}-5-chloro-1,3-thiazole-4-carboxylic acid **(322)** (460 mg, 1.3 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride - **(A2)** (311 mg, 1.56 mmol), DIPEA (0.75 ml, 4 mmol) and HATU (0.59 g, 2 mmol) in DCM (10 ml) afforded the title compound (479 mg, 80%) after purification by flash column chromatography (eluting with a gradient of 10-50% EtOAc / heptane).

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.34 (dt, J = 4.7, 1.1 Hz, 1H), 8.26 - 8.20 (m, 1H), 7.38 - 7.31 (m, 1H), 7.23 - 7.16 (m, 1H), 4.75 (m, 2H), 4.70 (m, 2H), 4.35 (m, 2H), 1.40 (s, 9H)

HPLCMS (Method A): [*m/z*]: 460.95 $[M+H]^+$

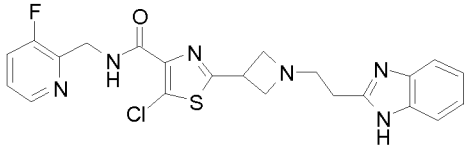
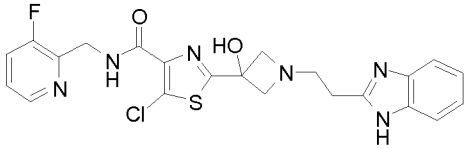
5-Chloro-2-(3-chloroazetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (324)



In a similar fashion to general procedure 2, tert-butyl 3-chloro-3-(5-chloro-4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)azetidine-1-carboxylate **(323)** (479 mg, 1.04 mmol) and 12 M HCl (2 ml) in MeOH (20 ml) gave the title compound (375 mg, quant.) as a white solid following purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then eluting with 7 N ammonia in MeOH.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 9.05 - 8.96 (m, 1H), 8.40 (dt, J = 4.6, 1.4 Hz, 1H), 7.78 - 7.66 (m, 1H), 7.48 - 7.37 (m, 1H), 4.66 (dd, J = 5.8, 1.6 Hz, 2H), 4.41 (d, J = 10.5 Hz, 2H), 4.07 (d, J = 10.5 Hz, 2H)
HPLCMS (Method A): [*m/z*]: 360.8 $[M+H]^+$

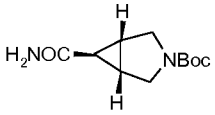
2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 209) and 2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-3-hydroxyazetidin-3-yl}-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 211)

In a similar fashion to general procedure 8, 5-chloro-2-(3-chloroazetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(324)** (375 mg, 1.04 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (219 mg, 1.14 mmol) and DBU (0.17 ml, 1.14 mmol) in MeCN (20 ml) gave a crude mixture which was further reacted with iron powder (0.2 g) in AcOH (5 ml). Purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) gave the title compound **(Example Compound No. 209)** (60 mg, 14%) as a white solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.14 (s, 1H), 8.77 (t, J = 5.6 Hz, 1H), 8.38 (dt, J = 4.6, 1.3 Hz, 1H), 7.75 - 7.67 (m, 1H), 7.56 - 7.37 (m, 3H), 7.12 (dd, J = 5.9, 2.6 Hz, 2H), 4.66 - 4.60 (m, 2H), 3.89 (ddd, J = 13.1, 7.4, 5.6 Hz, 1H), 3.61 (t, J = 7.2 Hz, 2H), 2.94 - 2.88 (m, 2H), 2.87 - 2.81 (m, 2H). One CH_2 signal is obscured by the water peak.
HPLCMS (Method C): [*m/z*]: 471.1 $[M+H]^+$
A byproduct was also isolated by basic prep-HPLC to give 2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]-3-hydroxyazetidin-3-yl}-5-chloro-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(Example Compound No. 211)** (2 mg) as a white solid.
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.16 (s, 1H), 8.86 (t, J = 5.5 Hz, 1H), 8.35 (dt, J = 4.6, 1.4 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.54 - 7.48 (m, 1H), 7.44 - 7.34 (m, 2H), 7.15 - 7.07 (m, 2H), 4.65 (d, J = 5.5 Hz, 2H), 3.70 (d, J = 8.3 Hz, 2H), 3.43 (d, J = 8.3 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H)
HPLCMS (Method C): [*m/z*]: 487.1 $[M+H]^+$

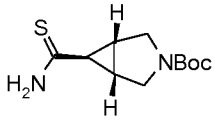
General Scheme 22 above:

Tert-butyl (1R,5S,6S)-6-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (325)



In a similar fashion to general procedure 12, (1R,5S,6S)-3-[(tert-butoxy)carbonyl]-3-azabicyclo[3.1.0]hexane-6-carboxylic acid (1 g, 4.4 mmol), TEA (1.04 ml, 0.01 mol), isobutyl chloroformate (0.86 ml, 0.01 mol) and NH_3 28% aqueous (1.33 ml, 0.07 mol) in THF (15 ml) gave the crude title product (1.20 g) as a pale yellow solid. The material was used directly in the next step.
HPLCMS (Method A): [*m/z*]: 249.05 $[M+Na]^+$

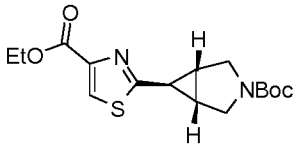
Tert-butyl (1R,5S,6S)-6-carbamothioyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (326)



In a similar fashion to general procedure 11, tert-butyl (1R,5S,6S)-6-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate **(325)** (1.2 g, 5.3 mmol) and Lawesson reagent (1.18 g, 2.9 mmol) in DCM (40 ml) gave the

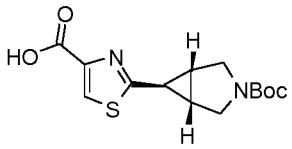
title compound (939 mg, 73%) as a white foam after purification by flash column chromatography using a gradient elution of 0-10% EtOAc / heptane.
HPLCMS (Method A): [*m/z*]: 242.95 $[M+H]^+$

Tert-butyl (1R,5S,6R)-6-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (327)



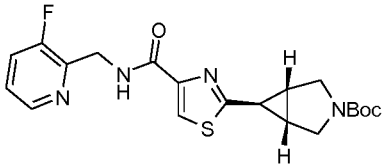
In a similar fashion to general procedure 1, tert-butyl (1R,5S,6S)-6-carbamothioyl-3-azabicyclo[3.1.0]hexane-3-carboxylate **(326)** (939 mg, 3.87 mmol), ethyl 3-bromo-2-oxopropanoate (0.53 ml, 4 mmol) and $CaCO_3$ (0.21 g, 2 mmol) in EtOH (20 ml) afforded the title compound (546 mg, 42%) as a colourless residue after purification by flash column chromatography using a isocratic elution of 30% EtOAc / heptane followed by a second flash column chromatography using a gradient elution of 0-40% EtOAc / heptane.
HPLCMS (Method A): [*m/z*]: 339.1 $[M+H]^+$

2-[(1R,5S,6R)-3-[(Tert-butoxy)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]-1,3-thiazole-4-carboxylic acid (328)



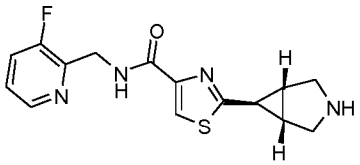
In a similar fashion to general procedure 5, tert-butyl (1R,5S,6R)-6-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]-3-azabicyclo[3.1.0]hexane-3-carboxylate **(327)** (546 mg, 1.61 mmol) and LiOH (0.12 g, 5 mmol) in THF (20 ml) and water (10 ml) afforded the crude title compound (500 mg, 1.61 mmol) as a pale yellow oil which was used in the next step without purification.
HPLCMS (Method A): [*m/z*]: 311.1 $[M+H]^+$

Tert-butyl (1R,5S,6S)-6-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (329)



In a similar fashion to general procedure 6, 2-[(1R,5S,6R)-3-[(tert-butoxy)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]-1,3-thiazole-4-carboxylic acid **(328)** (500 mg, 1.61 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (352.7 mg, 1.77 mmol), DIPEA (0.93 ml, 5.31 mmol) and HATU (0.74 g, 1.93 mmol) in DCM (30 ml) afforded the title compound (650 mg, 96%) as a colourless foam after purification by flash column chromatography eluting with a gradient of 20-100% EtOAc / heptane.
HPLCMS (Method A): [*m/z*]: 419.1 $[M+H]^+$

2-[(1R,5S,6S)-3-Azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (330)

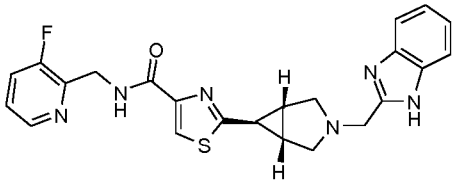


In a similar fashion to general procedure 4, tert-butyl (1R,5S,6S)-6-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-3-azabicyclo[3.1.0]hexane-3-carboxylate **(329)** (624 mg, 1.49 mmol) and 12 M HCl (2 ml) in MeOH (20 ml) afforded the title compound (475 mg, 83%) after purification using an SCX-2 cartridge, rinsing with DCM and MeOH, then elution with 7 N ammonia in MeOH.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.65 (t, J = 5.6 Hz, 1H), 8.39 (dt, J = 4.6, 1.3 Hz, 1H), 8.03 (s, 1H), 7.75 - 7.69 (m, 1H), 7.45 - 7.39 (m, 1H), 4.67 - 4.63 (m, 2H), 3.05 (m, 3H), 2.78 (d, J = 11.4 Hz, 2H), 2.38 (t, J = 3.3 Hz, 1H), 2.03 - 2.00 (m, 2H)

HPLCMS (Method A): [*m/z*]: 319.05 $[M+H]^+$

2-[(1R,5S,6S)-3-(1H-1,3-Benzodiazol-2-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (331)

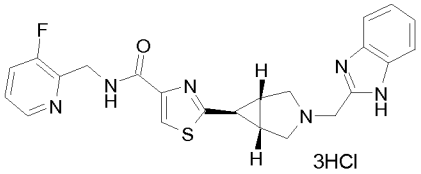


In a similar fashion to general procedure 3, 2-[(1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(330)** (200 mg, 0.63 mmol), 1H-1,3-benzodiazole-2-carbaldehyde (110.17 mg, 0.75 mmol), DIPEA (0.33 ml, 2 mmol) and $MgSO_4$ (300mg) in MeOH (10 ml) at room temperature for 18 h, followed by addition of $NaBH_4$ (48 mg, 1.3 mmol) gave the title compound (62 mg, 22%) as a pale yellow solid after trituration of the residue in 1:1 DMSO / MeCN followed by rinsing with MeOH.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.63 (t, J = 5.7 Hz, 1H), 8.40 (d, J = 4.6 Hz, 1H), 8.04 (s, 1H), 7.76 - 7.67 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.44 - 7.39 (m, 1H), 7.20 - 7.09 (m, 2H), 4.66 (d, J = 4.9 Hz, 2H), 3.91 (s, 2H), 3.15 (d, J = 9.1 Hz, 2H), 2.96 (t, J = 2.8 Hz, 1H), 2.66 - 2.60 (m, 2H), 2.14 - 2.10 (m, 2H)

HPLCMS (Method C): [*m/z*]: 449.1 $[M+H]^+$

2-[(1R,5S,6S)-3-(1H-1,3-Benzodiazol-2-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 213)

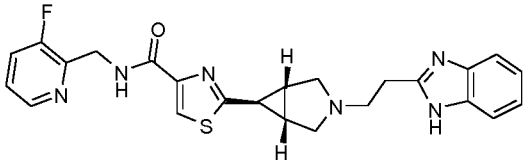


2-[(1R,5S,6S)-3-(1H-1,3-benzodiazol-2-ylmethyl)-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(331)** (20 mg, 0.44 mmol) was suspended in MeOH (3 ml) and treated with 12 M HCl (0.5 ml), causing dissolution. The mixture was stirred for 1 h, evaporated under vacuum to give the title compound (25 mg, quant.) as a yellow solid.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.58 - 8.55 (m, 1H), 8.19 - 8.13 (m, 1H), 8.05 (s, 1H), 7.86 - 7.78 (m, 3H), 7.66 - 7.61 (m, 2H), 4.90 (s, 2H), 4.52 (s, 2H), 3.60 - 3.52 (m, 2H), 3.22 - 3.13 (m, 2H), 3.11 (t, J = 3.1 Hz, 1H), 2.43 (s, 2H)

HPLCMS (Method C): [*m/z*]: 449.1 $[M+H]^+$

2-[(1R,5S,6S)-3-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 218)



In a similar fashion to general procedure 8, 2-[(1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl]-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(330)** (264 mg, 0.83 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (175 mg, 0.91 mmol) and DBU (0.14 ml, 0.91 mmol) in MeCN (15 ml) gave acrude intermediate which was further reacted with iron powder (180 mg, 3.2 mmol) in AcOH (5 ml) to give the title compound (4 mg, 1%) as a colourless residue after purification by sequential flash chromatography (eluting with a gradient of 0-40% MeOH / DCM), basic prep-HPLC and flash column chromatography (eluting with a gradient of 0-5% MeOH / DCM).

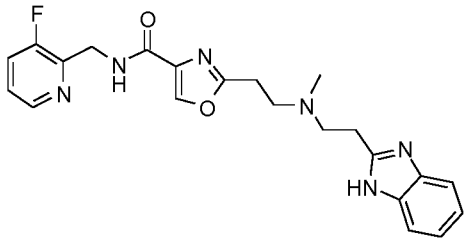
1H-NMR (MeOD, 500 MHz): d[ppm]= 8.38 (d, J = 4.7 Hz, 1H), 7.94 (s, 1H), 7.61 (ddd, J = 9.7, 8.4, 1.2 Hz, 1H), 7.53 (m, 2H), 7.43 - 7.38 (m, 1H), 7.22 (m, 2H), 4.77 (d, J = 1.5 Hz, 2H), 3.30 (m, 2H), 3.09 (m, 2H), 3.01 (m, 2H), 2.66 (m, 1H), 2.58 (m, 2H), 2.15 (s, 2H)

HPLCMS (Method C): [*m/z*]: 463.1 $[M+H]^+$

General Scheme 23



2-(2-{[2-(1H-1,3-Benzodiazol-2-yl)ethyl](methyl)amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 223)



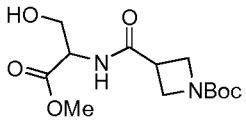
2-(2-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}ethyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide **(Example Compound No. 127)** (59 mg, 0.14 mmol), TEA (60 µl, 0.43 mmol) in DMF (1 ml) were stirred at room temperature for 1 h. MeI (8.9 µl, 0.14 mmol) was added and stirred at room temperature for 24 h. The reaction mixture was re-treated with MeI (62.9 µl, 0.79 mmol) and TEA (80 µl, 0.58 mmol) and left stirring at room temperature for 2 d. The mixture was vigorously reduced *in vacuo* to give a yellow oil (200 mg) which was purification by basic prep-HPLC, followed by kp-NH column chromatography (eluting with a gradient of 0-10% MeOH / DCM) and flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM) to give the title compound (13 mg, 21%) as an off-white solid.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.34 - 8.29 (m, 1H), 8.15 (s, 1H), 7.61 - 7.54 (m, 1H), 7.44 (br s, 2H), 7.38 - 7.33 (m, 1H), 7.19 - 7.13 (m, 2H), 4.69 (d, J = 1.6 Hz, 2H), 3.09 - 3.04 (m, 2H), 3.04 - 2.99 (m, 2H), 2.98 - 2.91 (m, 4H), 2.39 (s, 3H)

HPLCMS (Method G): [*m/z*]: 423.1 $[M+H]^+$

General Scheme 25 above:

Tert-butyl 3-[(3-hydroxy-1-methoxy-1-oxopropan-2-yl)carbamoyl]azetidine-1-carboxylate (339)

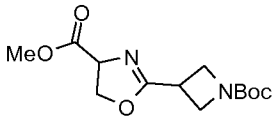


A stirring solution of methyl serinate hydrochloride (1:1) (2.3 g, 14.78 mmol) and TEA (2.27 ml, 16.26 mmol) in DCM (150 ml) was cooled to 0 °C. 1-[(tert-butoxy)carbonyl]azetidine-3-carboxylic acid (2.97 g, 14.78 mmol) was added followed by addition of DCC (3.36 g, 16.26 mmol) portion wise, the reaction was then allowed to warm to room temperature. After 24 h the mixture was concentrated and dissolved in EtOAc (~250 ml). The reaction mixture was left stirring at 50 °C for 45 min. The precipitate was then filtered off and the filtrate was concentrated to give the crude product as a white solid. Purification by flash column chromatography using a gradient elution of 100% TBME followed by DCM / MeOH afforded the title compound (4.5 g, 91 %) as a yellow solid.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 6.75 (d, 1H), 4.66 (dt, 1H), 4.14 - 4.02 (m, 4H), 3.99 (dd, 1H), 3.88 (d, 1H), 3.77 (s, 3H), 3.29 (ddd, 1H), 1.42 (s, 9H)

HPLCMS (Method A): [*m/z*]: 246.95 $[M-{}^{t}Bu]^{+}$

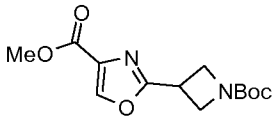
Methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-4,5-dihydro-1,3-oxazole-4-carboxylate (340)



In a similar fashion to general procedure 14, tert-butyl 3-[(3-hydroxy-1-methoxy-1-oxopropan-2-yl)carbamoyl]azetidine-1-carboxylate **(339)** (4.5 g, 13.4 mmol) and DAST (2.3 ml, 17.42 mmol) in DCM (120 ml) afforded the title compound (3.3 g, 78%) as a pale yellow oil. Compound was used into the next step without further purification.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 4.78 (m, 1H), 4.60 - 4.53 (m, 1H), 4.47 (m, 1H), 4.12 (m, 4H), 3.80 (s, 3H), 3.48 - 3.36 (m, 1H), 1.43 (s, 9H)

Methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylate (341)

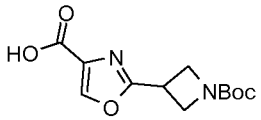


In a similar fashion to general procedure 15, methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-4,5-dihydro-1,3-oxazole-4-carboxylate **(340)** (3.3 g, 10.45 mmol), DBU (2.21 ml, 14.77 mmol) and bromo(trichloro)methane (2.57 ml, 26.12 mmol) in DCM (25 ml) afforded the title compound (2.3 g, 70%) as an yellow oil after purification by flash column chromatography using a gradient of 0-10 % MeOH in DCM.

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.21 (s, 1H), 4.30 - 4.24 (m, 4H), 3.96 - 3.89 (m, 4H), 1.44 (s, 9H)

HPLCMS (Method A): [*m/z*]: 305.00 $[M+Na]^{+}$

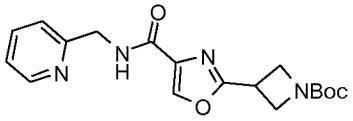
2-{1-[(Tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid (342)



In a similar fashion to general procedure 5, methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylate **(341)** (2.3 g, 7.33 mmol) and LiOH (0.26 g, 0.01 mol) in THF (35 ml) and water (8.5 ml) at

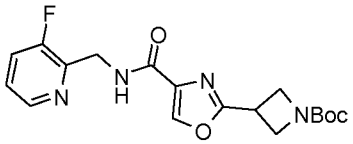
room temperature for 4 h afforded the title compound (2.0 g, 86%) as a pale yellow oil. The crude material was used in the next step without further purification.
HPLCMS (Method A): [*m/z*]: 290.95 $[M+Na]^+$

2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid (343)



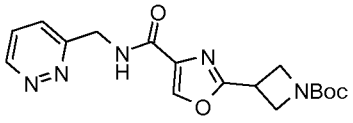
In a similar fashion to general procedure 6, tert-butyl 3-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}azetidine-1-carboxylate **(342)** (1 g, 3.17 mmol), pyridin-2-ylmethanamine (0.343 g, 3.17 mmol), TEA (0.42 ml, 3.17 mmol) and HATU (1.81 g, 4.75 mmol) in DMF (10 ml) at room temperature for 48 h afforded the title compound (1.07 g, 32%) as a brown oil after purification by flash column chromatography (eluting with a gradient of 40-80 % EtOAc / heptane).
1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.55 - 8.51 (m, 1H), 8.11 (s, 1H), 7.84 (s, 1H), 7.61 (td, J = 7.7, 1.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.15 (dd, J = 7.4, 4.9 Hz, 1H), 4.67 (d, J = 5.5Hz, 2H), 4.22 (t, J = 8.8 Hz, 2H), 4.16 (dd, J = 8.6, 6.2 Hz, 2H), 3.86 - 3.78 (m, 1H), 1.39 (s, 9H)
HPLCMS (Method A): [*m/z*]: 359.10 $[M+H]^+$

Tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)azetidine-1-carboxylate (344)



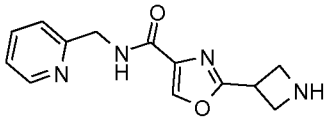
In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid **(342)** (1.0 g, 3.48 mmol), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.83 g, 4.17 mmol), DIPEA (2.42 ml, 13.91 mmol) and HATU (1.59 g, 4.17 mmol) in THF (50 ml) and DMF (10 ml) afforded the title compound (1.56 g, 90%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 20-100 % EtOAc / heptane).
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.68 - 8.54 (m, 2H), 8.38 (d, J = 4.6 Hz, 1H), 7.75 - 7.63 (m, 1H), 7.40 (m, 1H), 4.66 - 4.57 (m, 2H), 4.31 - 4.15 (m, 2H), 4.11 - 3.95 (m, 3H), 1.39 (s, 9H)
HPLCMS (Method A): [*m/z*]: 377.15 $[M+H]^+$

Tert-butyl 3-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}azetidine-1-carboxylate (345)



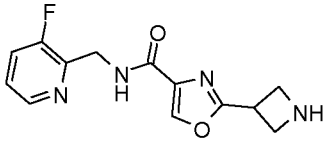
In a similar fashion to general procedure 6, 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid **(342)** (0.8 g, 2.98 mmol), 1-(pyridazin-3-yl)methanamine (0.42 g, 3.28 mmol, 85% purity), DIPEA (779 µl, 4.47 mmol) and HATU (1.36 g, 3.58 mmol) in DCM (20 ml) afforded the title compound (0.90 g, 84%) as a brown residue after purification by flash column chromatography (eluting with a gradient of 50-100% EtOAc / heptane followed by 0-20% MeOH / EtOAc).
HPLCMS (Method M): [*m/z*]: 360.00 $[M+H]^+$

2-(Azetidin-3-yl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide (346)



In a similar fashion to general procedure 2, tert-butyl 3-{4-[(pyridin-2-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}azetidine-1-carboxylate **(343)** (1.07 g, 2.99 mmol) and 12M HCl (2 ml) in MeOH (20 ml) at 50°C for 30 min afforded the title compound (0.457 g, 59 %) as a yellow solid after purification using an SCX-2 cartridge (10 g), rinsing with DCM and MeOH and then eluting with 7N NH_3 / MeOH. The basic eluent was then concentrated to give the title compound as the free base.
HPLCMS (Method A): [*m/z*]: 259.00 $[M+H]^+$

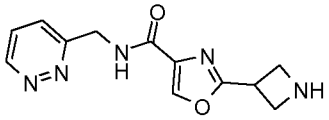
2-(Azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride (347)



2HCl

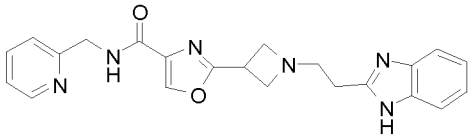
In a similar fashion to general procedure 2, tert-butyl 3-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-oxazol-2-yl)azetidine-1-carboxylate **(344)** (1.56 g, 3.12 mmol) and concentrated HCl (5.2 ml, 62.51 mmol) in MeOH (25 ml) at room temperature for 16 h affored the title compound (1.31 g, quant.) as an off-white solid. The crude material was used in the next step without purification.
HPLCMS (Method A): [*m/z*]: 277.05 $[M+H]^+$

2-(Azetidin-3-yl)-N-(pyridazin-3-ylmethyl)-1,3-oxazole-4-carboxamide (348)



In a similar fashion to general procedure 2, tert-butyl 3-{4-[(pyridazin-3-ylmethyl)carbamoyl]-1,3-oxazol-2-yl}azetidine-1-carboxylate **(345)** (900 mg, 2.5 mmol) and TFA (10 ml, 130.6 mmol) in DCM (10 ml) at room temperature for 40 min afforded the title compound (447 mg, 69%) as a beige solid after purification using an SCX-2 cartridge (10 g), rinsing with DCM and MeOH and then eluting with 7N NH_3 / MeOH. The basic eluent was then concentrated to give the title compound as the free base.
1H-NMR (DMSO-d6, 250MHz): d[ppm]= 9.14 (dd, J = 4.7, 1.7 Hz, 1H), 8.95 (t, J = 6.0 Hz, 1H), 8.60 (s, 1H), 7.67 (dd, J = 8.5, 4.7 Hz, 1H), 7.59 (dd, J = 8.5, 1.8 Hz, 1H), 4.73 (d, J = 6.2 Hz, 2H), 4.13 - 3.99 (m, 1H), 3.89 - 3.70 (m, 4H)
HPLCMS (Method M): [*m/z*]: 260.00 $[M+H]^+$

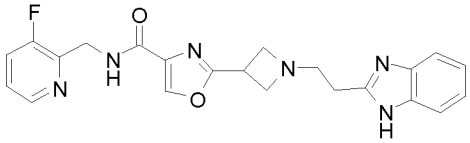
2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 207)



In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide **(346)** (457 mg, 1.769 mmol), *N*-(2-nitrophenyl)prop-2-enamide **(D)** (408 mg, 2.123 mmol) and DBU (0.32 ml, 2.123 mmol) in MeCN (20 ml) gave the crude intermediate which was purifiedby flash column chromatography (eluting with a gradient of 0-5 % MeOH / DCM). The intermediate was further reacted with iron powder (134 mg) in AcOH (3 ml) to give the title compound (26 mg, 8%) as a white solid after purification by basic prep-HPLC.

