N-((HETEROARYLMETHYL)-HETEROARYL-CARBOXAMIDE DERIVATIVES AS PLASMA KALLIKREIN INHIBITORS

This invention relates to enzyme inhibitors that are inhibitors of plasma kallikrein and to pharmaceutical compositions containing and the uses of, such inhibitors.

Background to the Invention

The heterocyclic derivatives of the present invention are inhibitors of plasma kallikrein and have a number of therapeutic applications, particularly in the treatment of retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Plasma kallikrein is a trypsin-like serine protease that can liberate kinins from kininogens (see K. D. Bhoola *et al.*, "Kallikrein-Kinin Cascade", *Encyclopedia of Respiratory Medicine*, p483-493; J. W. Bryant *et al.*, "Human plasma kallikrein-kinin system: physiological and biochemical parameters" *Cardiovascular and haematological agents in medicinal chemistry*, 7, p234-250, 2009; K. D. Bhoola *et al.*, *Pharmacological Rev.*, 1992, **44**, 1; and D. J. Campbell, "Towards understanding the kallikrein-kinin system: insights from the measurement of kinin peptides", *Brazilian Journal of Medical and Biological Research* 2000, **33**, 665-677). It is an essential member of the intrinsic blood coagulation cascade although its role in this cascade does not involve the release of bradykinin or enzymatic cleavage. Plasma prekallikrein is encoded by a single gene and synthesized in the liver. It is secreted by hepatocytes as an inactive plasma prekallikrein that circulates in plasma as a heterodimer complex bound to high molecular weight kininogen which is activated to give the active plasma kallikrein. Kinins are potent mediators of inflammation that act through G protein-coupled receptors and antagonists of kinins (such as bradykinin antagonists) have previously been investigated as potential therapeutic agents for the treatment of a number of disorders (F. Marceau and D. Regoli, Nature Rev., Drug Discovery, 2004, **3**, 845-852).

Plasma kallikrein is thought to play a role in a number of inflammatory disorders. The major inhibitor of plasma kallikrein is the serpin C1 esterase inhibitor. Patients who present with a genetic deficiency in C1 esterase inhibitor suffer from hereditary angioedema (HAE) which results in intermittent swelling of face, hands, throat, gastro-intestinal tract and genitals. Blisters formed during acute episodes contain high levels of plasma kallikrein which cleaves high molecular weight kininogen liberating bradykinin leading to increased vascular permeability. Treatment with a large protein plasma kallikrein inhibitor has been shown to effectively treat HAE by preventing the release of bradykinin which causes increased vascular permeability (A. Lehmann "Ecallantide (DX-88), a plasma kallikrein inhibitor for the treatment of hereditary angioedema and the prevention of blood loss in on-pump cardiothoracic surgery" *Expert Opin. Biol. Ther.* 8, p1187-99).

The plasma kallikrein-kinin system is abnormally abundant in patients with advanced diabetic macular edema. It has been recently published that plasma kallikrein contributes to retinal vascular dysfunctions in diabetic rats (A. Clermont *et al*. "Plasma kallikrein mediates retinal vascular dysfunction and induces retinal thickening in diabetic rats" *Diabetes*, 2011, 60, p1590-98). Furthermore, administration of the plasma kallikrein inhibitor ASP-440 ameliorated both retinal vascular permeability and retinal blood flow abnormalities in diabetic rats. Therefore a plasma kallikrein inhibitor should have utility as a treatment to reduce retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Other complications of diabetes such as cerebral haemorrhage, nephropathy, cardiomyopathy and neuropathy, all of which have associations with plasma kallikrein may also be considered as targets for a plasma kallikrein inhibitor.