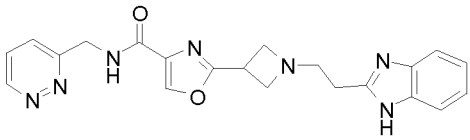
1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.50 (d, J = 4.3 Hz, 1H), 8.33 (s, 1H), 7.80 (m, 1H), 7.50 (s, 2H), 7.40 (d, J = 7.9 Hz, 1H), 7.34 - 7.29 (m, 1H), 7.22 - 7.16 (m, 2H), 4.67 (s, 2H), 3.88 (p, J = 7.3 Hz, 1H), 3.75 (t, J = 8.0 Hz, 2H), 3.54 (t, J = 7.5 Hz, 2H), 3.05 - 2.99 (m, 2H), 2.99 - 2.93 (m, 2H) HPLCMS (Method G): [*m/z*]: 403.2 $[M+H]^+$

2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 208)



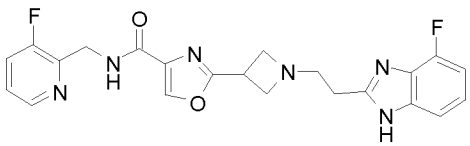
In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide dihydrochloride **(347)** (0.657 g, 1.571 mmol), DBU (0.703 ml, 4.713 mmol) and *N*-(2-nitrophenyl)prop-2-enamide **(D)** (0.332 g, 1.728 mmol) in MeCN (30 ml) at room temperature for 4 h gave the crude intermediate which was purified by flash column chromatography (eluting with a gradient of 0-3 % MeOH / DCM) to give a yellow oil (0.778 g). This was further reacted with iron powder (0.191 g) in AcOH (4 ml) at 80°C for 2 h to give the title compound (0.072 g, 15 %) as a white solid after purification by flash column chromatography (kp-NH, eluting with a gradient of 0-3% MeOH / DCM) followed by another flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).
1H-NMR (MeOD, 500 MHz): d[ppm]= 8.36 (d, J = 4.7 Hz, 1H), 8.32 (s, 1H), 7.62- 7.56 (m, 1H), 7.50 (br s, 2H), 7.41 - 7.36 (m, 1H), 7.22 - 7.17 (m, 2H), 4.75 (d, J = 1.5 Hz, 2H), 3.88 (p, J = 7.3 Hz, 1H), 3.75 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 7.5 Hz, 2H), 3.04 - 2.99 (m, 2H), 2.99 - 2.93 (m, 2H)
HPLCMS (Method C): [*m/z*]: 421.1 $[M+H]^+$

2-{1-[2-(1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-(pyridazin-3-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 244)



In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-(pyridazin-3-ylmethyl)-1,3-oxazole-4-carboxamide **(348)** (440 mg, 1.7 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (326 mg, 1.7 mmol) and DBU (279 µl, 1.87 mmol) in MeCN (20 ml) gave a crude intermediate which was further reacted with iron powder (302 mg, 5.41 mmol) in AcOH (5 ml) to afforded the title compound (82 mg, 15%) as a white solid after purification by basic prep-HPLC.
1H-NMR (MeOD, 500 MHz): d[ppm]= 9.12 (dd, J = 4.5, 2.1 Hz, 1H), 8.36 (s, 1H), 7.76 - 7.69 (m, 2H), 7.51 (s, 2H), 7.24 - 7.19 (m, 2H), 4.88 (s, 2H), 3.93 - 3.85 (m, 1H), 3.78 - 3.74 (m, 2H), 3.58 - 3.53 (m, 2H), 3.07 - 3.01 (m, 2H), 3.01 - 2.95 (m, 2H)
HPLCMS (Method B): [*m/z*]: 404.2 $[M+H]^+$

2-{1-[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 239)



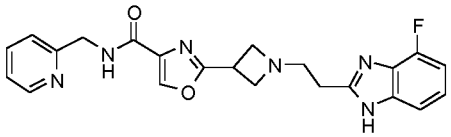
In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide; bis(trifluoroacetic acid) **(347)** (700 mg, 1.39 mmol), DBU (1.04 ml, 6.94 mmol) and N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (292 mg, 1.39 mmol) in MeCN (30 ml) gave a crude intermediate

which was further reacted with iron powder (173 mg, 3.1 mmol) in AcOH (5 ml) to afford the title compound (98 mg, 29%) as a pale pink solid after purification by flash column chromatography (eluting with a gradient of 0-8% MeOH / DCM).

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.38 (dt, J = 4.6, 1.1 Hz, 1H), 8.35 (s, 1H), 7.62 (ddd, J = 9.8, 8.4, 1.2 Hz, 1H), 7.41 (dt, J = 8.6, 4.5 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.18 (td, J = 8.1, 4.8 Hz, 1H), 6.95 (dd, J = 10.8, 8.0 Hz, 1H), 4.77 (d, J = 1.5 Hz, 2H), 3.94 - 3.86 (m, 1H), 3.78 (t, J = 7.9 Hz, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.08 - 3.03 (m, 2H), 3.02 - 2.97 (m, 2H)

HPLCMS (Method B): [*m/z*]: 439.2 $[M+H]^+$

2-{1-[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 258)

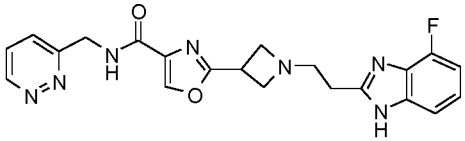


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-(pyridin-2-ylmethyl)-1,3-oxazole-4-carboxamide **(346)** (0.88 g, 3.21 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (0.80 g, 3.53 mmol) and DBU (580 µl, 3.86 mmol) in MeCN (30 ml) gave a crude intermediate which was further reacted with iron powder (0.57 g, 10.24 mmol) in AcOH (16 ml) to afford the title compound (0.59 g, 55%) as an off-white solid after purification by flash column chromatography (eluting with a gradient of 0-15% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.51 - 8.48 (m, 1H), 8.33 (s, 1H), 7.80 (td, *J* = 7.7, 1.8 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.16 (td, *J* = 8.1, 4.8 Hz, 1H), 6.92 (dd, *J* = 10.8, 8.1 Hz, 1H), 4.67 (s, 2H), 3.93 - 3.83 (m, 1H), 3.75 (t, *J* = 7.9 Hz, 2H), 3.54 (t, *J* = 7.5 Hz, 2H), 3.05 - 3.00 (m, 2H), 2.99 - 2.95 (m, 2H)

HPLCMS (Method C): [*m/z*]: 421.3 $[M+H]^+$

2-{1-[2-(4-Fluoro-1H-1,3-benzodiazol-2-yl)ethyl]azetidin-3-yl}-N-(pyridazin-3-ylmethyl)-1,3-oxazole-4-carboxamide (Example Compound No. 261)

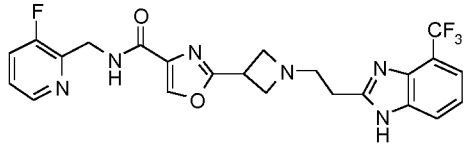


In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-(pyridazin-3-ylmethyl)-1,3-oxazole-4-carboxamide **(348)** (417 mg, 1.61 mmol), N-(3-fluoro-2-nitrophenyl)prop-2-enamide **(G)** (372 mg, 1.77 mmol) and DBU (264 µl, 1.77 mmol) in MeCN (50 ml) gave a crude intermediate which was further reacted with iron powder (261 mg, 4.67 mmol) in AcOH (10 ml) to afford the title compound (268 mg, 54%) as a white solid after purification by basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 9.12 (dd, J = 4.5, 2.1 Hz, 1H), 8.36 (s, 1H), 7.76 - 7.70 (m, 2H), 7.31 (d, J = 8.1 Hz, 1H), 7.18 (td, J = 8.1, 4.8 Hz, 1H), 6.97 - 6.91 (m, 1H), 4.88 (s, 2H), 3.89 (p, J = 7.3 Hz, 1H), 3.79 - 3.74 (m, 2H), 3.58 - 3.53 (m, 2H), 3.06 - 3.02 (m, 2H), 3.02 - 2.96 (m, 2H)

HPLCMS (Method B): [*m/z*]: 422.2 $[M+H]^+$

N-[(3-Fluoropyridin-2-yl)methyl]-2-(1-{2-[7-(trifluoromethyl)-1H-1,3-benzodiazol-2-yl]ethyl}azetidin-3-yl)-1,3-oxazole-4-carboxamide (Example Compound No. 273)



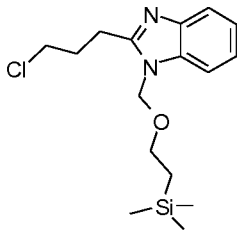
In a similar fashion to general procedure 8, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide **(347)** (393 mg, 1.42 mmol), N-[2-nitro-6-(trifluoromethyl)phenyl]prop-2-enamide **(K8)** (474 mg, 1.42 mmol, 78% purity) and DBU (0.23 ml, 1.56 mmol) in MeCN (18 ml) gave a crude intermediate which was further reacted with iron powder (280 mg, 5.01 mmol) in AcOH (8 ml) to afford the title compound (197 mg, 32%) as a light brown foam after purification by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.64 (s, 1H), 8.55 (s, 1H), 8.52 (t, J = 5.7 Hz, 1H), 8.39 - 8.35 (m, 1H), 7.76 (s, 1H), 7.71 - 7.65 (m, 1H), 7.48 - 7.43 (m, 1H), 7.43 - 7.37 (m, 1H), 7.30 - 7.26 (m, 1H), 4.66 - 4.58 (m, 2H), 3.81 (p, J = 7.4 Hz, 1H), 3.63 (t, J = 7.5 Hz, 2H), 3.35 (t, J = 7.2 Hz, 2H), 2.90 (s, 4H)

HPLCMS (Method D): [*m/z*]: 489.1 $[M+H]^+$

General Scheme 26 above:

2-(3-Chloropropyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole (349)

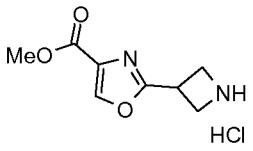


[2-(chloromethoxy)ethyl](trimethyl)silane (553 µl, 3.12 mmol) was added to a solution of 2-(3-chloropropyl)-1H-1,3-benzodiazole hydrochloride (555 mg, 2.4 mmol) and DIPEA (962 µl, 5.52 mmol) in THF (25 ml). The reaction mixture was stirred at room temperature for 18 h, then quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc (3 x 80 ml). The combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-50% EtOAc / heptane) afforded the title compound (571 mg, 73%) as a pale yellow oil.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 7.85 - 7.75 (m, 1H), 7.53 - 7.44 (m, 1H), 7.38 - 7.31 (m, 2H), 5.57 (s, 2H), 3.78 (t, J = 6.1 Hz, 2H), 3.60 (dd, J = 8.6, 7.7 Hz, 2H), 3.21 (t, J = 7.3 Hz, 2H), 2.59- 2.44 (m, 2H), 0.96 (dd, J = 8.6, 7.7 Hz, 2H), 0.00 (s, 9H)

HPLCMS (Method M): [*m/z*]: 325.50 $[M+H]^+$

Methyl 2-(azetidin-3-yl)-1,3-oxazole-4-carboxylate hydrochloride (350)

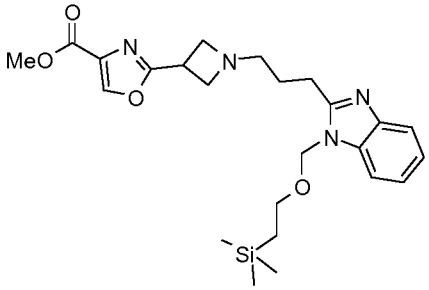


In a similar fashion to general procedure 4, methyl 2-{1-[(tert-butoxy)carbonyl]azetidin-3-yl}-1,3-oxazole-4-carboxylate **(341)** (634 mg, 2.25 mmol) and 12M HCl (0.89 ml) in MeOH (20 ml) at 60°C afforded the title compound (201 mg, 41%) as a white solid after trituration in DCM / Et_2O.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.91 (s, 1H), 4.36 - 4.15 (m, 5H), 3.83 (s, 3H)

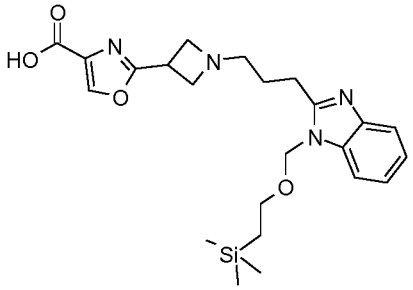
HPLCMS (Method M): [*m/z*]: 183.20 $[M+H]^+$

Methyl 2-{1-[3-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxylate (351)



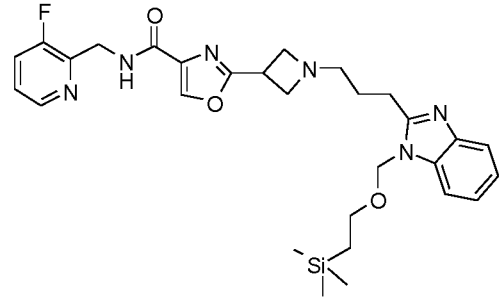
A suspension of methyl 2-(azetidin-3-yl)-1,3-oxazole-4-carboxylate hydrochloride **(350)** (300 mg, 1.37 mmol), 2-(3-chloropropyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazole **(349)** (758 mg, 2.33 mmol), DIPEA (837 µl, 4.8 mmol) and KI (228 mg, 1.37 mmol) in DMF (10 ml) was stirred at room temperature for 7 d. The reaction was quenched with saturated $NaHCO_3$ (aq) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were washed with brine (4 x 50 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 40-100% EtOAc / heptane followed by 2-40% MeOH / EtOAc) afforded the title compound (329 mg, 46%, 91% purity) as a yellow residue.
HPLCMS (Method M): [*m/z*]: 471.15 $[M+H]^+$

2-{1-[3-(1-{[2-(Trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid (352)



In a similar fashion to general procedure 5, 2-{1-[3-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxylate **(351)** (329 mg, 0.7 mmol) and LiOH (50 mg, 2.1 mmol) in THF (10 ml) and water (10 ml) afforded the title compound (363 mg, 91%, 80% purity) as a yellow residue. The compound was used in the next step without purification.
HPLCMS (Method M): [*m/z*]: 457.10 $[M+H]^+$

N-[(3-fluoropyridin-2-yl)methyl]-2-{1-[3-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxamide (353)

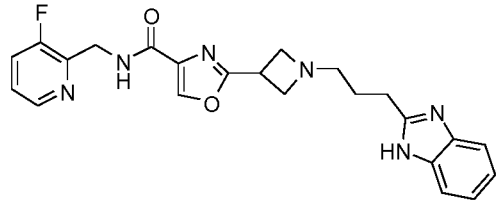


In a similar manner to general procedure 6, 2-{1-[3-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxylic acid **(352)** (363 mg, 0.64 mmol, 80% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (152 mg, 0.76 mmol), DIPEA (388 µl, 2.23 mmol)

and HATU (290 mg, 0.76 mmol) in DCM (20 ml) afforded the title compound (302 mg, 84%) as a pale yellow residue after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM).

HPLCMS (Method M): [*m/z*]: 565.15 $[M+H]^+$

2-{1-[3-(1H-1,3-Benzodiazol-2-yl)propyl]azetidin-3-yl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-4-carboxamide (Example Compound No. 233)



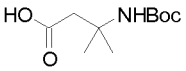
TFA (4 ml, 52.23 mmol) was added to a solution of N-[(3-fluoropyridin-2-yl)methyl]-2-{1-[3-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-1,3-benzodiazol-2-yl)propyl]azetidin-3-yl}-1,3-oxazole-4-carboxamide **(353)** (300 mg, 0.53 mmol) in DCM (4 ml). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water basified by the addition of 2M NaOH (aq). The mixture was then extracted with 4:1 $CHCl_3$ / IPA (4 x 50 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue was dissolved in a minimum volume of MeOH and loaded onto an SCX-2 cartridge (10 g). The cartridge was rinsed with DCM, followed by MeOH, and eluted with 7N NH_3 / MeOH. The basic eluent was evaporated under vacuum. Purification of the residue by basic prep-HPLC afforded the title compound (75 mg, 33%) as a white solid.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.37 (dt, *J* = 4.6, 1.1 Hz, 1H), 8.33 (s, 1H), 7.61 (ddd, *J* = 9.8, 8.4, 1.2 Hz, 1H), 7.50 (s, 2H), 7.41 (dt, *J* = 8.7, 4.4 Hz, 1H), 7.23 – 7.17 (m, 2H), 4.77 (d, *J* = 1.5 Hz, 2H), 3.93 – 3.84 (m, 1H), 3.75 (t, *J* = 8.0 Hz, 2H), 3.53 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.66 – 2.60 (m, 2H), 1.97 – 1.88 (m, 2H)

HPLCMS (Method B): [*m/z*]: 435.1 $[M+H]^+$

General Scheme 28 above:

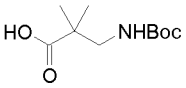
3-{[(Tert-butoxy)carbonyl]amino}-3-methylbutanoic acid (360)



1M KOH (15.19 ml) was added to a mixture of 3-amino-3-methylbutanoic acid (1.78 g, 15.19 mmol) and Boc_2O (3.48 g, 15.95 mmol) in 1,4-dioxane (30 ml) and stirred at room temperature for 40 h. The solvent was concentrated and diluted with water (60 ml). 1M LiOH was added until pH 13. The aqueous phase was extracted with Et_2O (3 x 30 ml), then the pH adjusted to 3 using 2M HCl and extracted with EtOAc (4 x 60 ml). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4), filtered and evaporated to give the title compound (2.13 g, 65%) as an off-white solid. Compound will be used in the next step without further purification.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.07 (s, 1H), 2.75 (s, 2H), 1.44 (s, 9H), 1.40 (s, 6H)

3-{[(Tert-butoxy)carbonyl]amino}-2,2-dimethylpropanoic acid (361)

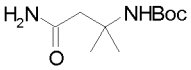


1M KOH (52.08 ml, 52.08 mmol) was added to a mixture of 3-amino-2,2-dimethylpropanoic acid hydrochloride (4 g, 26.04 mmol) and Boc_2O (5.97 g, 27.34 mmol) in 1,4-dioxane (80 ml) and stirred at room temperature for 20 h. The solvent was concentrated and diluted with water (50 ml). 1M LiOH was added

until pH 13. The aqueous phase was extracted with Et_2O (3 x 50 ml), then the pH adjusted to 3 using 2M HCl and extracted with EtOAc (4 x 50 ml). The combined organic layers were washed with brine (50 ml), dried (Na_2SO_4), filtered and evaporated to give the title compound (5.38 g, 95%) as a white solid. Compound will be used in the next step without further purification.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.01 (s, 1H), 3.29 - 3.18 (m, 2H), 1.45 (d, 9H), 1.23 (s, 6H)

Tert-butyl N-(1-carbamoyl-2-methylpropan-2-yl)carbamate (362)

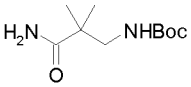


TEA (2.82 ml, 20.27 mmol) was added to an ice-cooled (0°C) solution of 3-{[(tert-butoxy)carbonyl]amino}-3-methylbutanoic acid **(360)** (2.59 g, 11.92 mmol) in THF (30 ml). The reaction mixture was stirred for 20 min before the addition of 2-methylpropyl carbonochloridate (2.78 ml, 17.88 mmol) dropwise at 0°C. The reaction was stirred for 1 h before the addition of 35% NH_3 (aqueous solution) (3.09 ml, 66.76 mmol) dropwise and the reaction warmed to room temperature and stirred for 18 h. Saturated $NaHCO_3$ (50 ml) was added and the aqueous layer extracted with DCM (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a pale yellow oil (4.11 g). Purification by flash column chromatography (eluting with a gradient of 0-10% MeOH-DCM) gave the title compound (1.7 g, 55%, 84% purity) as a clear oil which solidified on standing.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.85 (br s, 1H), 5.39 (br s, 1H), 4.89 (br s, 1H), 2.64 (s, 2H), 1.42 (s, 9H), 1.39 (s, 6H)

HPLCMS (Method A): [*m/z*]: 238.95 $[M+Na]^+$

Tert-butyl N-(2-carbamoyl-2,2-dimethylethyl)carbamate (363)

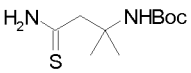


TEA (5.73 ml, 41.08 mmol) was added to an ice-cooled (0°C) solution of 3-{[(tert-butoxy)carbonyl]amino}-2,2-dimethylpropanoic acid **(361)** (5.25 g, 24.16 mmol) in THF (50 ml). The reaction was stirred for 20 min, before the addition of 2-methylpropyl carbonochloridate (4.7 ml, 36.3 mmol) dropwise at 0°C. The reaction was stirred for 1 h before the dropwise addition of 35% NH_3 (aqueous solution) (7.48 ml, 135.31 mmol). The reaction mixture was warmed to room temperature and stirred for 22 h. Saturated $NaHCO_3$ (100 ml) was added and the aqueous layer extracted with DCM (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white semi-solid (6.61 g). Purification by flash column chromatography (eluting with a gradient of 0-10% MeOH / DCM) gave the title compound (3.7 g, 71%) as a white solid.