Synthetic and small molecule plasma kallikrein inhibitors have been described previously, for example by Garrett et al. ("Peptide aldehyde...." *J. Peptide Res*. 52, p62-71 (1998)), T. Griesbacher *et al*. ("Involvement of tissue kallikrein but not plasma kallikrein in the development of symptoms mediated by endogenous kinins in acute pancreatitis in rats" *British Journal of Pharmacology* 137, p692-700 (2002)), Evans ("Selective dipeptide inhibitors of kallikrein" WO03/076458), Szelke *et al*. ("Kininogenase inhibitors" WO92/04371), D. M. Evans *et al*. (*Immunolpharmacology*, 32, p115-116 (1996)), Szelke *et al*. ("Kininogen inhibitors" WO95/07921), Antonsson *et al*. ("New peptides derivatives" WO94/29335), J. Corte et al. ("Six membered heterocycles useful as serine protease inhibitors" WO2005/123680), J. Stürzbecher *et al*. (*Brazilian J. Med. Biol. Res* 27, p1929-34 (1994)), Kettner *et al*. (US 5,187,157), N. Teno *et al*. (*Chem. Pharm. Bull*. 41, p1079-1090 (1993)), W. B. Young *et al*. ("Small molecule inhibitors of plasma kallikrein" *Bioorg. Med. Chem. Letts.* 16, p2034-2036 (2006)), Okada *et al*. ("Development of potent and selective plasmin and plasma kallikrein inhibitors and studies on the structure-activity relationship" *Chem. Pharm. Bull.* 48, p1964-72 (2000)), Steinmetzer *et al*. ("Trypsin-like serine protease inhibitors and their preparation and use" WO08/049595), Zhang *et al*. ("Discovery of highly potent small molecule kallikrein inhibitors" *Medicinal Chemistry 2*, p545-553 (2006)), Sinha *et al*. ("Inhibitors of plasma kallikrein" WO08/016883), Shigenaga et al. ("Plasma Kallikrein Inhibitors" WO2011/118672), and Kolte et al. ("Biochemical characterization of a novel high-affinity and specific kallikrein inhibitor", British Journal of Pharmacology (2011), 162(7), 1639-1649). Also, Steinmetzer *et al*. ("Serine protease inhibitors" WO2012/004678) describes cyclized peptide analogs which are inhibitors of human plasmin and plasma kallikrein.

To date, no small molecule synthetic plasma kallikrein inhibitor has been approved for medical use. The molecules described in the known art suffer from limitations such as poor selectivity over related enzymes such as KLK1, thrombin and other serine proteases, and poor oral availability. The large protein plasma kallikrein inhibitors present risks of anaphylactic reactions, as has been reported for Ecallantide. Thus there remains a need for compounds that selectively inhibit plasma kallikrein, that do not induce anaphylaxis and that are orally available. Furthermore, the vast majority of molecules in the known art feature a highly polar and ionisable guanidine or amidine functionality. It is well known that such functionalities may be limiting to gut permeability and therefore to oral availability. For example, it has been reported by *Tamie J. Chilcote and Sukanto Sinha* ("ASP-634: An Oral Drug Candidate for Diabetic MacularEdema", ARVO 2012 May 6th – May 9th, 2012, Fort Lauderdale, Florida, Presentation 2240) that ASP-440, a benzamidine, suffers from poor oral availability. It is further reported that absorption may be improved by creating a prodrug such as ASP-634. However, it is well known that prodrugs can suffer from several drawbacks, for example, poor chemical stability and potential toxicity from the inert carrier or from unexpected metabolites. In another report, indole amides are claimed as compounds that might overcome problems associated with drugs possessing poor or inadequate ADME-tox and physicochemical properties although no inhibition against plasma kallikrein is presented or claimed (Griffioen et al, "Indole amide derivatives and related compounds for use in the treatment of neurodegenerative diseases", WO2010, 142801).

BioCryst Pharmaceuticals Inc. have reported the discovery of the orally available plasma kallikrein inhibitor BCX4161 ("BCX4161, An Oral Kallikrein Inhibitor: Safety and Pharmacokinetic Results Of a Phase 1 Study In Healthy Volunteers", Journal of Allergy and Clinical Immunology, Volume 133, Issue 2, Supplement, February 2014, page AB39 and "A Simple, Sensitive and Selective Fluorogenic Assay to Monitor Plasma Kallikrein Inhibitory Activity of BCX4161 in Activated Plasma", Journal of Allergy and Clinical Immunology, Volume 133, Issue 2, Supplement February 2014, page AB40). However, human doses are relatively large, currently being tested in proof of concept studies at doses of 400 mg three times daily.

There are only few reports of plasma kallikrein inhibitors that do not feature guanidine or amidine functionalities. One example is Brandl *et al.* ("N-((6-amino-pyridin-3-yl)methyl)-heteroaryl-carboxamides as inhibitors of plasma kallikrein" WO2012/017020), which describes compounds that feature an amino-pyridine functionality. Oral efficacy in a rat model is demonstrated at relatively high doses of 30 mg/kg and 100 mg/kg but the pharmacokinetic profile is not reported. Thus it is not yet known whether such compounds will provide sufficient oral availability or efficacy for progression to the clinic. Other examples are Brandl *et al.* ("Aminopyridine derivatives as plasma kallikrein inhibitors" WO2013/111107)

and Flohr *et al.* ("5-membered heteroarylcarboxamide derivatives as plasma kallikrein inhibitors" WO2013/111108). However, neither of these documents report any *in vivo* data and therefore it is not yet known whether such compounds will provide sufficient oral availability or efficacy for progression to the clinic. Another example is Allen *et al.* "Benzylamine derivatives" WO2014/108679.

Therefore there remains a need to develop new plasma kallikrein inhibitors that will have utility to treat a wide range of disorders, in particular to reduce retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema. Preferred compounds will possess a good pharmacokinetic profile and in particular will be suitable as drugs for oral delivery.

Summary of the Invention

The present invention relates to a series of heterocyclic derivatives that are inhibitors of plasma kallikrein. These compounds demonstrate good selectivity for plasma kallikrein and are potentially useful in the treatment of impaired visual acuity, diabetic retinopathy, macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery. The invention further relates to pharmaceutical compositions of the inhibitors, to the use of the compositions as therapeutic agents, and to methods of treatment using these compositions.

The present invention provides compounds closely related to or falling within the scope of, but not specifically disclosed in, our co-pending application PCT/ GB2014/051592.

In a first aspect, the present invention provides compound selected from the group consisting of:

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride;

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide;

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

1-[2-(3,3-difluoro-pyrrolidin-1-yl)-pyrimidin-5-ylmethyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

3-(2-methoxy-ethyl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

3-ethoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-{[2-(pyrazol-1-ylmethyl)pyrimidin-5-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({3-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({2-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

3-cyclopropyl-1-(2-fluoro-4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-cyclopropyl-1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyridin-4-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-amino-N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyridin-4-yl]methyl}pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-3-cyano-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-[(6-ethoxy-5-fluoropyridin-3-yl)methyl]-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-({6-[isopropyl(methyl)amino]pyridin-3-yl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-amino-1-{[6-(benzyloxy)pyridin-3-yl]methyl}-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1H-pyrazole-4-carboxamide

3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(phenoxymethyl)pyridin-3-yl]methyl}-1H-pyrazole-4-carboxamide

3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-[(6-phenoxypyridin-3-yl)methyl]-1H-pyrazole-4-carboxamide

3-methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-[(2-methylquinolin-6-yl)methyl]pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-[(7-chloroquinolin-3-yl)methyl]-3-(methoxymethyl)pyrazole-4-carboxamide;

3-amino-N-[(3-chloro-1H-indol-5-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-amino-N-[(3-chloro-1H-indazol-5-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-({3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-cyclopropyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-({3-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-({4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({1-methylpyrazolo[3,4-b]pyridin-5-yl}methyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

3-amino-N-[(6-chloroisoquinolin-3-yl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

2-methyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-2-methyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-2-methyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

3-amino-N-[(3-chloro-1H-indazol-5-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-({3-chloro-1H-pyrazolo[3,4-b]pyridin-5-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-amino-N-[(7-chloroquinolin-2-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is a compound selected from the group consisting of:

N-((1-aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride;

N-((1-aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide;

3-cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

1-[2-(3,3-difluoro-pyrrolidin-1-yl)-pyrimidin-5-ylmethyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

3-(2-methoxy-ethyl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

3-ethoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({3-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({2-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

3-cyclopropyl-1-(2-fluoro-4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-cyclopropyl-1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-amino-N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyridin-4-yl]methyl}pyrazole-4-carboxamide;

1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-({6-[isopropyl(methyl)amino]pyridin-3-yl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

3-methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-[(2-methylquinolin-6-yl)methyl]pyrazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(6-chloroisoquinolin-3-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide;

2-methyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is a compound selected from the group consisting of:

N-((1-aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride;

N-((1-aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide;

3-methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

3-ethoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({3-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({2-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

3-cyclopropyl-1-(2-fluoro-4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-cyclopropyl-1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is a compound selected from the group consisting of:

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[2-(3,3-difluoro-pyrrolidin-1-yl)-pyrimidin-5-ylmethyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide;

and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is:

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide, and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is:

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide, and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is:

1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide, and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is:

N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide, and pharmaceutically acceptable salts and solvates thereof.

In a further aspect, provided is:

1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide, and pharmaceutically acceptable salts and solvates thereof.

In another aspect the present invention provides a prodrug of a compound of the invention, or a pharmaceutically acceptable salt thereof.

In yet another aspect the present invention provides an N-oxide of a compound of the invention, or a prodrug or pharmaceutically acceptable salt thereof.

It will be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms.

Therapeutic Applications

As previously mentioned, the compounds of the present invention are potent and selective inhibitors of plasma kallikrein. They are therefore useful in the treatment of disease conditions for which over-activity of plasma kallikrein is a causative factor.

Accordingly, the present invention provides a compound of the invention for use in medicine.