1H-NMR ($CDCl_3$, 250 MHz): d[ppm]= 5.95 (s, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 3.25 (d, J = 6.6 Hz, 2H), 1.43 (s, 9H), 1.21 (s, 6H)

HPLCMS (Method A): [*m/z*]: 239.10 $[M+Na]^+$

Tert-butyl N-(1-carbamothioyl-2-methylpropan-2-yl)carbamate (364)

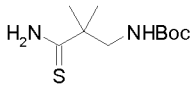


In a similar fashion to general procedure 11, Lawesson reagent (1.65 g, 4.08 mmol) and tert-butyl N-(1-carbamoyl-2-methylpropan-2-yl)carbamate **(362)** (1.7 g, 6.6 mmol, 84% purity) in DCM (50 ml) at room temperature for 19 h gave the title compound (0.914 g, 60%) as a yellow oil after purification by flash column chromatography (eluting with a gradient of 0-50% EtOAc / Heptane) which solidified on standing.

1H-NMR (MeOD, 250 MHz): d[ppm]= 2.91 (s, 2H), 1.43 (s, 9H), 1.38 (s, 6H)

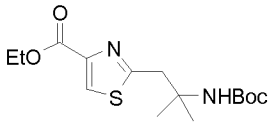
HPLCMS (Method A): [*m/z*]: 232.95 $[M+H]^+$

Tert-butyl N-(2-carbamothioyl-2,2-dimethylethyl)carbamate (365)



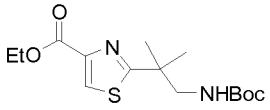
In a similar fashion to general procedure 11, Lawesson reagent (3.29 g, 8.14 mmol) and tert-butyl N-(2-carbamoyl-2,2-dimethylethyl)carbamate **(363)** (3.2 g, 14.8 mmol) in DCM (65 ml) at room temperature for 24 h gave the title compound (1.67 g, 49%) as a white solid after purification by flash column chromatography (eluting with a gradient of 0-50% EtOAc-Heptane).
1H-NMR (MeOD, 250 MHz): d[ppm]= 3.35 (s, 2H), 1.44 (s, 9H), 1.25 (s, 6H)
HPLCMS (Method A): [*m/z*]: 254.95 $[M+Na]^+$

Ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}-2-methylpropyl)-1,3-thiazole-4-carboxylate (366)



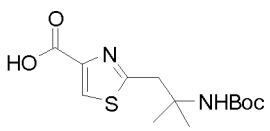
In a similar fashion to general procedure 1, tert-butyl N-(1-carbamothioyl-2-methylpropan-2-yl)carbamate **(364)** (0.91 g, 3.93 mmol), ethyl 3-bromo-2-oxopropanoate (0.64 ml, 4.33 mmol) and $CaCO_3$ (0.22 g, 2.16 mmol) in EtOH (10 ml) gave the title compound (0.285 g, 19%) as an orange oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane).
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.42 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.39 (s, 2H), 1.36 (s, 9H), 1.30 (d, J = 7.0 Hz, 3H), 1.20 (s, 6H)
HPLCMS (Method A): [*m/z*]: 329.00 $[M+H]^+$

Ethyl 2-(1-{[(tert-butoxy)carbonyl]amino}-2-methylpropan-2-yl)-1,3-thiazole-4-carboxylate (367)



In a similar fashion to general procedure 1, tert-butyl N-(2-carbamothioyl-2,2-dimethylethyl)carbamate **(365)** (1.67 g, 7.9 mmol), ethyl 3-bromo-2-oxopropanoate (1.2 ml, 7.9 mmol) and $CaCO_3$ (0.4 g, 3.95 mmol) in EtOH (20 ml) was stirred at room temperature for 72 h. The reaction was further treated with $MgSO_4$ (0.8 g) and $CaCO_3$ (0.4 g, 3.95 mmol) and heated at 80°C for 7 h. The reaction was cooled and the solvent evaporated to give a residue which was partitioned taken up in EtOAc (50 ml) and washed with saturated $NaHCO_3$ (7 ml). The aqueous layer was extracted with EtOAc (3 x 15 ml) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a brown oil (2.61 g). The oil was dissoloved in DCM (50 ml) and TEA (2.9 ml, 20.58 mmol) was added followed by dropwise addition of di-tert-butyl dicarbonate (3.74 g, 17.15 mmol) in DCM (20 ml). The reaction was stirred at room temperature for 22 h. The reaction mixture was diluted with DCM (10 ml) and the organic layer was washed with water (20 ml), brine (20 ml), dried ($MgSO_4$), filtered and evaporated to give a brown oil (4.82 g). Purification by flash column chromatography (eluting with 0-50% EtOAc-heptane) gave the title compound (1.4 g, 36%) as a yellow oil.
1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.06 (s, 1H), 5.19 (br s, 1H), 4.40 (q, J = 7.1 Hz, 2H), 3.50 (br s, 2H), 1.44 (s, 6H), 1.42 (s, 9H)
HPLCMS (Method A): [*m/z*]: 329.00 $[M+H]^+$

2-(2-{[(Tert-butoxy)carbonyl]amino}-2-methylpropyl)-1,3-thiazole-4-carboxylic acid (368)

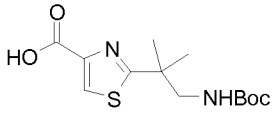


In a similar fashion to general procedure 5, ethyl 2-(2-{[(tert-butoxy)carbonyl]amino}-2-methylpropyl)-1,3-thiazole-4-carboxylate **(366)** (0.285 g, 0.867 mmol, 85% purity) and LiOH (88 mg, 3.67 mmol) in THF (4 ml) and H_2O (2 ml) at room temperature for 5 h gave the title compound (0.215 g, 66%, 68% purity) as a dark yellow oil. Compound was used in the next step without further purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.35 (s, 1H), 3.38 (s, 2H), 1.43 (s, 9H), 1.21 (s, 6H)

HPLCMS (Method A): [*m/z*]: 301.00 $[M+H]^+$

2-(1-{[(Tert-butoxy)carbonyl]amino}-2-methylpropan-2-yl)-1,3-thiazole-4-carboxylic acid (369)

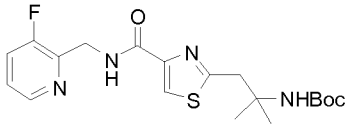


In a similar fashion to general procedure 5, ethyl 2-(1-{[(tert-butoxy)carbonyl]amino}-2-methylpropan-2-yl)-1,3-thiazole-4-carboxylate **(367)** (1.4 g, 4.12 mmol) and LiOH (0.49 g, 20.6 mmol) in THF (20 ml) and water (10 ml) at room temperature for 3 h gave the title compound (1.5 g, 98%, 83% purity) as a yellow oil which solidified on standing. To be used without purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.32 (s, 1H), 6.98 - 6.88 (m, 1H), 3.18 (d, J = 6.5 Hz, 2H), 1.34 (s, 9H), 1.32 (s, 6H)

HPLCMS (Method A): [*m/z*]: 301.05 $[M+H]^+$

Tert-butyl N-[1-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-2-methylpropan-2-yl]carbamate (370)

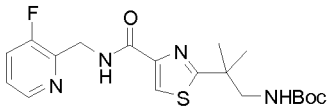


In a similar fashion to general procedure 6, 2-(2-{[(tert-butoxy)carbonyl]amino}-2-methylpropyl)-1,3-thiazole-4-carboxylic acid **(368)** (0.28 g, 0.63 mmol, 68% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.20 g, 1.01 mmol), HATU (0.4 g, 1.04 mmol) and DIPEA (0.4 ml, 2.29 mmol) in DMF (6 ml) were stirred at room temperature for 2 h, gave the title compound (0.33 g, 84%, 72% purity) as a dark yellow oil after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane). To be used without further purification.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.58 (t, J = 5.6 Hz, 1H), 8.39 (dt, J = 4.7, 1.5 Hz, 1H), 8.19 (s, 1H), 7.78 - 7.63 (m, 1H), 7.47 - 7.35 (m, 1H), 6.68 (s, 1H), 4.67 (dd, J = 5.6, 1.3 Hz, 2H), 3.41 (s, 2H), 1.41 (s, 9H), 1.23 (s, 6H)

HPLCMS (Method A): [*m/z*]: 409.05 $[M+H]^+$

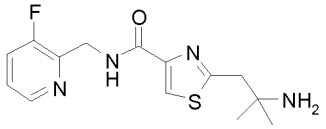
Tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-2-methylpropyl]carbamate (371)



In a similar fashion to general procedure 6, 2-(1-{[(tert-butoxy)carbonyl]amino}-2-methylpropan-2-yl)-1,3-thiazole-4-carboxylic acid **(369)** (0.64 g, 1.73 mmol, 83% purity), (3-fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** (0.41 g, 2.08 mmol), HATU (0.79 g, 2.08 mmol) and DIPEA (0.99 ml, 5.71 mmol) in DCM (8 ml) at room temperature for 17 h gave the title compound (1.78 g, 90% purity) after purification by flash column chromatography (eluting with a gradient of 0-100% EtOAc / heptane) as a yellow oil which solidified on standing.

1H-NMR (DMSO-d6, 250 MHz): d[ppm]= 8.71 (t, J = 5.8 Hz, 1H), 8.43 - 8.33 (m, 1H), 8.15 (s, 1H), 7.76 - 7.65 (m, 1H), 7.47 - 7.34 (m, 1H), 6.97 (t, J = 6.3 Hz, 1H), 4.67 (dd, J = 5.8, 1.5 Hz, 2H), 3.25 (d, J = 6.5 Hz, 2H), 1.34 (s, 6H), 1.34 (s, 9H)
HPLCMS (Method A): [*m/z*]: 409.45 $[M+H]^+$

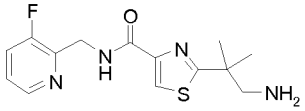
2-(2-Amino-2-methylpropyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (372)



2HCl

In a similar fashion to general procedure 2, tert-butyl N-[1-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-2-methylpropan-2-yl]carbamate **(370)** (0.33 g, 0.58 mmol, 72% purity) and 12M HCl (0.73 ml, 8.78 mmol) in MeOH (5 ml) at 50°C for 2 h gave the title compound (0.26 g, 90%, 76% purity) as a beige residue which was used in the next step without purification.
1H-NMR (MeOD, 250 MHz): d[ppm]=8.53 (dd, J = 5.3, 1.0 Hz, 1H), 8.24 (s, 1H), 8.16 - 8.06 (m, 1H), 7.82 - 7.73 (m, 1H), 4.91 (d, J = 1.4 Hz, 2H), 3.42 (s, 2H), 1.46 (s, 6H)
HPLCMS (Method A): [*m/z*]: 308.95 as the freebase $[M+H]^+$

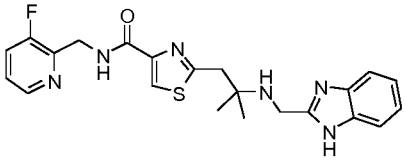
2-(1-Amino-2-methylpropan-2-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride (373)



2HCl

In a similar fashion to general procedure 2, tert-butyl N-[2-(4-{[(3-fluoropyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)-2-methylpropyl]carbamate **(371)** (1.78 g, 3.93 mmol, 90% purity) and 12M HCl (6.61 ml, 79.3 mmol) in MeOH (30 ml) at room temperature for 70 h gave the title compound (1.54 g, 98%) as a brown foam. To be used without purification.
1H-NMR (MeOD, 250 MHz): d[ppm]= 8.49 - 8.44 (m, 1H), 8.24 (s, 1H), 7.98 - 7.88 (m, 1H), 7.68 - 7.59 (m, 1H), 4.88 (d, J = 1.5 Hz, 2H), 3.37 (s, 2H), 1.58 (s, 6H)
HPLCMS (Method A): [*m/z*]: 309.00 as the freebase $[M+H]^+$

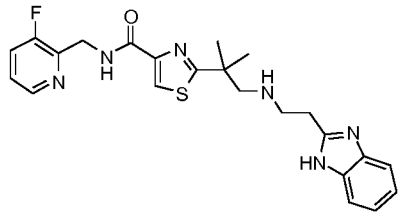
2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]-2-methylpropyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 231)



In a similar fashion to general procedure 3, 2-(2-amino-2-methylpropyl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(372)** (0.26 g, 0.52 mmol, 77% purity) 1H-1,3-benzodiazole-2-carbaldehyde (0.106 g, 0.73 mmol), DIPEA (0.36 ml, 2.09 mmol) in MeOH (5 ml) at 50°C for 3.5 h, followed by the addition of $NaBH_4$ (35 mg, 0.93 mmol) at 0°C, gave the title compound (0.054 g, 24%) as a cream solid after purification by kp-NH flash column chromatography (eluting with a gradient of 0-6% MeOH / DCM) followed by flash column chromatography (eluting with a gradient of 0-20% MeOH / DCM).
1H-NMR (MeOD, 500 MHz): d[ppm]=8.14 - 8.12 (m, 1H), 8.11 (s, 1H), 7.52 - 7.46 (m, 1H), 7.46 - 7.41 (m, 2H), 7.27 - 7.22 (m, 1H), 7.17 - 7.12 (m, 2H), 4.70 (d, J = 1.5 Hz, 2H), 4.21 (s, 2H), 3.27 (s, 2H), 1.25 (s, 6H)

HPLCMS (Method C): [*m/z*]: 439.1 $[M+H]^+$

2-(1-{[2-(1H-1,3-benzodiazol-2-yl)ethyl]amino}-2-methylpropan-2-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (Example Compound No. 242)



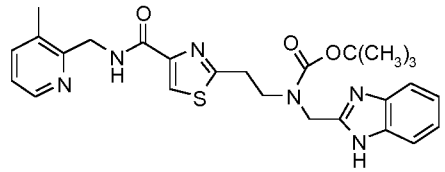
In a similar fashion to general procedure 8, 2-(1-amino-2-methylpropan-2-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide dihydrochloride **(373)** (1.54 g, 3.85 mmol), N-(2-nitrophenyl)prop-2-enamide **(D)** (0.81 g, 4.24 mmol) and DBU (1.73 ml, 11.56 mmol) in MeCN (35 ml) at room temperature for 18 h gave a mixture of mono : bis-alkylated adducts (3.7:1) (2.23 g) as an orange oil. This was further reacted with iron powder (0.86 g) in AcOH (10 ml) at 75°C for 0.5 h to give the title compound (0.29 g, 17%) as an off-white solid after purification by flash column chromatography (eluting with a gradient of 0-40% MeOH / DCM) followed by kp-NH column chromatography (eluting with a gradient of 0-5% MeOH / DCM) and basic prep-HPLC.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.30 - 8.25 (m, 1H), 7.97 (s, 1H), 7.57 - 7.52 (m, 1H), 7.43 - 7.35 (m, 2H), 7.34 - 7.29 (m, 1H), 7.18 - 7.13 (m, 2H), 4.65 (d, J = 1.5 Hz, 2H), 3.09 - 3.05 (m, 2H), 3.05 - 3.01 (m, 2H), 2.98 (s, 2H), 1.46 (s, 6H)

HPLCMS (Method C): [*m/z*]: 453.1 $[M+H]^+$

General Scheme 1 above:

N-(1H-1,3-Benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate (441)

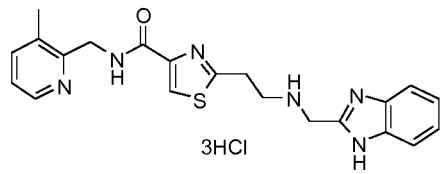


In a similar fashion to general procedure 6, 2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)[(tert-butoxy)carbonyl]amino]ethyl}-1,3-thiazole-4-carboxylic acid **(8)** (2.75 g, 6.49 mmol), 1-(3-methylpyridin-2-yl)methanamine (1.19 g, 9.74 mmol), DIPEA (3.39 ml, 19.47 mmol) and HATU (4.94 g, 12.98 mmol) in DMF (50 ml) for 16 h, gave the title compound (1.7 g, 51%) as an yellow foam after purification by flash column chromatography (Kp-NH, eluting with a gradient of 20-100% EtOAc / heptane) followed by azeotroping with heptane.

1H-NMR (MeOD, 250 MHz): d[ppm]= 8.32 (d, J = 4.4 Hz, 1H), 8.09 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.53 (s, 2H), 7.30 - 7.14 (m, 3H), 4.74 (s, 2H), 4.69 (s, 2H), 3.86 (s, 2H), 3.34 (s, 3H), 2.40 (s, 3H), 1.40 (s, 10H)

HPLCMS (Method C): [*m/z*]: 507.1 $[M+H]^+$

2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-methylpyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide trihydrochloride (Example Compound No. 55)



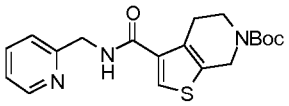
In a similar fashion to general procedure 2, tert-butyl N-(1H-1,3-benzodiazol-2-ylmethyl)-N-[2-(4-{[(3-methylpyridin-2-yl)methyl]carbamoyl}-1,3-thiazol-2-yl)ethyl]carbamate **(441)** (1.7 g, 3.36 mmol) and 4M HCl / dioxane (8.4 ml) in dioxane (30 ml) at room temperature for 16 h gave the title compound (1.09 g, 63%) as a white solid after trituration from Et_2O (2 x 30 ml), DCM (2 x 20 ml) and Et_2O (2 x 30 ml) followed by recrystalisation from DCM / MeOH and Heptane.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 10.29 (s, 1H), 9.56 (t, J = 5.6 Hz, 1H), 8.64 - 8.57 (m, 1H), 8.37 (d, J = 7.7 Hz, 1H), 8.29 (s, 1H), 7.85 (dd, J = 7.8, 5.8 Hz, 1H), 7.73 (dt, J= 6.6, 3.3 Hz, 2H), 7.41 (dt, J = 6.1, 3.3 Hz, 2H), 4.85 (d, J = 5.7 Hz, 3H), 4.74 (s, 2H), 3.64 (dt, J = 35.5, 7.0 Hz, 5H), 2.50 (s, 3H)

HPLCMS (Method C): [*m/z*]: 407.05 $[M+H]^+$

General Scheme 41 above:

Tert-butyl 3-[(pyridin-2-ylmethyl)carbamoyl]-4H,5H,6H,7H-thieno[2,3-c]pyridine-6-carboxylate (449)

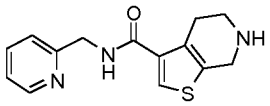


In a similar fashion to general procedure 6, 6-(tert-butoxycarbonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid (220 mg, 0.77 mmol), 1-(pyridin-2-yl)methanamine (88 µl, 0.85 mmol), DIPEA (407 µl, 2.33 mmol) and HATU (443 mg, 1.17 mmol) in DCM (12 ml) at room temperature for 1 h gave the title compound (466 mg) as a yellow oil after purification by flash column chromatography (eluting with a gradient 50-100% EtOAc / heptane).

1H-NMR ($CDCl_3$, 500 MHz): d[ppm]= 8.55 (d, J = 4.8 Hz, 1H), 7.68 (td, J = 7.7, 1.8 Hz, 1H), 7.64 (s, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.2, 5.2 Hz, 1H), 4.70 (d, J = 4.8 Hz, 2H), 4.62 (s, 2H), 3.76- 3.61 (m, 2H), 2.99 (s, 2H), 1.48 (s, 9H), 1.44 (d, J = 6.6 Hz, 1H)

HPLCMS (Method E): [*m/z*]: 374.05 $[M+H]^+$

N-(pyridin-2-ylmethyl)-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide (450)

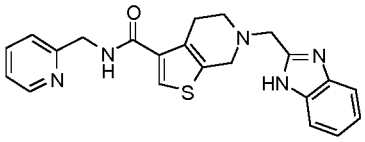


In a similar fashion to general procedure 2, tert-butyl 3-[(pyridin-2-ylmethyl)carbamoyl]-4H,5H,6H,7H-thieno[2,3-c]pyridine-6-carboxylate **(449)** (466 mg, 1.09 mmol) and TFA (940 µl) in DCM (5 ml) at room temperature for 16 h gave the title compound (130 mg, 44%) as an yellow oil. The compound was used in the nnext step without purification.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.49 (d, J =4.3 Hz, 1H), 7.92 (s, 1H), 7.82 (td, J = 7.7, 1.8 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.37 - 7.27 (m, 1H), 4.59 (s, 2H), 4.16 (s, 2H), 3.21 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H)

HPLCMS (Method E): [*m/z*]: 273.95 $[M+H]^+$

6-(1H-1,3-Benzodiazol-2-ylmethyl)-N-(pyridin-2-ylmethyl)-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide (Example Compound No. 48)



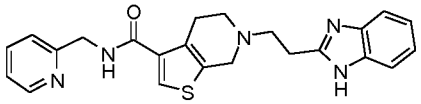
In a similar fashion to general procedure 7, N-(pyridin-2-ylmethyl)-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide **(450)** (65 mg, 0.24 mmol), K_2CO_3 (49 mg, 0.36 mmol) and 2-(chloromethyl)-1H-benzimidazole (44 mg, 0.26 mmol) in acetone (3 ml) at room temperature for 72 h, gave the title compound

(25 mg, 26%) as a pale yellow solid after purification flash column chromatography (kp-NH, eluting with a gradient of 0-10% MeOH / DCM) followed by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.36 (s, 1H), 8.78 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 4.7 Hz, 1H), 7.95 (s, 1H), 7.76 (td, J = 7.7, 1.7 Hz, 1H), 7.49 (s, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.29- 7.23 (m, 1H), 7.14 (dd, J = 5.9, 3.1 Hz, 2H), 4.49 (d, J = 6.0 Hz, 2H), 3.93 (s, 2H), 3.73 (s, 2H), 2.89 (d, J = 5.5 Hz, 2H), 2.79 (t, J = 5.7 Hz, 2H)

HPLCMS (Method D): [*m/z*]: 404.2 $[M+H]^+$

6-[2-(1H-1,3-Benzodiazol-2-yl)ethyl]-N-(pyridin-2-ylmethyl)-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide (Example Compound No. 49)



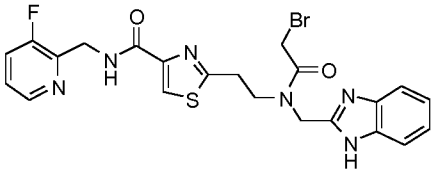
In a similar fashion to general procedure 7, N-(pyridin-2-ylmethyl)-4H,5H,6H,7H-thieno[2,3-c]pyridine-3-carboxamide **(450)** (65 mg, 0.24 mmol), K_2CO_3 (49 mg, 0.36 mmol) and 2-(2-chloroethyl)-1H-benzimidazole (47 mg, 0.26 mmol) in acetone (3 ml) at room temperature for 24 h, followed by the addition of DMF (5 ml), NaI (39 mg, 0.26 mmol), DIPEA (0.16 ml, 0.95 mmol) and 2-(2-chloroethyl)-1H-benzimidazole (94 mg, 0.52 mmol) at room temperature for 72 h, gave the title compound (9 mg, 9%) as an orange solid after purification by basic prep-HPLC.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 12.17 (s, 1H), 8.75 (t, J = 6.0 Hz, 1H), 8.50 (d, J = 4.2 Hz, 1H), 7.94 (s, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.46 (s, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.10 (dd, J = 6.0, 3.1 Hz, 2H), 4.48 (d, J = 6.0 Hz, 2H), 3.71 (s, 2H), 3.05 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.82 (d, J = 5.3 Hz, 2H), 2.75 (t, J = 5.7 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 418.2 $[M+H]^+$

General Scheme 42 above:

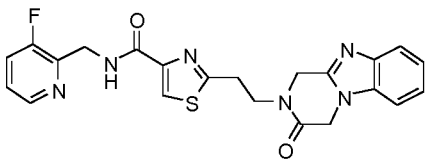
2-{2-[N-(1H-1,3-benzodiazol-2-ylmethyl)-2-bromoacetamido]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (451)



2-{2-[(1H-1,3-benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide (**Example Compound No. 40**) (150 mg, 0.37 mmol) and TEA (127 µl, 0.91 mmol) were dissolved in DCM (10 ml) and bromoacetyl chloride (61 µl, 0.73 mmol) was added dropwise. The mixture was stirred at room temperature for 15 mins, then quenched with saturated $NaHCO_3$ (aq) (20 ml) and extracted with DCM (3 x 30 ml) and 4:1 chloroform / IPA (30ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by flash column chromatography (eluting with a gradient of 0-5% MeOH / DCM) afforded the title compound (224 mg, 82% purity) as a brown residue. Compound was used in the next step without further purification.

HPLCMS (Method M): [*m/z*]: 530.85 / 532.85 $[M+H]^+$

N-[(3-fluoropyridin-2-yl)methyl]-2-(2-{12-oxo-1,8,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,8-tetraen-11-yl}ethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 275)

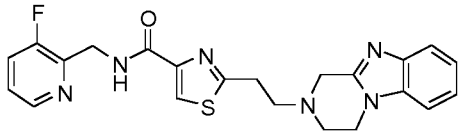


2-{2-[N-(1H-1,3-benzodiazol-2-ylmethyl)-2-bromoacetamido]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(451)** (220 mg, 0.41 mmol, 82% purity) was dissolved in THF (10 ml) and NaH (60%, 50 mg, 1.24 mmol) was added. The mixture was stirred at room temperature for 10 mins. The reaction was quenched with saturated $NaHCO_3$ (aq) (20 ml) and extracted with DCM (3 x 20 ml) and 4:1 chloroform / IPA (20 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Purification by basic prep-HPLC afforded the title compound (15 mg, 8%) as an off-white solid.

1H-NMR (DMSO-d6, 500 MHz): d[ppm]= 8.65 (t, J = 5.6 Hz, 1H), 8.36 - 8.32 (m, 1H), 8.18 (s, 1H), 7.71 - 7.64 (m, 1H), 7.61 (dt, J = 5.4, 3.4 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.40 - 7.34 (m, 1H), 7.26 - 7.21 (m, 2H), 4.91 (s, 2H), 4.88 (s, 2H), 4.63 - 4.57 (m, 2H), 3.93 (t, J = 7.2 Hz, 2H), 3.42 (t, J = 7.2 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 451.2 $[M+H]^+$

N-[(3-fluoropyridin-2-yl)methyl]-2-(2-{1,8,11-triazatricyclo[7.4.0.0^{2,7}]trideca-2(7),3,5,8-tetraen-11-yl}ethyl)-1,3-thiazole-4-carboxamide (Example Compound No. 276)

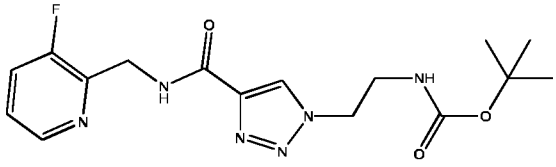


2-{2-[(1H-1,3-Benzodiazol-2-ylmethyl)amino]ethyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3-thiazole-4-carboxamide **(Example Compound No. 40)** (150 mg, 0.37 mmol) and TEA (509 µl, 3.65 mmol) were combined in DMF (4 ml) and 1,2-dibromoethane (315 µl, 3.65 mmol) was added. The mixture was heated at 100°C for 40 mins, then cooled to room temperature and quenched with saturated $NaHCO_3$ (aq). The mixture was extracted with DCM (3 x 50 ml) and the combined organic extracts were washed with aqueous LiCl (2M, 50 ml), dried (Na_2SO_4) and evaporated *in vacuo*. Purification by basic prep-HPLC followed by flash column chromatography (eluting with a gradient 0-4% MeOH / DCM) afforded the title compound (45 mg, 28%) as a pale yellow solid.

1H-NMR (MeOD, 500 MHz): d[ppm]= 8.37 (dt, J = 4.7, 1.2 Hz, 1H), 8.09 (s, 1H), 7.64 - 7.57 (m, 2H), 7.51 - 7.46 (m, 1H), 7.42 - 7.37 (m, 1H), 7.32 - 7.26 (m, 2H), 4.80 (d, J = 1.6 Hz, 2H), 4.23 (t, J = 5.5 Hz, 2H), 4.04 (s, 2H), 3.41 (t, J = 6.8 Hz, 2H), 3.25 - 3.20 (m, 2H), 3.16 (t, J = 6.8 Hz, 2H)

HPLCMS (Method B): [*m/z*]: 437.1 $[M+H]^+$

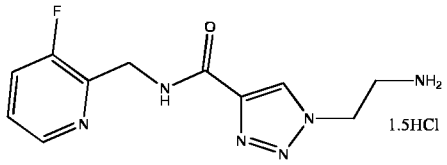
tert-butyl (2-(4-(((3-fluoropyridin-2-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)ethyl)carbamate (452)



1-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid **(commercial available)** (2.0 g, 7.8 mmol) in 50ml DCM was cooled to -5°C and N-methylmorpholine (0.94 ml, 8.6 mmol) and

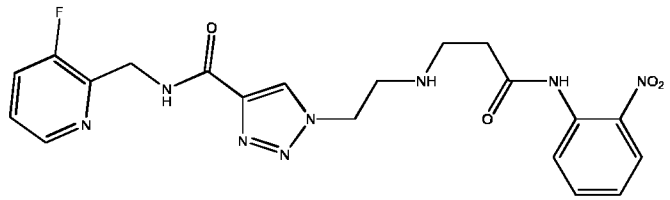
ethylchlorofomate were added to the mixture. During the addition temperature was kept below 0°C and after addition the mixture was stirred at 0°C for one hour. A second portion of N-methylmorpholine (2.7 ml, 24.2 mmol) and (3-Fluoropyridin-2-yl)methanamine dihydrochloride **(A2)** were added. The reaction was allowed to warm to room temperature and stirred overnight. 50ml of water were added to the reaction and extracted with DCM. The organic phase was dried (Na2SO4), filtered and concentrated in vacuo to the crude product which was purified by flash column chromatographyto give the title compound (2.1 g, 74%).
1H-NMR (DMSO, 400 MHz): d[ppm]= 8.82 (t, 1H), 8.50 (s, 1H), 8.38 (d, 1H), 7.70 (m, 1H), 7.40 (m, 1H), 7.01 (s, 1H), 4.65 (d, 2H), 4.46 (m, 2H), 3.39 (m, 2H), 1.40 - 1.24 (m, 9H)

1-(2-aminoethyl)-N-((3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide hydrochloride (453)



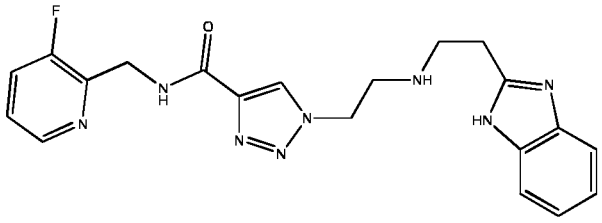
16ml conc. HCl was added to a solution of tert-butyl (2-(4-(((3-fluoropyridin-2-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)ethyl)carbamate **(452)** (2.00 g, 5.49mmol) in 100ml methanol and stirred at room temperature for 2h. The mixture was evaporated in vacuo to afford the title compound (1.74 g, 99%) as a white solid.
1H-NMR (DMSO, 400 MHz): d[ppm]= 8.99 (t, 1H), 8.73 (s, 1H), 8.51 (s, 3H), 8.45 (d, 1H), 7.87 (m, 1H), 7.53 (m, 1H), 4.78 (m, 2H), 4.71 (d, 2H), 3.37 (m, 2H)

N-((3-fluoropyridin-2-yl)methyl)-1-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxamide (454)



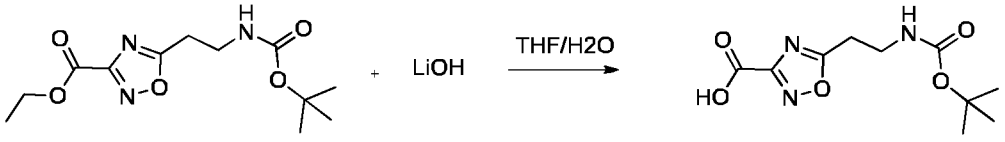
1-(2-aminoethyl)-N-((3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide hydrochloride **(453)** (4.46 g, 13.2mmol) and DBU (10.1 g, 66.1 mmol) were suspended in 120ml acetonitrile.N-(2-Nitrophenyl)prop-2-enamide **(D)** (2.54 g, 13.2 mmol) in 10ml acetonitrile was added dropwise to the reaction mixture within 1h and stirred at room temperature overnight. The reaction was evaporated to dryness and redissolved in 100ml DCM. 50ml water were added and extracted with DCM. The organic phases was dried (Na_2SO_4), filtered and concentrated in vacuo to the crude product which was purified by flash column chromatography to give the title compound (2.1 g, 35%).
1H-NMR (DMSO, 400 MHz): d[ppm]= 10.55 (s, 1H), 8.78 (t, 1H), 8.57 (s, 1H), 8.38 (d, 1H), 7.93 (m, 1H), 7.76-7.62 (m, 3H), 7.40 (m, 1H), 7.32 (m, 1H), 4.65 (d, 2H), 4.50 (m, 2H), 3.02 (t, 2H), 2.81 (t, 2H), 2.51 (m, 2H)

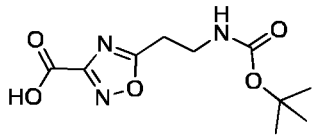
1-(2-((2-(1H-benzo[d]imidazol-2-yl)ethyl)amino)ethyl)-N-((3-fluoropyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (Example Compound No. 277)



N-((3-fluoropyridin-2-yl)methyl)-1-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxamide **(454)** (900 mg, 1.97 mmol) and iron powder (335 mg, 5.92 mmol) were suspended in 10ml acetic acid and stirred under nitrogen at 80°C for 2h. The reaction mixture was evaporated to dryness and the residue treated with 60ml chloroform/isopropanpol (1:4). The pH was adjusted to 11 by addition of 1N NaOH and the phases were separated. After extraction of the aqueous phase with chloroform the combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo to the crude product which was purified by flash column chromatography to give the title compound (430 mg, 53%).
1H-NMR (d4-methanol, 400 MHz): d[ppm]= 8.40 (s, 1H), 8.38 (m, 1H), 7.63-7.58 (m, 1H), 7.50-7.45 (m, 2H), 7.41-7.36 (m, 1H), 7.18-12 (m, 2H), 4.78 (d, 2H), 4.56 (m, 2H), 3.16 (t, 2H), 3.10-3.0 (m, 4H)

5-(2-((tert-butoxycarbonyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxylic acid

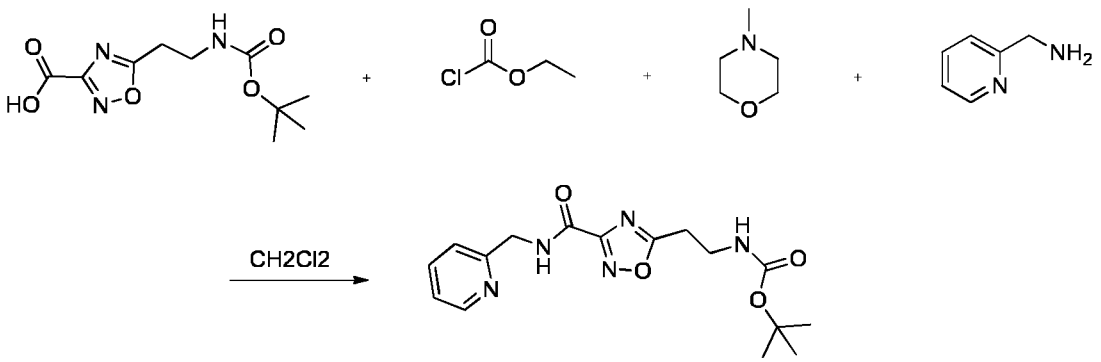


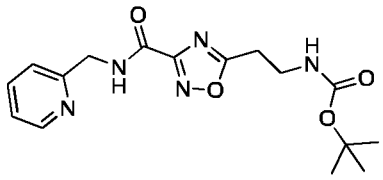


5-(2-((*tert*-butoxycarbonyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxylic acid

To a round bottomed flask was added ethyl 5-(2-((tert-butoxycarbonyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxylate (4 g, 14.06 mmol), THF (80 ml) and water (20 ml) with stirring at room temperature. Lithium hydroxide (1 g, 41.75 mmol) was then added to the solution and the reaction mixture stirred at room temperature for 2 hr. The reaction mixture was then acidified to pH2.8 (using aq. 32% HCl), extracted with ethyl acetate (3 x 80 ml), dried (Na2SO4), filtered and evaporated to afford the title compound as a brown oil (2.95 g), which was used without purification.

tert-butyl (2-(3-((pyridin-2-ylmethyl)carbamoyl)-1,3,4-oxadiazol-5-yl)ethyl)carbamate



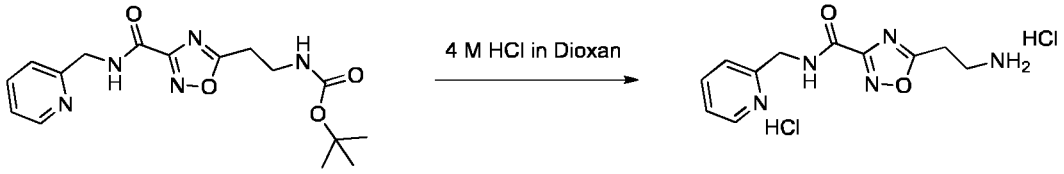


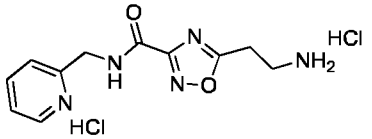
tert-butyl (2-(3-((pyridin-2-ylmethyl)carbamoyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate

To a solution of 5-(2-((tert-butoxycarbonyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxylic acid (2.95 g, 11.47 mmol) in 100 ml dichloromethane at 0°C was added 4-methylmorpholine (2.8 ml, 25.47 mmol) and ethylchloroformate (1 ml, 10.46 mmol). After 60 min stirring at 0°C, 2-picolylamine (1.7 ml, 16.82) was added and the reaction mixture was stirred 2 h at RT. The reaction mixture washed with water (100 ml), dried (Na2SO4), filtered and evaporated. The crude product was purified using a 100 g SNAP Ultra column (eluted with a gradient of 0 to 100% ethylacetate in petrolether) to give a pale brown oil (2.29 g, 6.6 mmol, 58%).

^{1}H NMR (400 MHz, CDCl3): δ 8.5 (s, 1H), 8.1 (m, 2H), 7.7 (m, 1H), 7.3 (m, 2H), 6.8 (s, 1H), 4.6 (s, 2H), 3.4 (m, 2H), 2.5 (m, 2H), 1.4 (s, 9H).

5-(2-aminoethyl)-N-(pyridine-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride

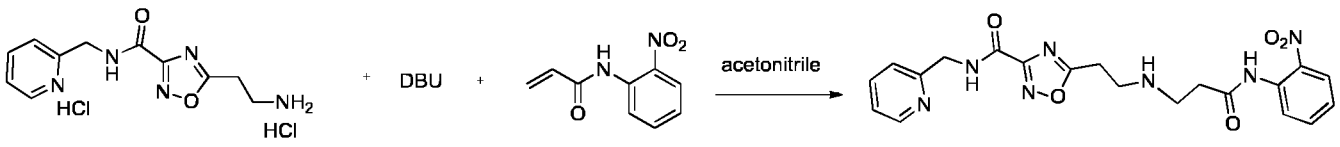


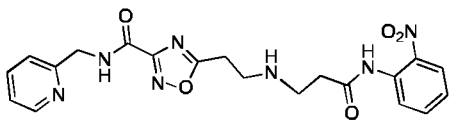


5-(2-aminoethyl)-*N*-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride

To a solution of tert-butyl (2-(3-((pyridin-2-ylmethyl)carbamoyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate (2.41 g, 6.94 mmol) in dioxane (25 ml) and was added 4 M HCl in dioxane (25 ml). After stirring at RT for 2 hours the reaction mixture was evaporated to afford the title compound as a brown oil (2.83 g), which was used without purification.

5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-N-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide

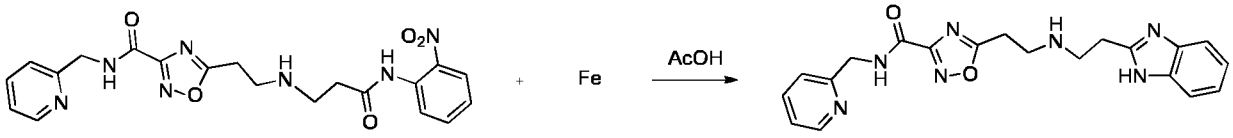


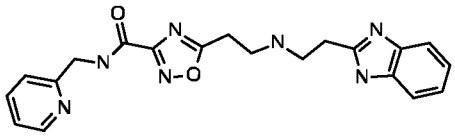


5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-*N*-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide

In a round bottomed flask, 5-(2-aminoethyl)-N-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride (3.48 g, 9.76 mmol) was suspended in acetonitrile (100 ml) under nitrogen and 1,8-diazabicycloundec-7-ene (DBU) (7.1 ml, 47.48 mmol, 4.9 eq) was added dropwise followed by N-(2-nitrophenyl)prop-2-enamide (1.9 g, 9.89). The reaction was stirred at room temperature overnight, then evaporated, diluted with 100 ml dichloromethane, washed with 50 ml water, dried (Na_2SO_4), filtered and evaporated. The crude product was purified using a 100 g SNAP Ultra column (eluted each time with a gradient of 0 to 25% methanol in dichloromethane) to give a pale brown oil (0.74 g, 1.7 mmol, 17%).
^{1}H NMR (400 MHz, CDCl3): δ 8.5 (s, 1H), 8.1 (m, 2H), 7.8 (m, 1H), 7.6 (m, 1H), 7.3 (m, 3H), 4.4 (s, 2H), 3.1 (m, 4H), 2.7 (m, 2H), 2.5 (m, 2H).

5-(2-((2-(1 H-benzo[d]imidazol-2-yl)ethyl)amino)ethyl)- N-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide (Example Compound No. 278)

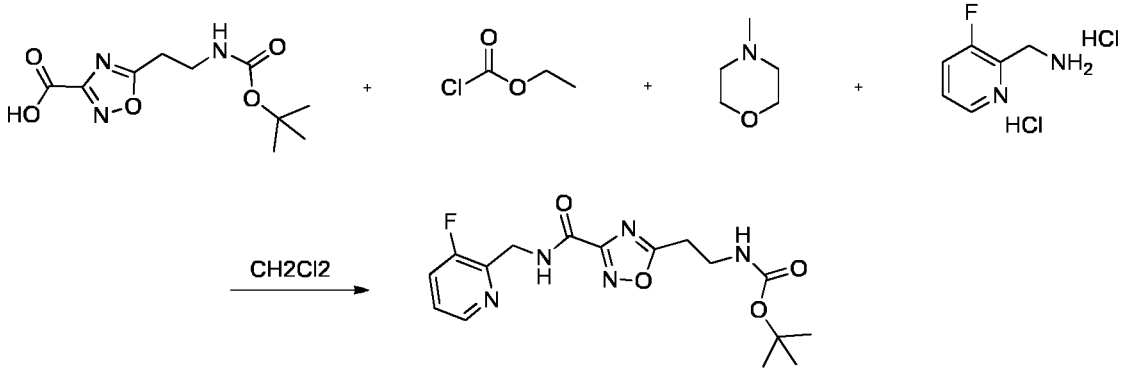


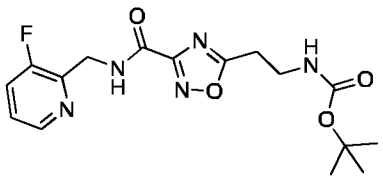


5-(2-((2-(1 *H*-benzo[*d*]imidazol-2-yl)ethyl)amino)ethyl)- *N*-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide

5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-N-(pyridin-2-ylmethyl)-1,2,4-oxadiazole-3-carboxamide (0.74 g, 1.68 mmol) was dissolved in acetic acid (5 ml) under nitrogen and iron powder (0.3 g) was added. The reaction mixture was heated to 80°C for 3 hours. After cooling at RT, toluene (50 ml) was added and the mixture evaporated. A mixture of chloroform : IPA (4:1, 40 ml) was added, the reaction mixture cooled to 0 °C, basified using 6M NaOH solution to pH 10-12, filtered, dried (Na_2SO_4), filtered and evaporated. The crude product was purified using a 50 g SNAP KP-Sil column (eluted with a gradient of 0 to 25% methanol in dichloromethane) to give a pale brown oil (0.31 g, 0.8 mmol, 47%).
^{1}H NMR (400 MHz, MeOD): δ 8.4 (s, 1H), 7.9 (s, 1H), 7.7 (m, 2H), 7.3 (m, 1H), 7.2 (m, 1H), 7.1 (m, 2H), 4.4 (s, 2H), 3.1 (m, 4H), 2.9 (m, 2H), 2.5 (m, 2H).

tert-butyl (2-(3-(((3-fluoropyridin-2-yl)methyl)carbamoyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate



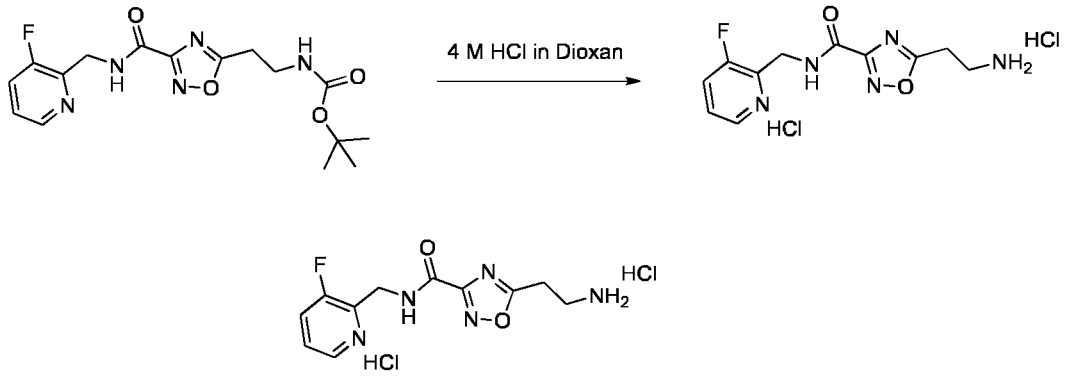


tert-butyl (2-(3-(((3-fluoropyridin-2-yl)methyl)carbamoyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate

To a solution of 5-(2-((tert-butoxycarbonyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxylic acid (8.16 g, 31.72 mmol) in 400 ml dichloromethane at -5°C was added 4-methylmorpholine (20 ml, 182 mmol) and ethylchloroformate (2.7 ml, 28.24 mmol). After 60 min stirring at -5°C, (3-fluoropyridin-2-yl)methanamine dihydrochloride (9.50, 47.73) was added and the reaction mixture was stirred 2 h at RT. The reaction mixture washed with water (400 ml), dried (Na2SO4), filtered and evaporated. The crude product was purified using a 100 g SNAP Ultra column (eluted with a gradient of 0 to 100% ethylacetate in petrolether) to give a pale brown oil (4.15 g, 11.4 mmol, 36%).

^{1}H NMR (400 MHz, CDCl3): δ 8.3 (s, 1H), 7.4 (m, 1H), 7.3 (m, 1H), 6.9 (s, 1H), 4.6 (s, 2H), 3.4 (m, 2H), 2.5 (m, 2H), 1.4 (s, 9H).

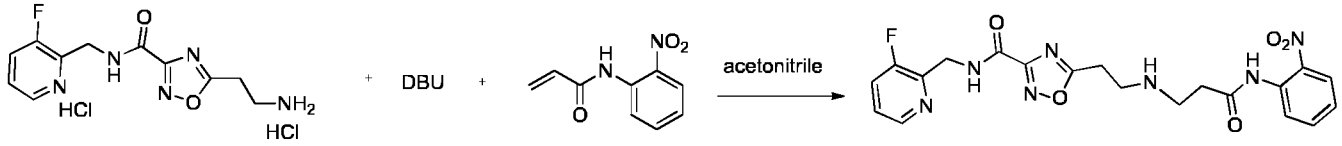
5-(2-aminoethyl)-N-((3-fluoropyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride

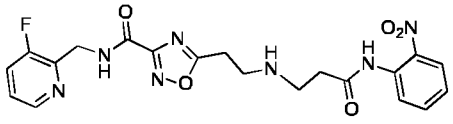


5-(2-aminoethyl)-*N*-((3-fluoropyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride

To a solution of tert-butyl (2-(3-(((3-fluoropyridin-2-yl)methyl)carbamoyl)-1,2,4-oxadiazol-5-yl)ethyl)carbamate (4.23 g, 11.58 mmol) in dioxane (50 ml) and was added 4 M HCl in dioxane (50 ml). After stirring at RT for 3 hours the reaction mixture was evaporated to afford the title compound as a brown oil (3.78 g), which was used without purification.

N-((3-fluoropyridin-2-yl)methyl)-5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxamide



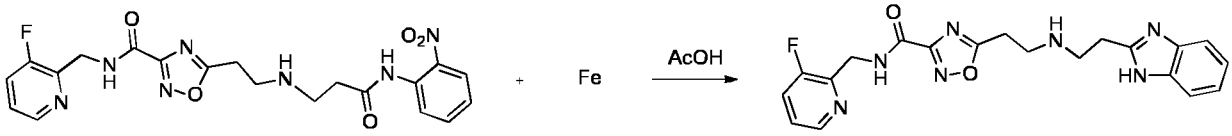


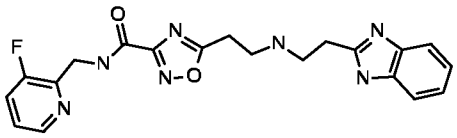
N-((3-fluoropyridin-2-yl)methyl)-5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxamide

In a round bottomed flask, 5-(2-aminoethyl)-N-((3-fluoropyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide dihydrochloride (3.72 g, 9.93 mmol) was suspended in acetonitrile (100 ml) under nitrogen and 1,8-diazabicycloundec-7-ene (DBU) (7.42 ml, 49.65 mmol, 5 eq) was added dropwise followed by N-(2-nitrophenyl)prop-2-enamide (1.91 g, 9.93). The reaction was stirred at room temperature overnight, then evaporated, diluted with 100 ml dichloromethane, washed with 50 ml water, dried (Na_2SO_4), filtered and evaporated. The crude product was purified using a 100 g SNAP KP-Sil column (eluted with a gradient of 0 to 25% methanol in dichloromethane) to give a pale brown oil (1.7 g, 3.7 mmol, 37%).

^{1}H NMR (400 MHz, MeOD): δ 8.3 (s, 1H), 8.1 (m, 2H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (m, 2H), 4.5 (s, 2H), 3.0 (m, 4H), 2.7 (m, 2H), 2.5 (m, 2H).

5-(2-((2-(1 H-benzo[d]imidazol-2-yl)ethyl)amino)ethyl)- N-((3-fluoropyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide (Example Compound No. 279)



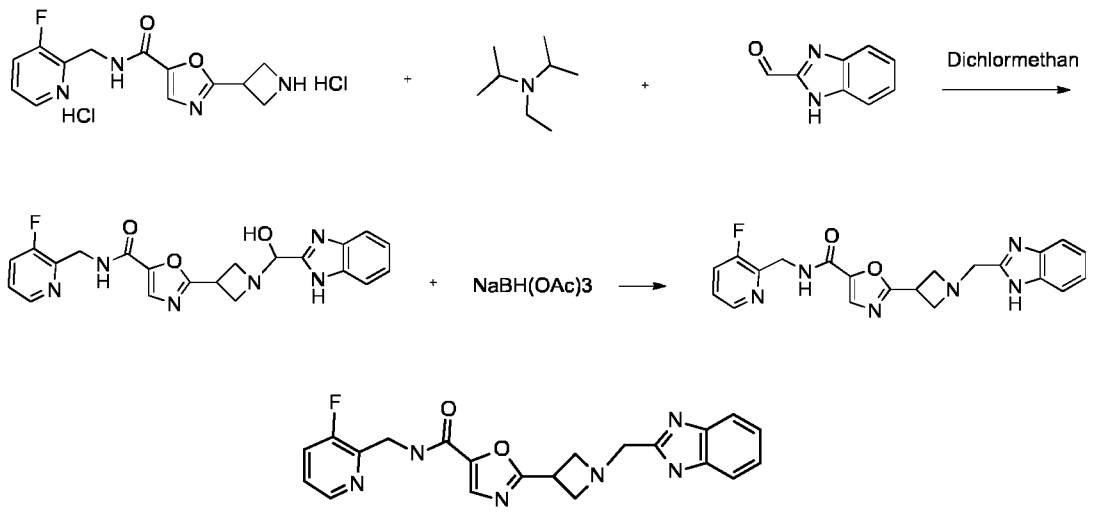


5-(2-((2-(1 *H*-benzo[*d*]imidazol-2-yl)ethyl)amino)ethyl)- *N*-((3-fluoropyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide

N-((3-fluoropyridin-2-yl)methyl)-5-(2-((3-((2-nitrophenyl)amino)-3-oxopropyl)amino)ethyl)-1,2,4-oxadiazole-3-carboxamide (2.3 g, 5.03 mmol) was dissolved in acetic acid (20 ml) under nitrogen and iron powder (1.4 g) was added. The reaction mixture was heated to 80°C for 3 hours. After cooling at RT, toluene (200 ml) was added and the mixture evaporated. A mixture of chloroform : IPA (4:1, 100 ml) was added, the reaction mixture cooled to 0 °C, basified using 6M NaOH solution to pH 10-12, filtered, dried (Na_2SO_4), filtered and evaporated. The crude product was purified using a 100 g SNAP KP-Sil column (eluted with a gradient of 0 to 25% methanol in dichloromethane) to give a pale brown oil (1.51 g, 3.7 mmol, 74%).

^{1}H NMR (400 MHz, MeOD): δ 8.2 (s, 1H), 7.5 (m, 3H), 7.3 (m, 1H), 7.1 (m, 2H), 4.5 (s, 2H), 3.1 (m, 4H), 2.9 (m, 2H), 2.4 (m, 2H).

2-(1-((1 H-benzo[d]imidazol-2-yl)methyl)azetidin-3-yl)- N-((3-fluoropyridin-2-yl)methyl)oxazole-5-carboxamide (Example Compound No. 280)



2-(1-((1 *H*-benzo[*d*]imidazol-2-yl)methyl)azetidin-3-yl)- *N*-((3-fluoropyridin-2-yl)methyl)oxazole-5-carboxamide

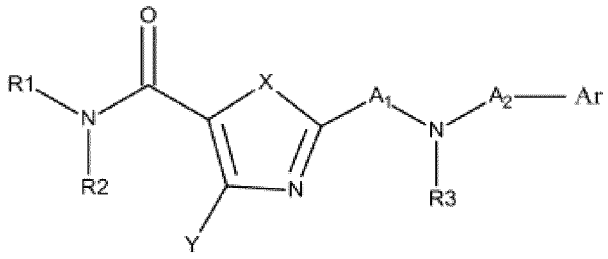
In a round bottomed flask, 2-(azetidin-3-yl)-N-[(3-fluoropyridin-2-yl)methyl]-1,3-oxazole-5-carboxamide dihydrochloride (similar starting compound as in the preparation of Example Compound No. 2 above) (4 g, 11.5 mmol) was diluted in dichloromethane (1600 ml) under nitrogen and diisopropylethylamine (20 ml, 115 mmol, 11 eq) was added dropwise. The reaction stirred for 10 min at RT and then 1H-benzo[d]imidazole-2-carbaldehyde (2 g, 13.7 mmol, 1.3 eq) was added. The reaction stirred at RT for 18 h and then sodium triacetoxyborohydride (5 g, 23.6 mmol, 2.3 eq) added and the reaction stirred at RT for 18 h. The reaction mixture washed with water (1000 ml), separated, dried (MgSO4), filtered and evaporated. The crude product was purified using a 100 g SNAP Ultra column and then a 55 g SNAP NH column (eluted each time with a gradient of 0 to 25% methanol in dichloromethane) to give a pale brown oil (1.34 g, 3.3 mmol, 29%).

^{1}H NMR (400 MHz, CDCl3): δ 7.99 (m, 1H), 7.51 (m, 1H), 7.15 (m, 2H), 7.01 (m, 1H), 6.88 (m, 1H), 6.81 (m, 2H), 4.4 (s, 2H), 3.6 (2H), 3.42 (m, 1H), 3.35 (m, 2H), 3.28 (m, 2H).

MS (ESI+): m/z 407 $[M+H]^+$.

Further Embodiments of the invention:

1. Compounds according to formula (I)



(I)

wherein

R^1 and R^2 are the same or different and are independently selected from the group consisting of

- hydrogen,
- optionally substituted alkyl,
- optionally substituted aryl,
- optionally substituted heteroaryl, or

- R^1 and R^2 together with the nitrogen atom to which they are bonded form an optionally substituted 3- to 6-membered ring, which may optionally contain further heteroatoms;

X is O or S;

Y is hydrogen, optionally substituted alkyl or halogen,

A^1 is
- optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl,
- a direct bond, or
- a sulfonyl group;

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered aliphatic mono- or bicyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered aliphatic ring;

and

Ar is
- optionally substituted aryl,
- optionally substituted monocyclic heteroaryl, or
- optionally substituted bicyclic heteroaryl, which may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded;

or pharmaceutically acceptable salts thereof.

2. Compounds according to embodiment 1, wherein

R^1 and R^2 are the same or different and are independently selected from the group consisting of
- hydrogen,
- optionally substituted alkyl, or
- R^1 and R^2 together with the nitrogen atom to which they are bonded form and optionally substituted 3- to 6-membered ring, which may optionally contain further heteroatoms;

X is O or S;

Y is hydrogen or C_1-C_3-alkyl, such as preferably hydrogen or methyl;

A^1 is optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl, or

- a direct bond;

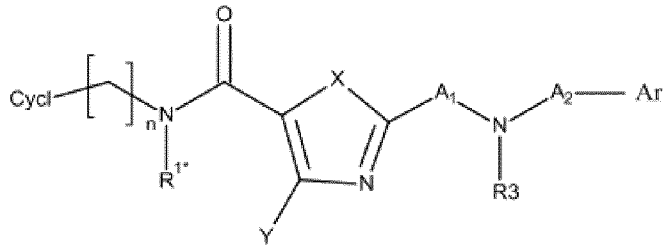
R^3 is
- hydrogen, or
- C_1-C_3-alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered aliphatic monocyclic ring; or

R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7- membered aliphatic ring; and

Ar is optionally substituted bicyclic heteroaryl.

3. Compounds according to embodiment 1 or 2, wherein
at least one of R^1 and R^2 is a linear, branched or cyclic alkyl group, which is substituted with a cyclic group "Cycl", designated as R^{2*}, forming compounds according to formula (III)



(III)

wherein
Cycl is selected from
- optionally substituted aryl, and
- optionally substituted heteroaryl,

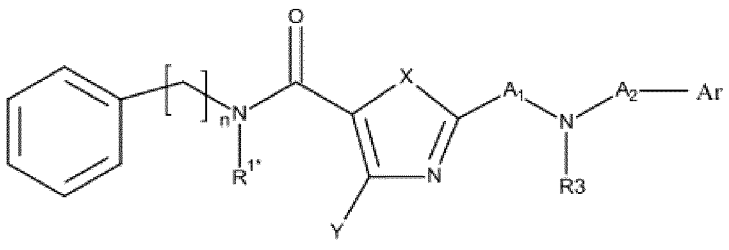
n is an integer of 1 to 3;

the remaining of R^1 or R^2, designated as R^{1*}, is selected from
- hydrogen, and
- optionally substituted alkyl, and

X, Y, R^3, A^1, A^2 and Ar have the meaning as defined in the preceding embodiments;
or pharmaceutically acceptable salts thereof.

4. Compounds according to any one of the preceding embodiments, wherein the compounds are defined by

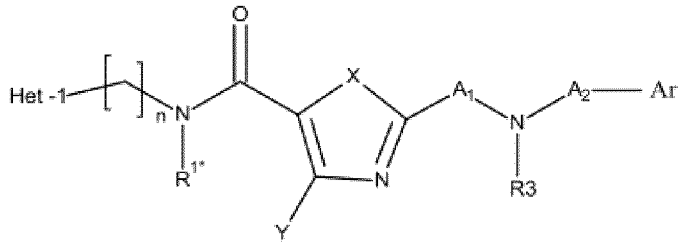
- formula (IIIa)



(IIIa)

, or

- formula (IIIb)



(IIIb)

with Het-1 being

- an optionally substituted, optionally fused 5- to 6-membered heteroaryl, or
- an optionally substituted 5- or 6-membered aliphatic heterocyclyl, preferably a 6-membered aliphatic heterocyclyl,

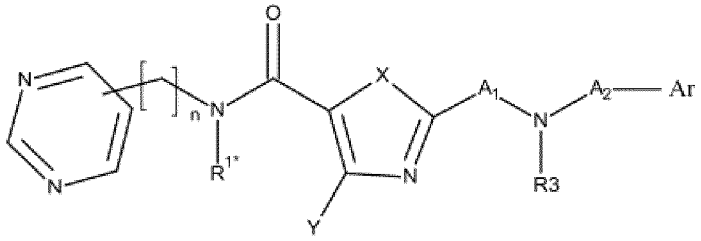
which contain 1 or 2 identical or different heteroatoms selected from the group consisting of N, O and S, preferably N;
and wherein in each case n is an integer of 1 to 3;
the remaining of R^1 or R^2, designated as R^{1*}, is selected from

- hydrogen, and
- optionally substituted alkyl; and

X, Y, R^3, A^1, A^2 and Ar have the meaning as defined in the preceding embodiments;
or pharmaceutically acceptable salts thereof.

5. Compounds according to any one of the preceding embodiments, wherein the compounds are defined by

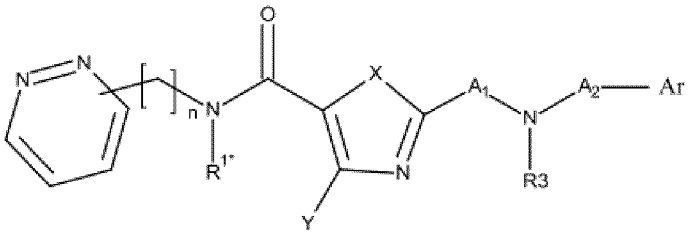
- formula (IIIb-c)



(IIIb-c)

,

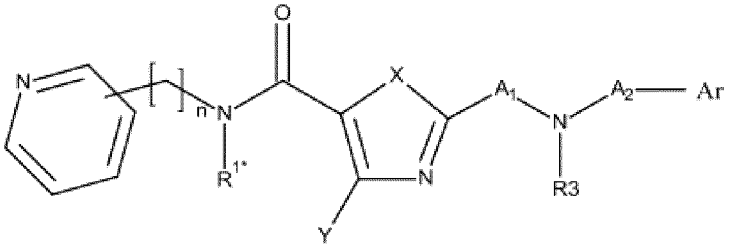
- formula (IIIb-d)



(IIIb-d)

, and

- formula (IIIb-e)



(IIIb-e)

;

wherein the pyrimidinyl, pyridazinyl and pyridinyl ring each may carry 1 to 3, preferably 1 or 2 further substituents;
and wherein in each case n is an integer of 1 to 3;

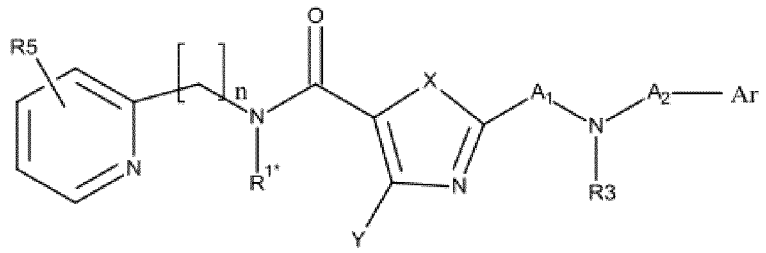
the remaining of R^1 or R^2, designated as R^{1*}, is selected from

- hydrogen, and
- optionally substituted alkyl; and

X, Y, R^3, A^1, A^2 and Ar have the meaning as defined in the preceding embodiments;
or pharmaceutically acceptable salts thereof.

6. Compounds according to any one of the preceding embodiments, wherein the compounds are defined by

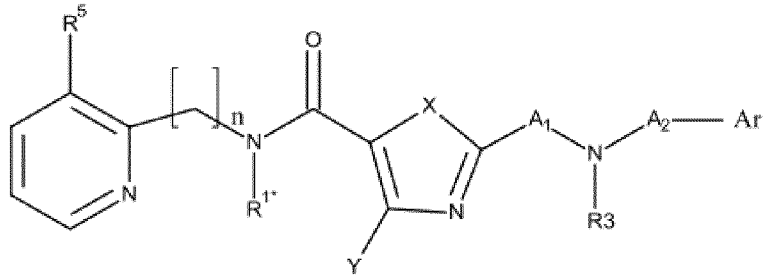
- formula (IIIb-f)



(IIIb-f)

wherein R^5 indicates 1 to 3, preferably 1 or 2 optional substituents, which are preferably selected from C_1-C_3-alkyl and halogen, such as in particular compounds of

- formula (IIIb-g)



(IIIb-g)

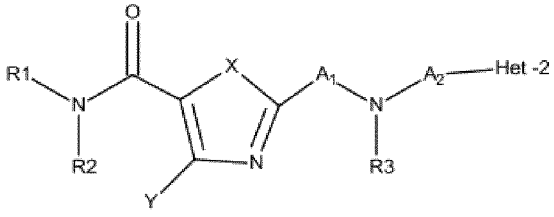
wherein R^5 is preferably selected from C_1-C_3-alkyl and halogen, such as preferably F;

and wherein in each case n is an integer of 1 to 3;
the remaining of R^1 or R^2, designated as R^{1*}, is selected from

- hydrogen, and
- optionally substituted alkyl; and

X, Y, R^3, A^1, A^2 and Ar have the meaning as defined in the preceding embodiments;
or pharmaceutically acceptable salts thereof.

7. Compounds according to any one of the preceding embodiments, wherein
Ar is an optionally substituted mono- or bicyclic heteroaryl, forming compounds according to formula (IV)



(IV)

,

with Het-2 being

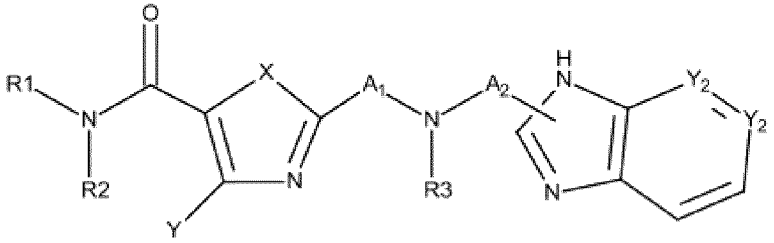
- an optionally substituted, 5- or 6-membered monocyclic heteroaryl, or

- an optionally substituted bicyclic heteroaryl, which may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded;

and wherein X, Y, R^3, A^1, A^2 and Ar have the meaning as defined in any one of the preceding embodiments;
or pharmaceutically acceptable salts thereof.

8. Compounds according to any one of the preceding claims, which are defined by

- formula (IVc)

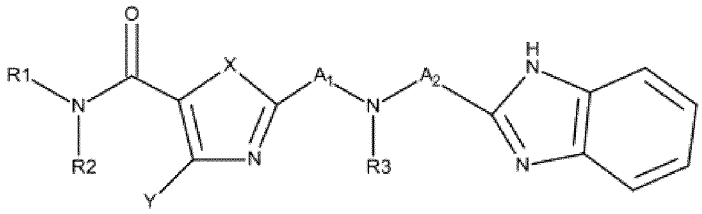


(IVc)

with

- both Y^2 being C or
- one Y^2 being N and one Y^2 being C,

such as in particular compounds according to formula (IVd)



(IVd)

,

wherein in each case the bicyclic heteroaryl ring of Het-2 may carry 1 to 3 substituents, preferably 1 or 2 substituents; and wherein the bicyclic heteroaryl ring of Het-2 of formula (IVc) or (IVd), may be fused with a ring formed by R^3 and A^2 together with the nitrogen atom to which they are bonded, and
wherein in each case R^1, R^2, X, Y, R^3, A^1 and A^2 have the meaning as defined in the preceding embodiments;
or pharmaceutically acceptable salts thereof.

9. Compounds according to any one of the preceding embodiments, wherein

A^1 and A^2 are optionally substituted alkanediyl and are the same or different and are independently selected from optionally substituted

- methylene and
- ethane-1,2-diyl, or wherein
- A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- membered aliphatic monocyclic ring;

or pharmaceutically acceptable salts thereof.

10. Compounds according to any one of the preceding embodiments for the use as a medicament.

11. Compounds according to any one of the preceding embodiments for the use as ferroportin inhibitor.

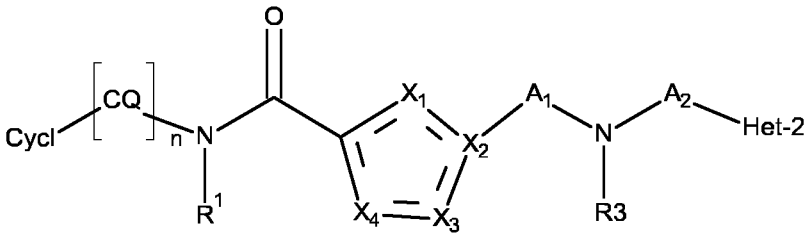
12. Compounds as defined in any one of the preceding embodiments for the use in the inhibition of iron transport mediated by ferroportin or for the use in the prophylaxis and/or treatment of iron metabolism disorders leading to increased iron levels, iron overload, diseases related to or caused by increased iron levels or tissue iron overload, diseases associated with ineffective erythropoiesis, diseases caused by reduced levels of hepcidin, or to limit the amount of iron available to pathogenic microorganisms, such as the bacterium Vibrio vulnificus, and thereby for the use as adjunctive therapy to treat infections.

13. Compounds as defined in any one of the preceding embodiments for the use according to embodiment 12 wherein the diseases related to or caused by increased iron levels or iron overload comprise thalassemia (beta- thalassemia), haemochromatosis, neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, formation of radicals, reactive oxygen species (ROS) and oxidative stress, cardiac, liver and endocrine damage caused by iron overload, and inflammation triggered by excess iron; and wherein the diseases associated with ineffective erythropoiesis comprise myelodysplastic syndromes (MDS, myelodysplasia), polycythemia vera.

14. A medicament containing one or more of the compounds as defined in any one of the preceding embodiments, the medicament being preferably for the use as defined in embodiments 12 and 13, and which may further contain one or more pharmaceutical carriers and/or auxiliaries and/or solvents and/or at least one further pharmaceutically active compound, in particular a compound for the prophylaxis and treatment of iron overload, thalassemia, haemochromatosis, neurodegenerative diseases (such as Alzheimer's disease or Parkinson's disease) and the associated symptoms, preferably an iron-chelating compound; and wherein the medicament is preferably for oral or parenteral administration.

CLAIMS:

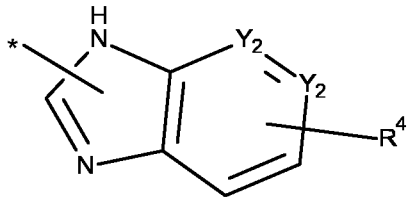
1. Compounds according to formula (A-I)



(A-I)

wherein

Het-2 is an optionally substituted bicyclic heteroaryl of the formula



wherein * indicates the binding site to A^2 and
R^4 indicates 1, 2 or 3 optional substituents, which may independently be selected from the group consisting of

- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted alkoxy, and
- a carboxyl group;

X^1 is C, N, S or O;
X^2 is C or N;
X^3 is C, N, S or O; and
X^4 is C, N, or S
with the proviso that 1 to 3 heteroatoms X are present,
and wherein X^1, X^3 and X^4, when having the meaning of C or N, may carry a further substituent;

R^1 is selected from the group consisting of
- hydrogen and
- optionally substituted alkyl;

Cycl is selected from the group consisting of
- substituted aryl and
- substituted or unsubstituted heteroaryl;

Q is

- hydrogen or
- C_1-C_4-alkyl, which may form a fused 5- or 6-membered ring with Cycl;

n is 0 or an integer of 1 to 8, preferably n is 0 or 1 to 4, preferably n is 0, 1, 2 or 3;

A^1 is
- optionally substituted alkanediyl;

A^2 is
- optionally substituted alkanediyl or
- a direct bond;

R^3 is
- hydrogen, or
- optionally substituted alkyl; or

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 6-membered mono- or bicyclic ring; or

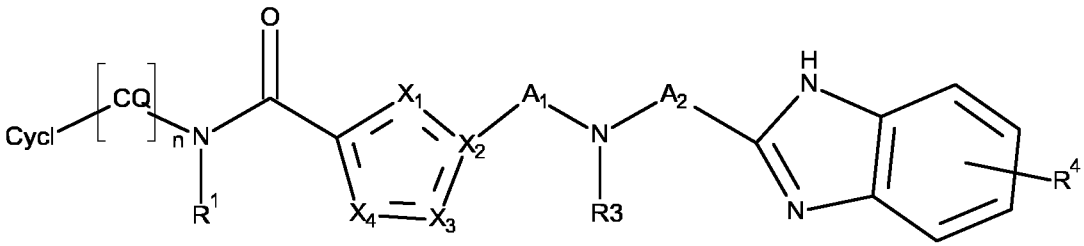
R^3 and A^2 together with the nitrogen atom to which they are bonded form an optionally substituted 4- to 7-membered ring;

and

Y^2 is C or N, wherein
- both Y^2 may be C or
- one Y^2 may be N and one Y^2 may be C;

or pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, having the formula (A-II)

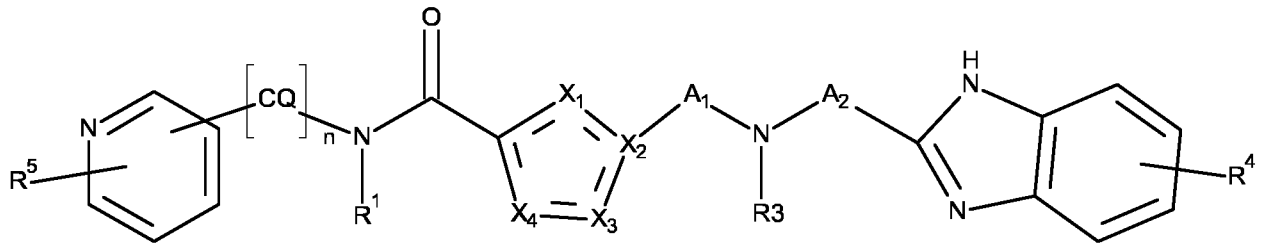


(A-II)

or pharmaceutically acceptable salts thereof.

3. Compounds according to claim 1 or 2, wherein Cycl is substituted or unsubstituted heteroaryl, or pharmaceutically acceptable salts thereof.

4. Compounds according to any one of the preceding claims, wherein Cycl is a substituted or unsubstituted heteroaryl, which is selected from a substituted or unsubstituted pyridinyl, forming compounds according to formula (A-IIIa) or (A-IIIb)

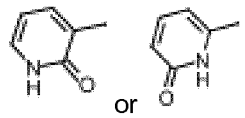


(A-IIIb)

wherein

R^5 indicates 1 to 4 optional substituents, which may independently be selected from the group consisting of

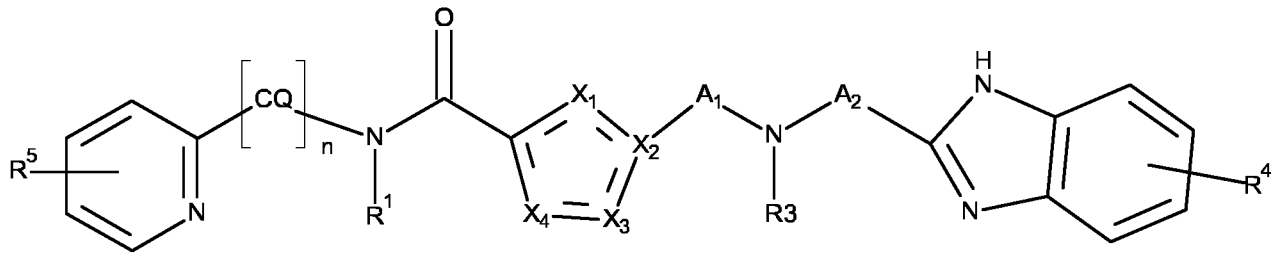
- halogen, preferably F and Cl,
- optionally substituted alkyl, preferably methyl, trifluoromethyl, hydroxymethyl,
- hydroxy,
- alkoxy, preferably methoxy,
- an oxo group (=O), forming a substituted pyridinyl-group of the formula



- an amino group, such as $-NH_2$, mono- or dialkylamino, preferably dialkylamino
- an aminocarbonyl group, preferably NH_2-(C=O)-,
- cyano, and
- a heterocyclyl group, preferably a morpholinyl-group,

or pharmaceutically acceptable salts thereof.

5. Compounds according to claim 4, having the formula (A-IVa) or (A-IVb)



(A-IVb)

or pharmaceutically acceptable salts thereof.

6. Compounds according to claim 4 or 5, wherein R^5 indicates 1 to 3 substituents, which may independently be selected from the group consisting of

- halogen
- optionally substituted alkyl,
- hydroxy, and

- alkoxy,

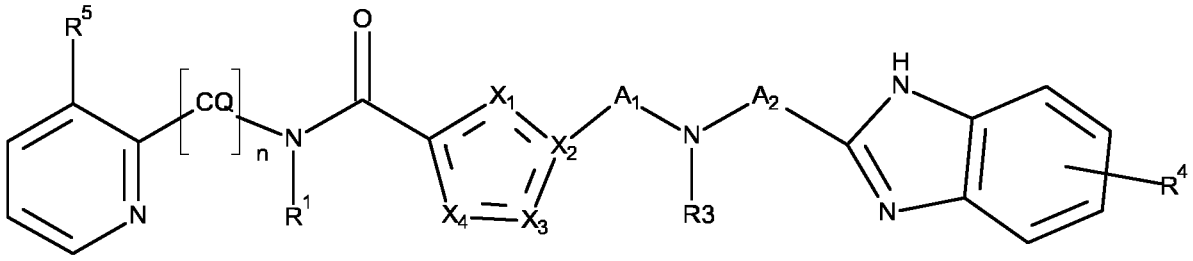
or pharmaceutically acceptable salts thereof.

7. Compounds according to claim 6, wherein R^5 indicates 1 substituent, which is selected from the group consisting of

- halogen
- optionally substituted alkyl,
- hydroxy, and
- alkoxy,

or pharmaceutically acceptable salts thereof.

8. Compounds according to any one of claims 5 to 7, having the formula (A-IVc) or (A-IVd)



(A-IVd)

or pharmaceutically acceptable salts thereof.

9. Compounds according to any one of claims 5 to 8, wherein R^5 is selected from the group consisting of

- halogen and
- optionally substituted alkyl,

or pharmaceutically acceptable salts thereof.

10. Compounds according to any one of claims 5 to 9, wherein R^5 is selected from a halogen,
or pharmaceutically acceptable salts thereof.

11. Compounds according to claim 10, wherein R^5 is selected from Cl and F, preferably R^5 is F,
or pharmaceutically acceptable salts thereof.

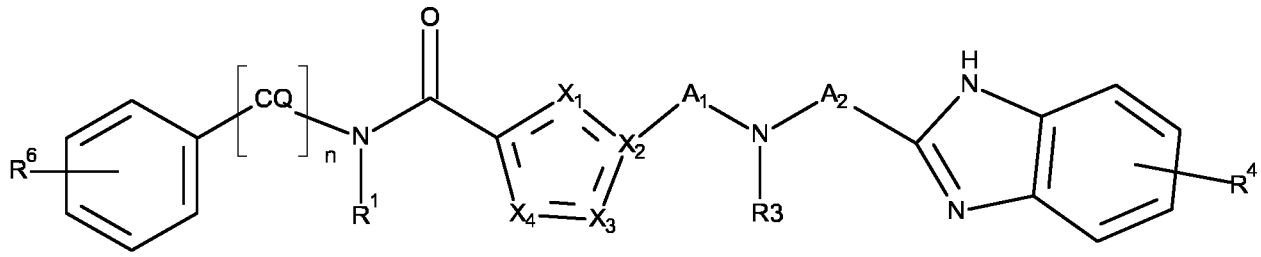
12. Compounds according to claim 1 or 2, wherein Cycl is an aryl group, which is substituted with 1 to 3 substituents selected from the group consisting of

- hydroxy,
- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino,

- optionally substituted acyl,
- optionally substituted alkoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl, and
- optionally substituted heterocyclylyl;

or pharmaceutically acceptable salts thereof.

13. Compounds according to claim 12, wherein Cycl is a substituted phenyl group, forming compounds according to formula (A-Va) or (A-Vb)



(A-Vb)

wherein R^6 indicates 1, 2 or 3 substitutens which are independently selected from the group consisting of

- hydroxy,
- halogen,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino,
- optionally substituted acyl,
- optionally substituted alkoxy,
- optionally substituted aryloxy,
- optionally substituted heterocyclyloxy,
- optionally substituted aryl, and
- optionally substituted heterocyclylyl;

or pharmaceutically acceptable salts thereof.

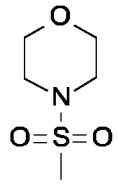
14. Compounds according to claim 12 or 13, wherein R^6 indicates 1 or 2 substituents as defined in claim 12,
or pharmaceutically acceptable salts thereof.

15. Compounds according to claim 13 or 14, wherein R^6 indicates 1 substituent selected from the group as defined in claim 12,
or pharmaceutically acceptable salts thereof.

16. Compounds according to any one of claims 13 to 15, wherein R^6 is selected from the group consisting of

- hydroxy,

- halogen, preferably F and Cl,
- cyano,
- optionally substituted alkyl,
- optionally substituted amino, such as (-NH_2) or mono- or dialkylamino, preferably dimethylamino,
- optionally substituted alkoxy, preferably methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl, and
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula

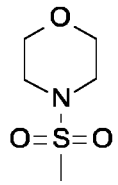


;

or pharmaceutically acceptable salts thereof.

17. Compounds according to any one of claims 13 to 16, wherein R^6 is selected from the group consisting of

- halogen, preferably F,
- cyano,
- dimethylamino,
- methoxy, di-fluoromethoxy and trifluoromethoxy,
- optionally substituted heterocyclylyl, preferably optionally substituted pyrrolininyl, morpholinyl, and piperazinyl, and
- an optionally substituted sulfonyl-group, such as preferably heterocyclyl-substituted sulfonyl, preferably of the formula

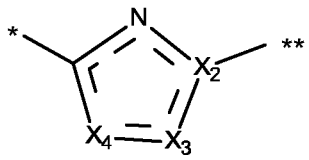


or pharmaceutically acceptable salts thereof.

18. Compounds according to any one of the preceding claims, wherein

X^1 is N

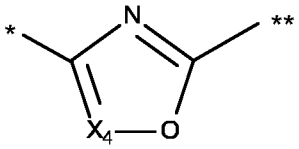
and wherein one or two further heteroatoms X (X^2, X^3, X^4) are present, and wherein
X^2 is C or N;
X^3 is C, N, S or O; and
X^4 is C or N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
with the proviso that in case of two further heteroatoms both are selected to be N or one is N and one (except X^2) is O;
and wherein X^3 and X^4, when having the meaning of C or N, may carry a further substituent,
or pharmaceutically acceptable salts thereof.

19. Compounds according to any one of the preceding claims, wherein

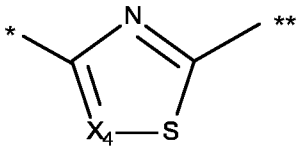
X^1 is N,
X^2 is C and
X^3 is O; and
X^4 is N or C, preferably C,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^4 may carry a further substituent,
or pharmaceutically acceptable salts thereof.

20. Compounds according to any one of the preceding claims, wherein

X^1 is N,
X^2 is C and
X^3 is S; and
X^4 is N or C, preferably C,
forming a group

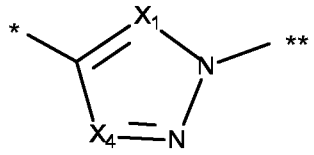


wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^4 may carry a further substituent,

or pharmaceutically acceptable salts thereof.

21. Compounds according to any one of the preceding claims, wherein

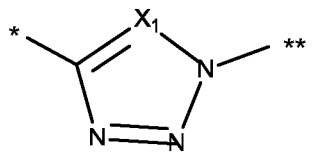
X^2 and X^3 are both N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^1 and X^4 are C;
and wherein X^1 and/or X^4 may carry a further substituent,
or pharmaceutically acceptable salts thereof.

22. Compounds according to any one of the preceding claims, wherein

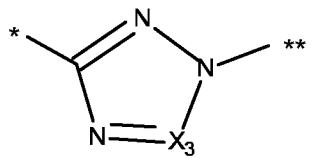
X^1 is C, and
X^2, X^3 and X^4 are N,
forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^1 may carry a further substituent,
or pharmaceutically acceptable salts thereof.

23. Compounds according to any one of the preceding claims, wherein

X^1, X^2 and X^4 are N, and
X^3 is C,
forming a group

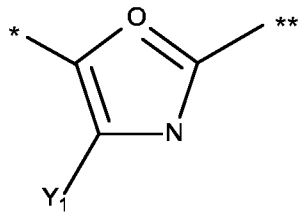


wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
and wherein
X^3 may carry a further substituent,
or pharmaceutically acceptable salts thereof.

24. Compounds according to any one of the preceding claims, wherein

X^1 is O,
X^2 is C,
X^3 is N, and
X^4 is C, and wherein
Y^1 indicates
- hydrogen or
- an optional subsitutent to X^4;

forming a group

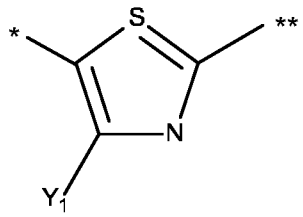


wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
or pharmaceutically acceptable salts thereof.

25. Compounds according to any one of the preceding claims, wherein

X^1 is S,
X^2 is C,
X^3 is N, and
X^4 is C, and wherein
Y^1 indicates
- hydrogen or
- an optional subsitutent to X^4;

forming a group



wherein * indicates the binding site to the aminocarbonyl-group and ** indicates the binding site to the A^1-group;
or pharmaceutically acceptable salts thereof.

26. Compounds according to any one of the preceding claims, wherein the further substituents of X^1, X^3 and X^4 are selected from the group consisting of

- halogen, and
- optionally substituted alkyl,

or pharmaceutically acceptable salts thereof.

27. Compounds according to claims 26, wherein the further substituents of X^1, X^3 and X^4 are selected from the group consisting of

- Cl, and
- linear or branched C_1-C_3-alkyl, which may be substituted with 1 to 3 halogens or with a methylene-group; such as preferably a methyl-group, an iso-propyl-group, a CF_3-group or a methylene-substituted ethyl-group

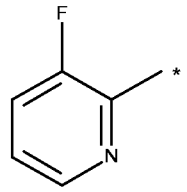
or pharmaceutically acceptable salts thereof.

28. Compounds according to any one of the preceding claims, wherein n is 1,
or pharmaceutically acceptable salts thereof.

29. Compounds according to any one of the preceding claims, wherein Q is H,
or pharmaceutically acceptable salts thereof.

30. Compounds according to any one of the preceding claims, wherein R^1 is H,
or pharmaceutically acceptable salts thereof.

31. Compounds according to any one of the preceding claims, wherein Cycl is a group of the formula



wherein * indicates the binding site,
or pharmaceutically acceptable salts thereof.

32. Compounds according to any one of the preceding claims, wherein
A^1 and A^2 are optionally substituted alkanediyl and are the same or different and are independently selected from optionally substituted

- methylene and
- ethane-1,2-diyl, or wherein

A^1 and R^3 together with the nitrogen atom to which they are bonded form an optionally substituted 4-membered aliphatic monocyclic ring;
or pharmaceutically acceptable salts thereof.

33. Compounds according to any one of the preceding claims, which are selected from

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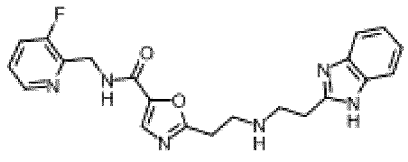
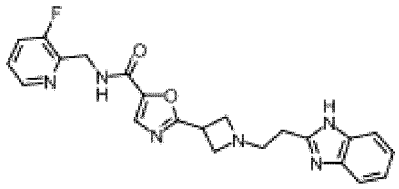
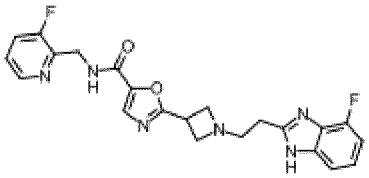
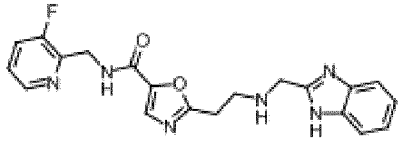
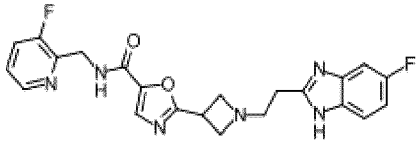
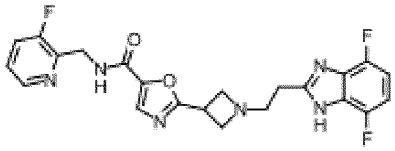
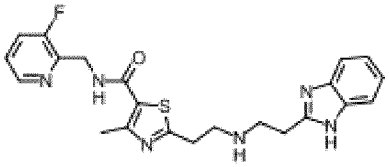
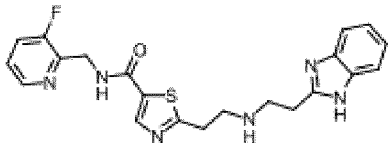
1		2	
3		4	
5		6	
7		8	

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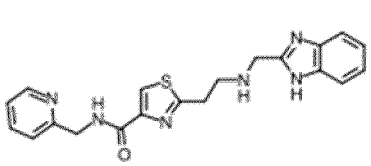
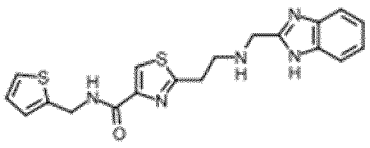
12	
16	

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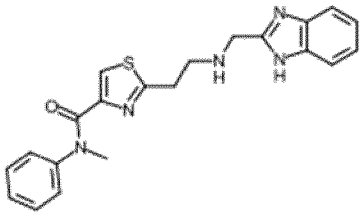
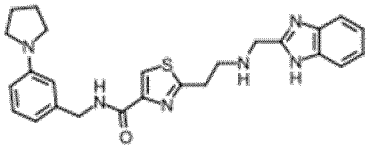
19	
21	

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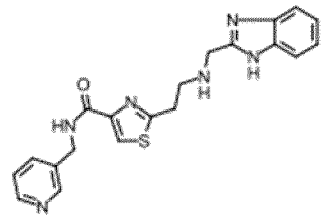
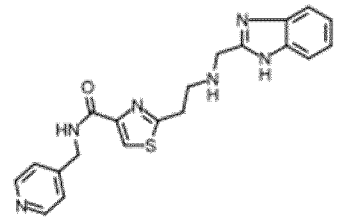
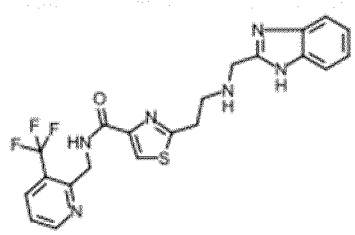
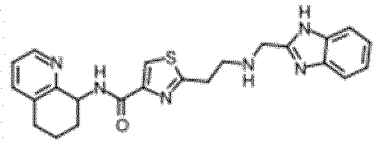
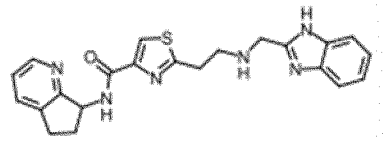
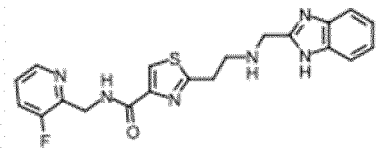
35	
36	
37	
38	
39	
40	

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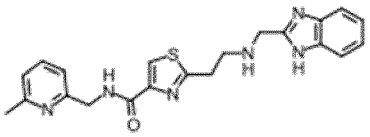
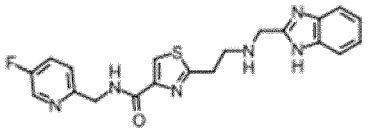
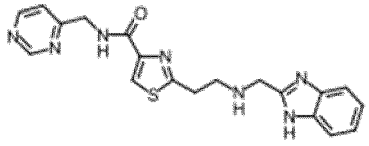
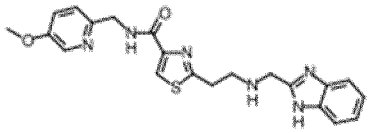
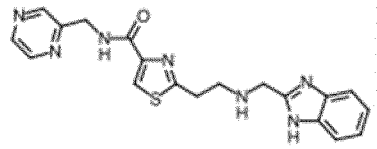
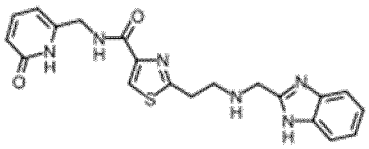
42	
43	
44	
45	
46	
47	

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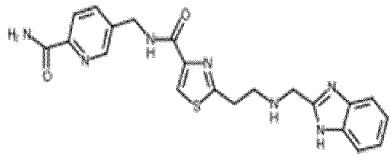
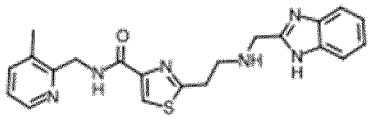
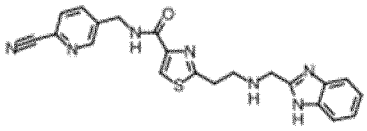
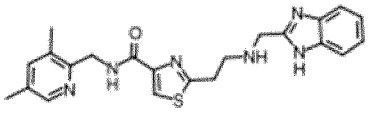
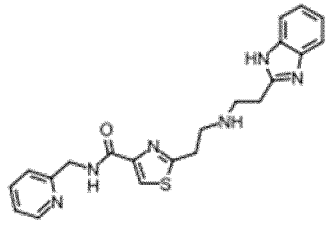
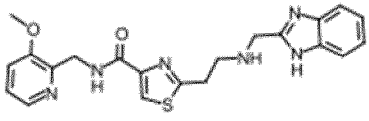
54	
55	
56	
57	
58	
59	

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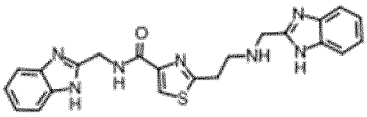
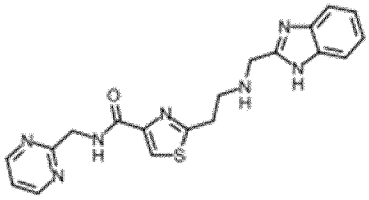
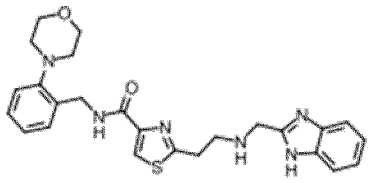
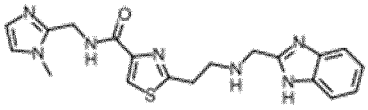
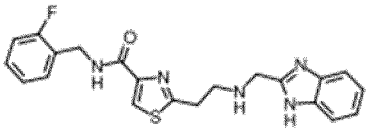
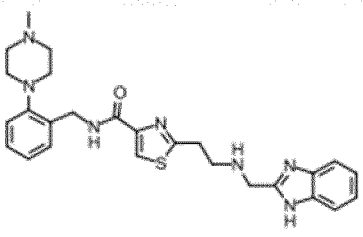
60	
61	
63	
64	
65	
68	

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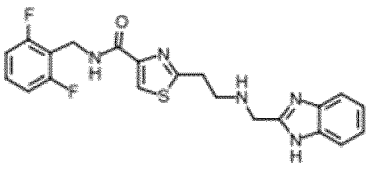
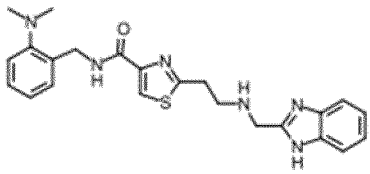
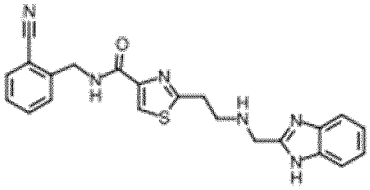
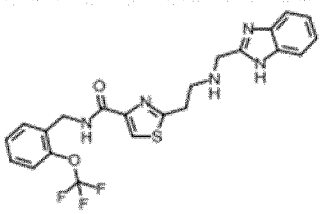
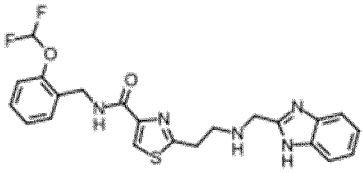
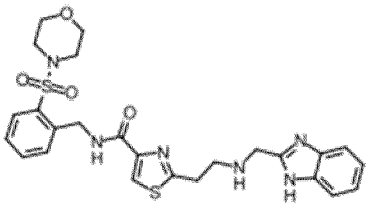
69	
70	
71	
72	
74	
75	

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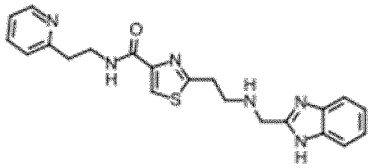
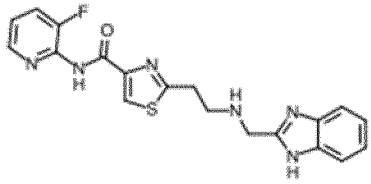
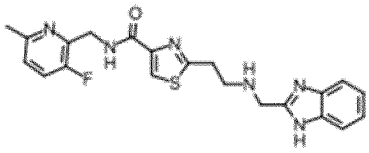
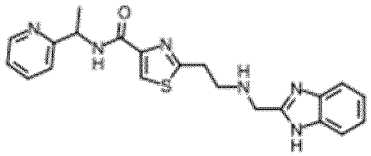
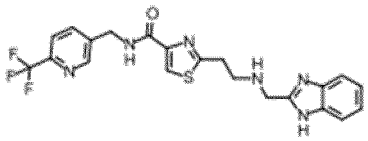
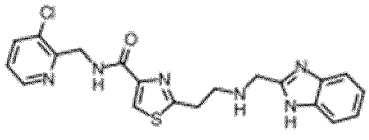
76	
77	
79	
80	
81	
82	

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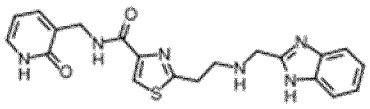
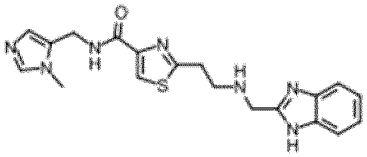
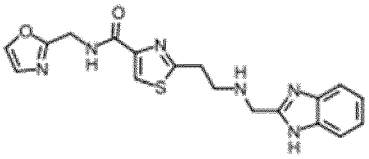
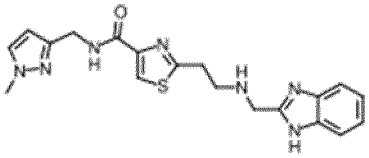
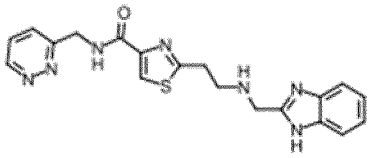
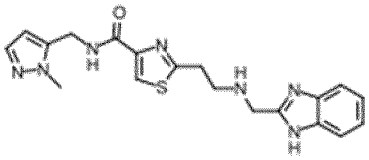
83	
84	
85	
86	
87	
88	

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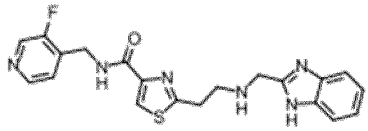
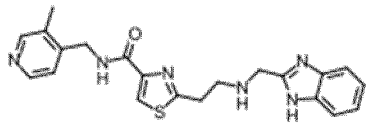
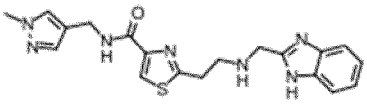
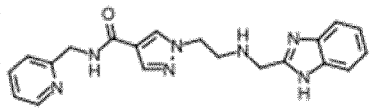
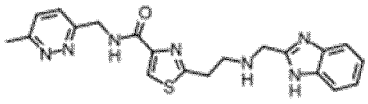
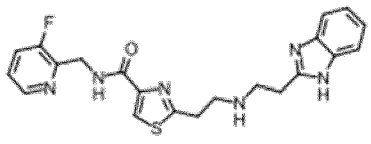
89	
90	
91	
92	
93	
94	

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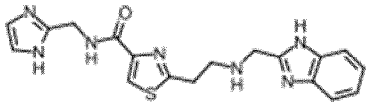
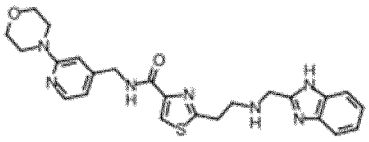
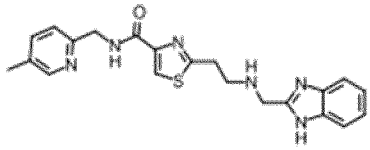
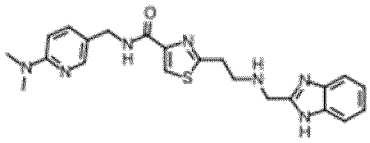
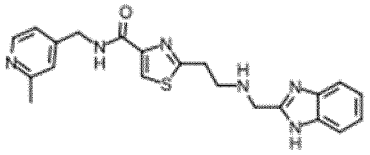
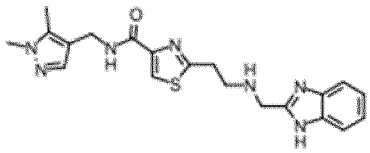
95	
96	
97	
98	
99	
100	

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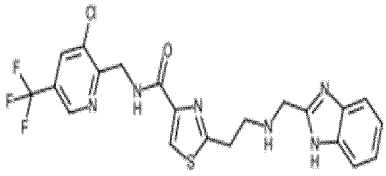
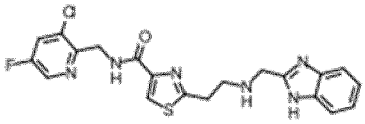
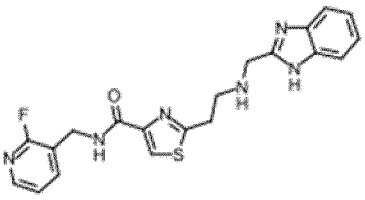
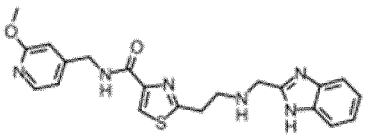
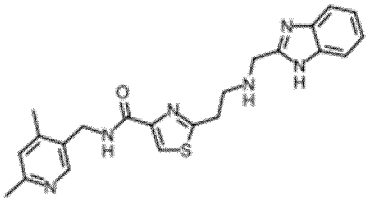
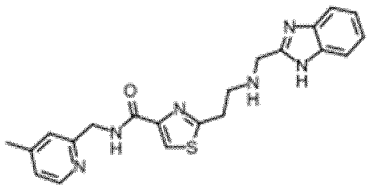
101	
102	
103	
104	
105	
106	

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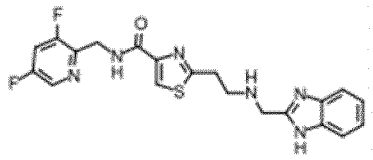
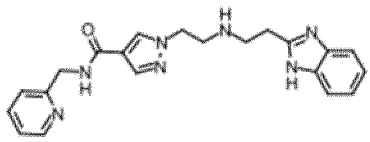
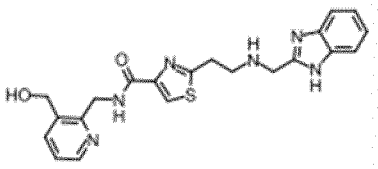
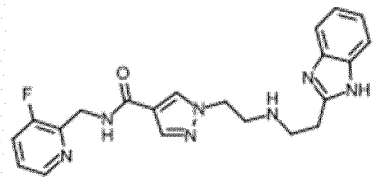
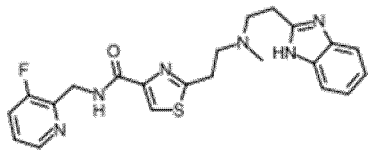
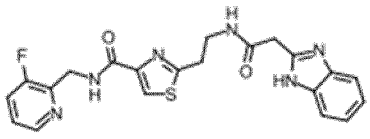
108	
109	
110	
111	
112	
113	

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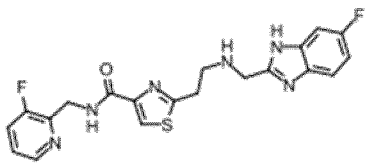
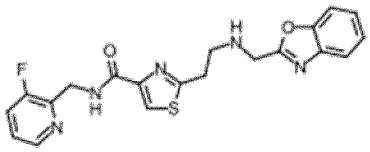
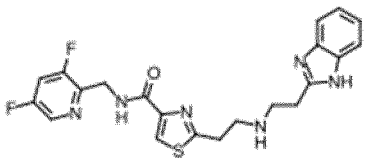
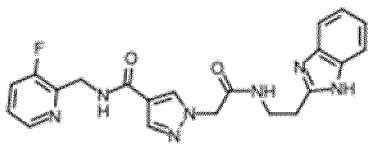
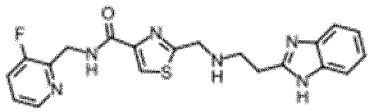
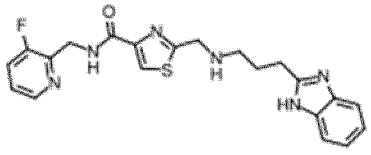
114	
115	
116	
117	
118	
119	

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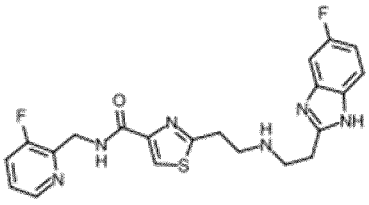
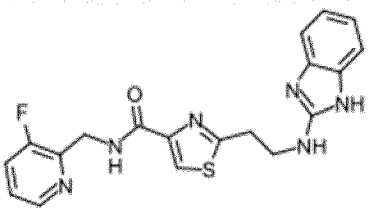
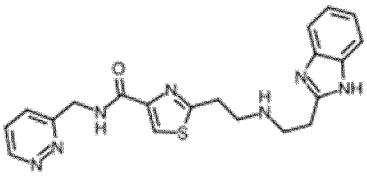
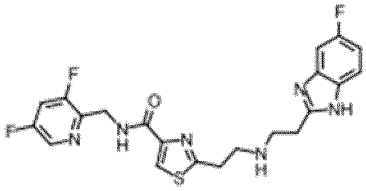
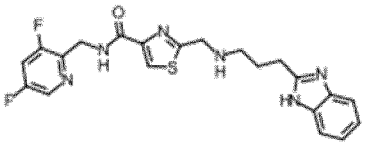
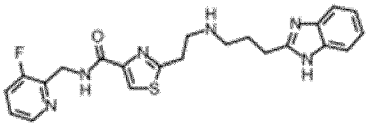
120	
121	
122	
123	
124	
125	

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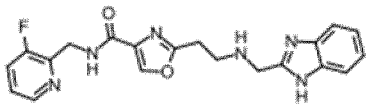
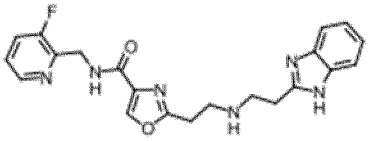
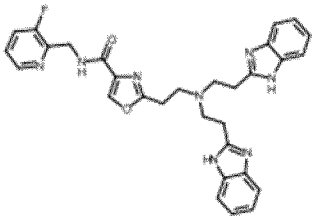
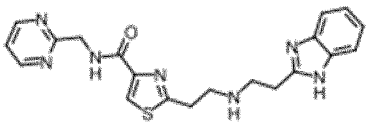
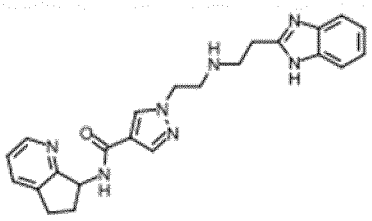
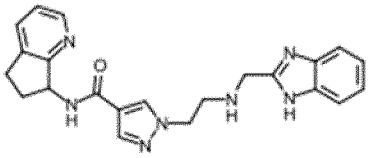
126	
127	
128	
129	
131	
132	

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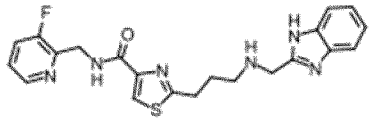
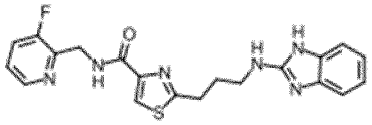
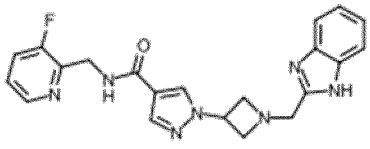
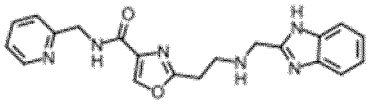
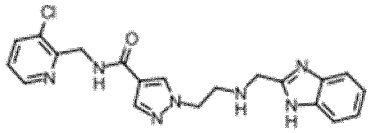
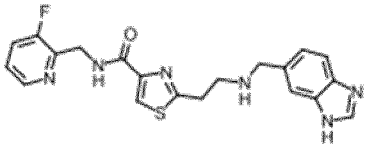
134	
135	
136	
137	
138	
139	

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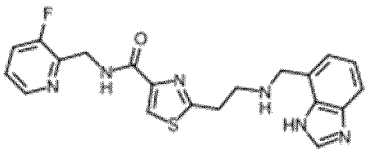
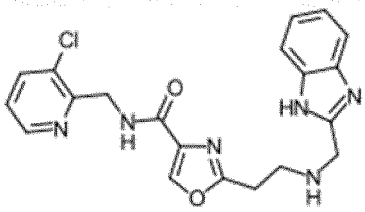
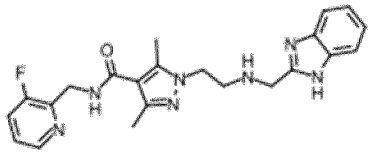
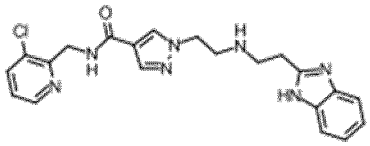
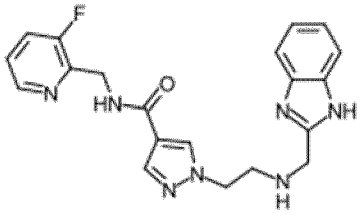
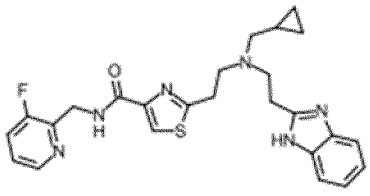
140	
141	
142	
144	
145	
148	

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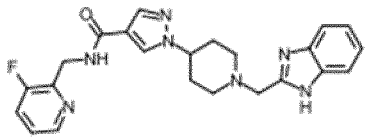
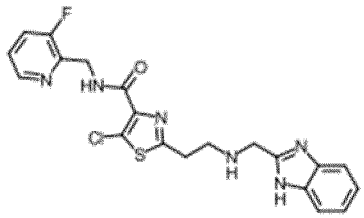
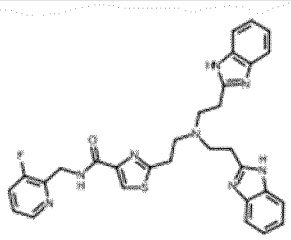
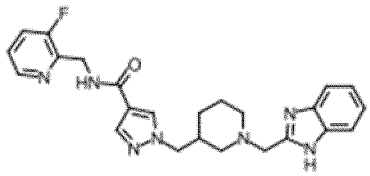
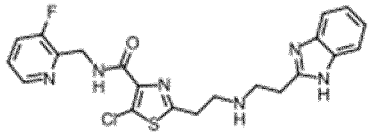
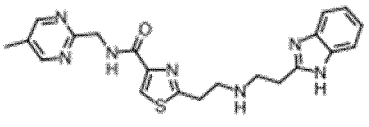
150	
151	
152	
153	
154	
155	

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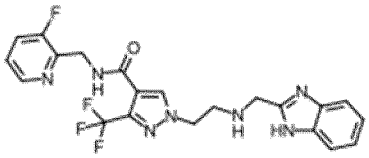
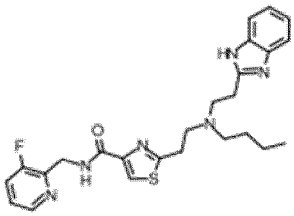
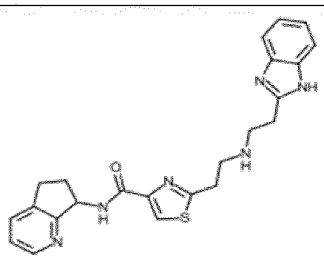
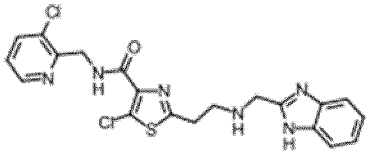
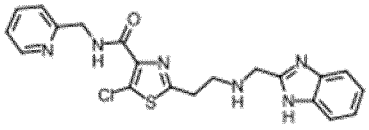
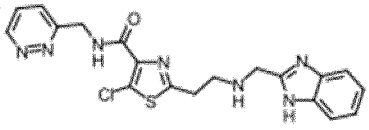
156	
157	
158	
159	
160	
161	

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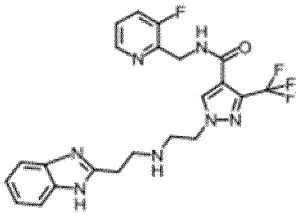
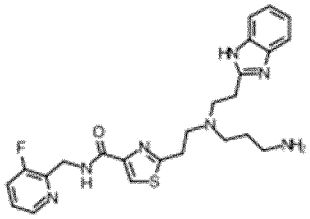
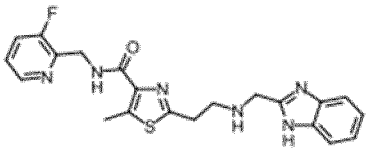
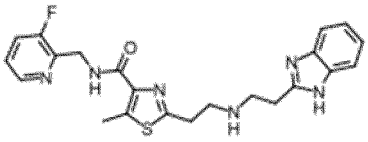
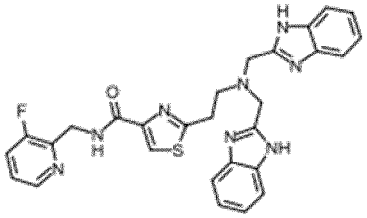
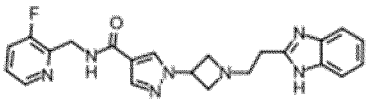
162	
163	
164	
165	
166	
167	

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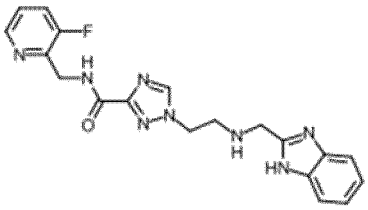
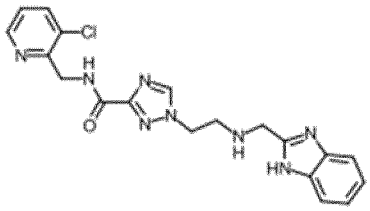
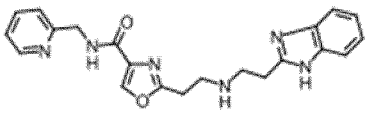
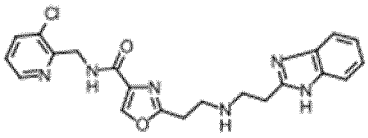
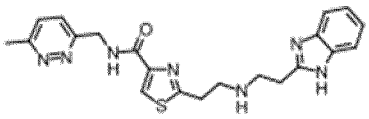
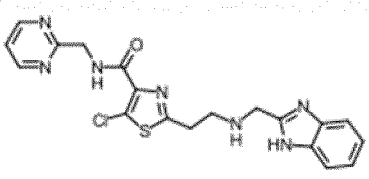
169	
170	
171	
173	
174	
175	

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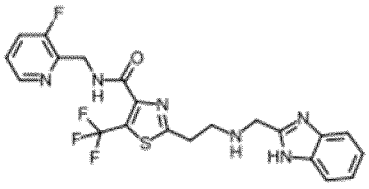
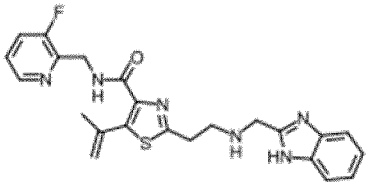
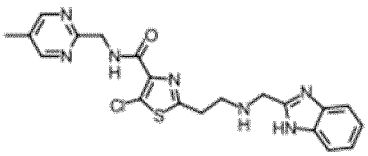
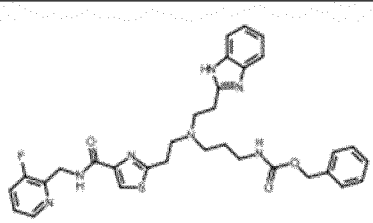
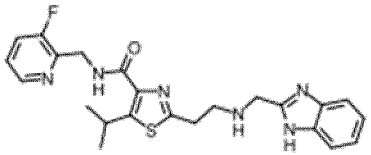
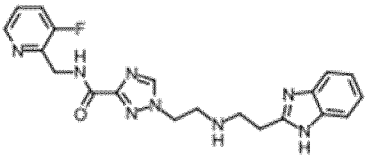
176	
177	
178	
179	
180	
181	

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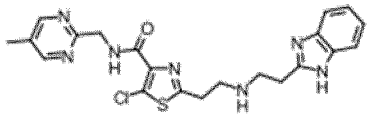
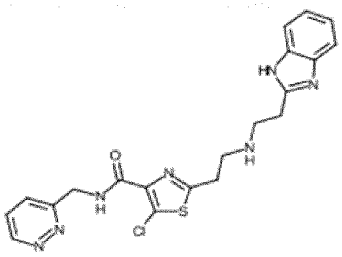
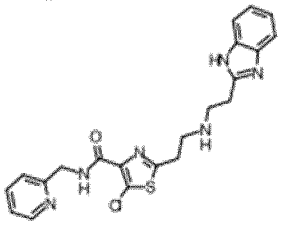
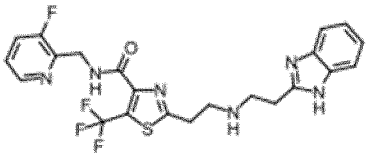
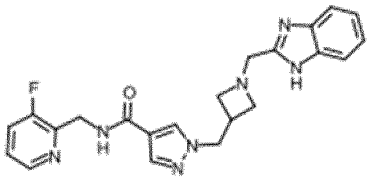
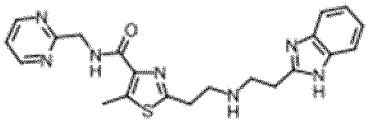
182	
183	
184	
186	
187	
188	

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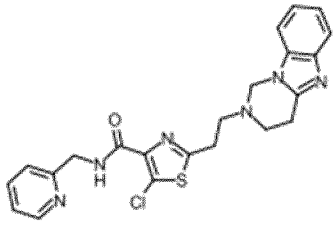
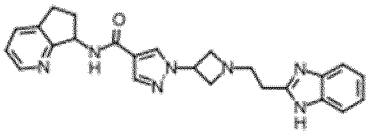
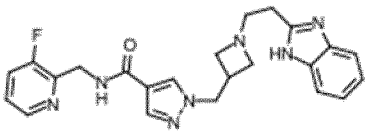
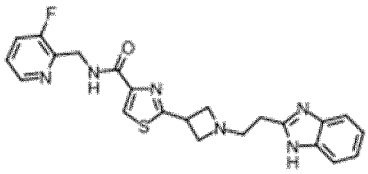
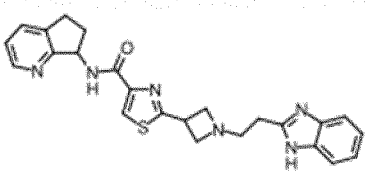
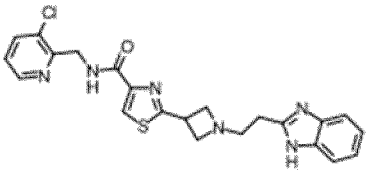
189	
191	
192	
193	
194	
195	

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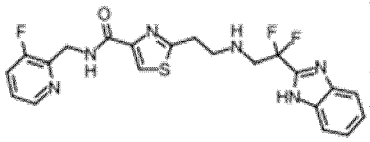
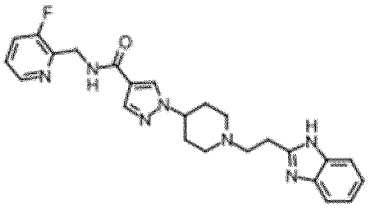
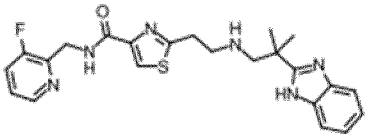
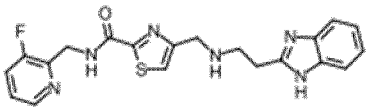
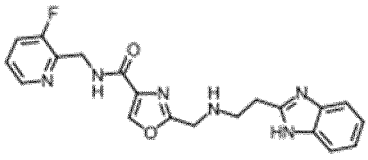
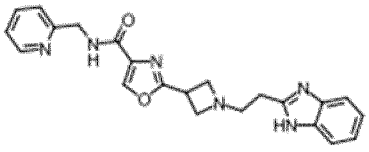
196	
198	
199	
205	
206	
207	

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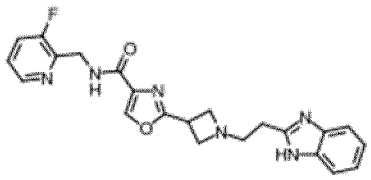
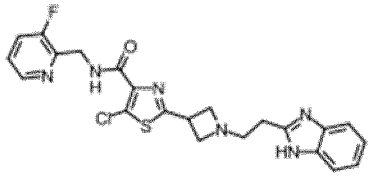
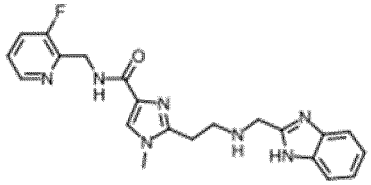
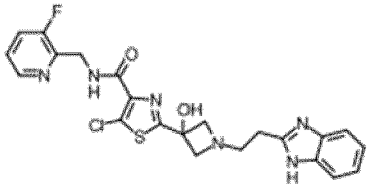
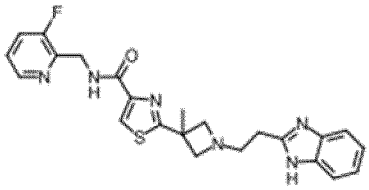
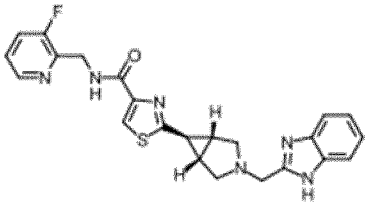
208	
209	
210	
211	
212	
213	

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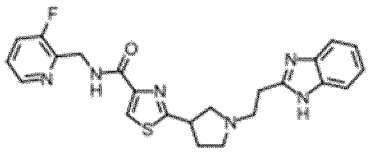
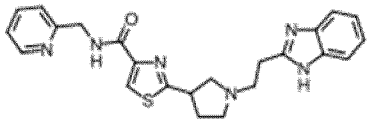
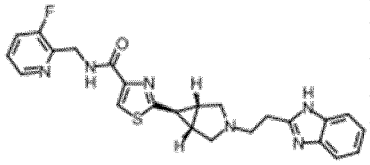
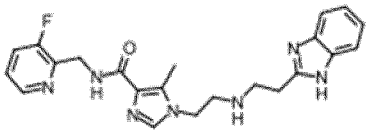
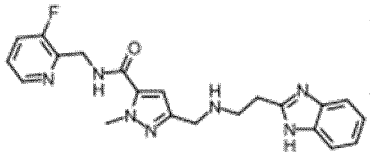
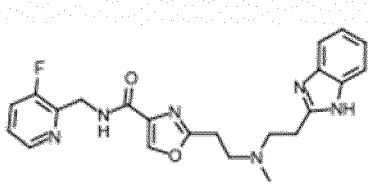
214	
215	
218	
219	
220	
223	

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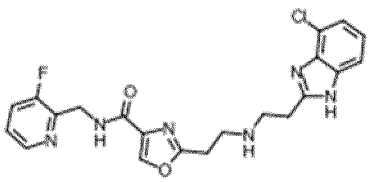
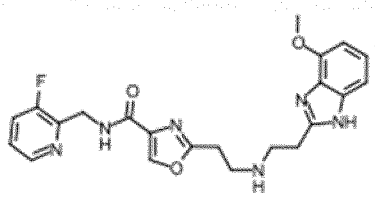
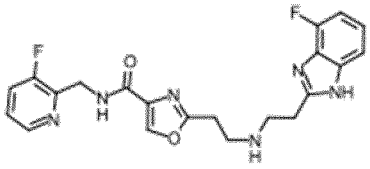
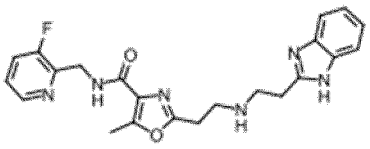
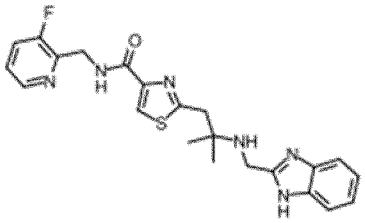
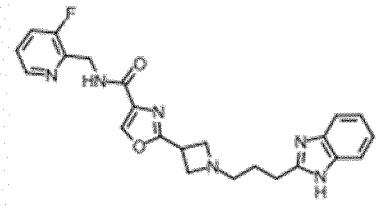
226	
227	
228	
230	
231	
233	

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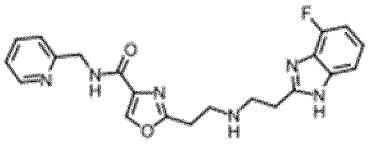
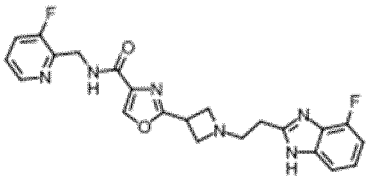
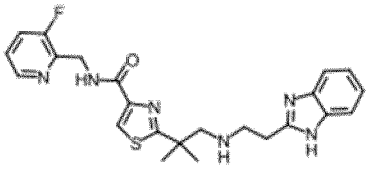
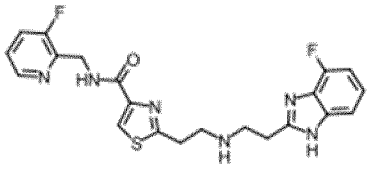
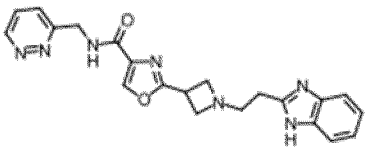
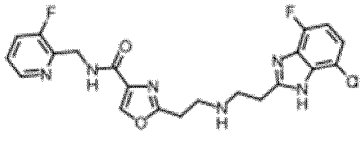
236	
239	
242	
243	
244	
247	

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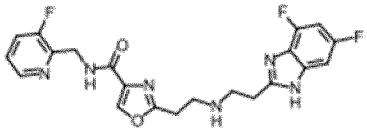
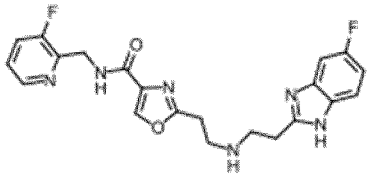
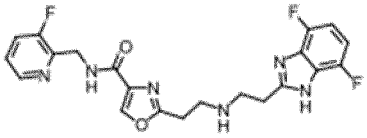
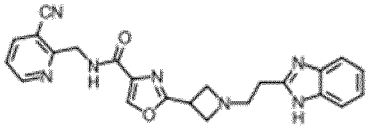
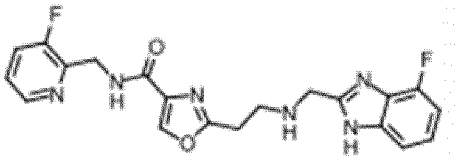
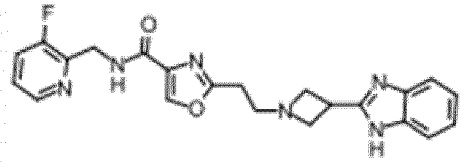
249	
250	
251	
252	
253	
255	

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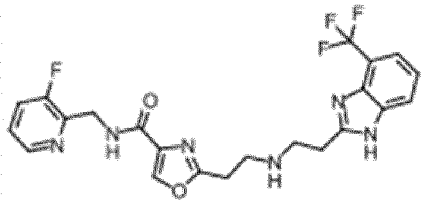
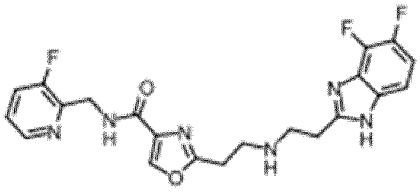
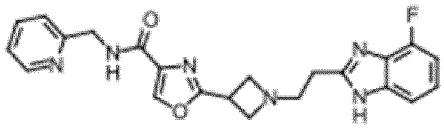
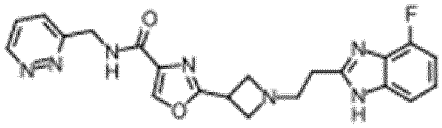
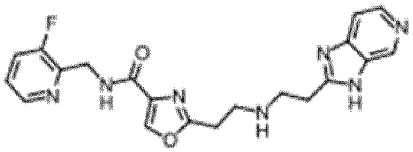
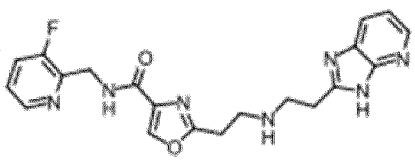
256	
257	
258	
261	
262	
263	

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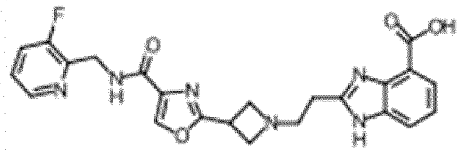
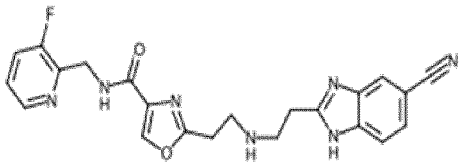
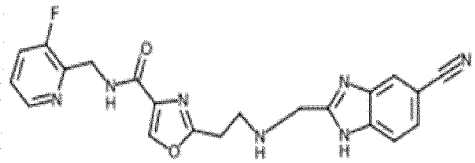
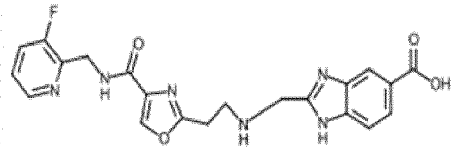
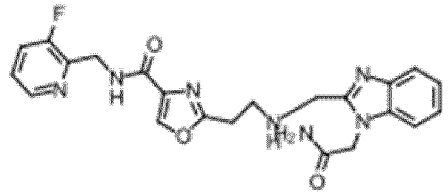
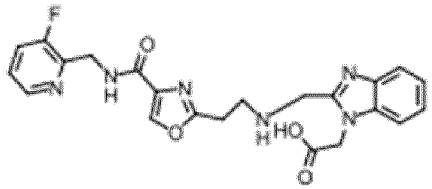
264	
265	
266	
267	
268	
269	

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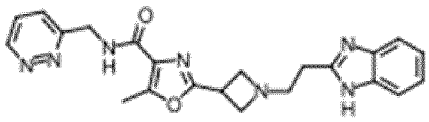
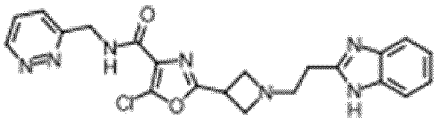
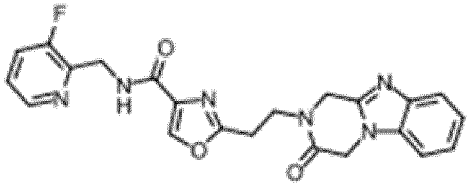
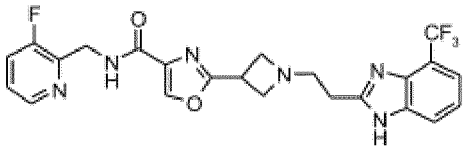
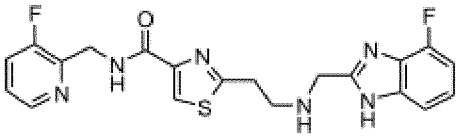
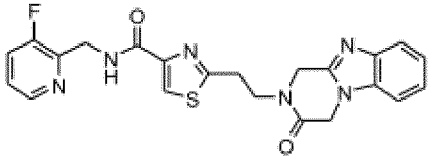
270	
271	
272	
273	
274	
275	

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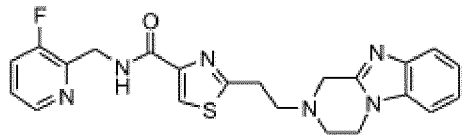
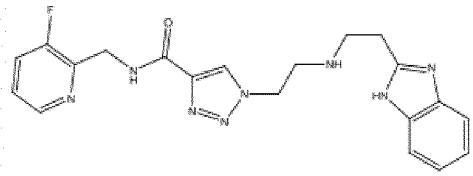
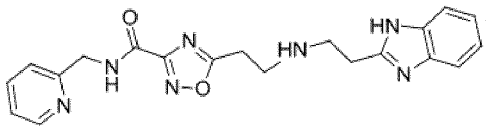
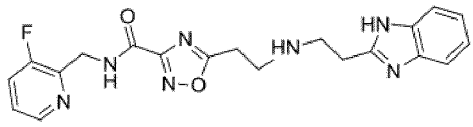
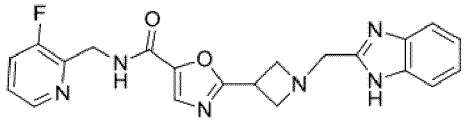
276	
277	
278	
279	
280	

or pharmaceutically acceptable salts thereof.

34. Compounds according to any one of the preceding claims for the use as a medicament.

35. Compounds according to any one of the preceding claims for the use as ferroportin inhibitor.

36. Compounds as defined in any one of the preceding claims for the use in the inhibition of iron transport mediated by ferroportin.

37. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of iron metabolism disorders leading to increased iron levels or increased iron absorption.

38. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of iron overload.

39. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of diseases related to or caused by increased iron levels, increased iron absorption or iron overload.

40. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of diseases associated with ineffective erythropoiesis, such as myelodysplastic syndromes (MDS, myelodysplasia), polycythemia vera and congenital dyserythropoietic anemia.

41. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of diseases caused by reduced levels of hepcidin.

42. Compounds as defined in any one of the preceding claims for the use in an adjunctive therapy by limiting the amount of iron available to pathogenic microorganisms, such as the bacterium Vibrio vulnificus, thereby treating infections caused by said pathogenic microorganisms.

43. Compounds as defined in any one of the preceding claims for the use according to claim 39, wherein the diseases, which are related to or caused by increased iron levels, increases ironabsorption or iron overload are selected from thalassemia, hemoglobinopathy, hemoglobin E disease, hemoglobin H disease, haemochromatosis, hemolytic anemia.

44. Compounds as defined in any one of the preceding claims for the use according to claim 43, wherein the thalassemia includes alpha-thalassemia, beta-thalassemia and delta-thalassemia.

45. Compounds as defined in any one of the preceding claims for the use according to claim 43, wherein the hemolytic anemia is sickle cell anemia or congenital dyserythropoietic anemia.

46. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease by limiting the deposition or increase of iron in tissue or cells.

47. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of formation of radicals, reactive oxygen species (ROS) and oxidative stress.

48. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of cardiac, liver and endocrine damage caused by iron overload.

49. Compounds as defined in any one of the preceding claims for the use in the prophylaxis and/or treatment of inflammation triggered by excess iron.

50. A medicament containing one or more of the compounds as defined in any one of the preceding claims.

51. The medicament according to claim 50 for the use as defined in any one of claims 35 to 49.

52. The medicament according to claim 50 and 51, which further contains one or more pharmaceutical carriers and/or auxiliaries and/or solvents.

53. The medicament according to any one of claims 50 to 52, which further contains at least one additional pharmaceutically active compound.

54. The medicament according to claim 53, wherein the at least one additional pharmaceutically active compound is selected from active compounds for the prophylaxis and treatment of iron overload, thalassemia, or haemochromatosis.

55. The medicament according to claim 53, wherein the at least one additional pharmaceutically active compound is selected from active compounds for the prophylaxis and treatment of neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, and the associated symptoms.

56. The medicament according to any one of claims 50 to 55, which contains at least one additional pharmaceutically active compound, which is an iron-chelating compound.

57. The medicament according to any one of claims 50 to 56, which is in the form of a formulation for oral or parenteral administration.

58. Compounds as defined in any one of the preceding claims for the use in a combination therapy, comprising co-administration of the compounds as defined in any of the preceding claims with at least one additional pharmaceutically active compound.

59. Compounds for the use according to claim 58, wherein the co-administration of the combination therapy is carried out in a fixed dose combination therapy by co-administration of the compounds as defined in any of the preceding claims with at least one additional pharmaceutically active compound in a fixed-dose formulation.

60. Compounds for the use according to claim 58, wherein the co-administration of the combination therapy is carried out in a free dose combination therapy by co-administration of the compounds as defined in any of the preceding claims and the at least one additional pharmaceutically active compound in free doses of the respective compounds, either by simultaneous administration of the individual compounds or by sequential use of the individual compounds distributed over a time period.

61. Compounds for the use according to any one of claims 58 to 60, wherein the combination therapy comprises co-administration of the compounds as defined in any of the preceding claims with one or more

other pharmaceutically active compounds for reducing iron overload, which are selected from Tmprss6-ASO, iron chelators, curcumin, SSP-004184, Deferitrin, deferasirox, deferoxamine and/or deferiprone.

62. Compounds for the use according to any one of claims 58 to 61, wherein the combination therapy comprises co-administration of the compounds as defined in any of the preceding claims with one or more other pharmaceutically active compounds which are selected from antioxidants, such as n-acetyl cysteine; anti-diabetics, such as GLP-1 receptor agonists; antibiotics, such as vancomycin (Van) or tobramycin; drugs for the treatment of malaria; anticancer agents; antifungal drugs; drugs for the treatment of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, comprising dopamine agonists such as Levodopa; anti-viral drugs, such as interferon-α or ribavirin; immunosuppressents, such as cyclosporine A or cyclosporine A derivatives; iron supplements; vitamin supplements; red cell production stimulators; anti-inflammatory biologies; anti-thrombolytics; statins; vasopressors; and inotropic compounds.