The present invention also provides for the use of a compound of the invention in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

The present invention also provides a compound of the invention for use in the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated.

The present invention also provides a method of treatment of a disease or condition in which plasma kallikrein activity is implicated comprising administration to a subject in need thereof a therapeutically effective amount of a compound of the invention.

In one aspect, the disease or condition in which plasma kallikrein activity is implicated is selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

In a preferred aspect, the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

Combination Therapy

The compounds of the present invention may be administered in combination with other therapeutic agents. Suitable combination therapies include a compound of the invention combined with one or more agents selected from agents that inhibit platelet-derived growth factor (PDGF), endothelial growth factor (VEGF), integrin alpha5beta1, steroids, other agents that inhibit plasma kallikrein and other inhibitors of inflammation. Specific examples of therapeutic agents that may be combined with the compounds of the present invention include those disclosed in EP2281885A and by S. Patel in *Retina*, 2009 Jun;29(6 Suppl):S45-8.

When combination therapy is employed, the compounds of the present invention and said combination agents may exist in the same or different pharmaceutical compositions, and may be administered separately, sequentially or simultaneously.

In another aspect, the compounds of the present invention may be administered in combination with laser treatment of the retina. The combination of laser therapy with intravitreal injection of an inhibitor of VEGF for the treatment of diabetic macular edema is known (Elman M, Aiello L, Beck R, et al. "Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema" .Ophthalmology. 27 April 2010).

Definitions

"Pharmaceutically acceptable salt" means a physiologically or toxicologically tolerable salt and includes, when appropriate, pharmaceutically acceptable base addition salts and pharmaceutically acceptable acid addition salts. For example (i) where a compound of the invention contains one or more acidic groups, for example carboxy groups, pharmaceutically acceptable base addition salts that can be formed include sodium, potassium, calcium, magnesium and ammonium salts, or salts with organic amines, such as, diethylamine, *N*-methyl-glucamine, diethanolamine or amino acids (e.g. lysine) and the like; (ii) where a compound of the invention contains a basic group, such as an amino group, pharmaceutically acceptable acid addition salts that can be formed include hydrochlorides, hydrobromides, sulfates, phosphates, acetates, citrates, lactates, tartrates, mesylates, succinates, oxalates, phosphates, esylates, tosylates, benzenesulfonates, naphthalenedisulphonates, maleates, adipates, fumarates, hippurates, camphorates, xinafoates, p-acetamidobenzoates, dihydroxybenzoates, hydroxynaphthoates, succinates, ascorbates, oleates, bisulfates and the like.

Hemisalts of acids and bases can also be formed, for example, hemisulfate and hemicalcium salts.

For a review of suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

"Prodrug" refers to a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of the invention. Suitable groups for forming prodrugs are described in 'The Practice of Medicinal Chemistry, 2nd Ed. pp561-585 (2003) and in F. J. Leinweber, *Drug Metab. Res.*, 1987, **18**, 379.

The compounds of the invention can exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when the solvent is water.

Where compounds of the invention exist in one or more geometrical, optical, enantiomeric, diastereomeric and tautomeric forms, including but not limited to *cis*- and *trans*-forms, *E*- and *Z*-forms, *R*-, *S*- and *meso*-forms, keto-, and enol-forms. Unless otherwise stated a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Where

appropriate such isomers can be separated from their mixtures by the application or adaptation of known methods (e.g. chromatographic techniques and recrystallisation techniques). Where appropriate such isomers can be prepared by the application or adaptation of known methods (e.g. asymmetric synthesis).

In the context of the present invention, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

General Methods

The compounds of formula (I) should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, *etc.*, in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication. They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention which may impart either a functional (i.e., drug release rate controlling) and/or a non-functional (i.e., processing aid or diluent) characteristic to the formulations. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Compounds of the invention intended for pharmaceutical use may be administered as a solid or liquid, such as a tablet, capsule or solution. Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient.

For the treatment of conditions such as retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema, the compounds of the invention may be administered in a form suitable for injection into the ocular region of a patient, in particular, in a form suitable for intra-vitreal injection. It is envisaged that formulations suitable for such use will take the form of sterile

solutions of a compound of the invention in a suitable aqueous vehicle. The compositions may be administered to the patient under the supervision of the attending physician.

The compounds of the invention may also be administered directly into the blood stream, into subcutaneous tissue, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous or oily solutions. Where the solution is aqueous, excipients such as sugars (including but not restricted to glucose, manitol, sorbitol, etc.), salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

Parenteral formulations may include implants derived from degradable polymers such as polyesters (i.e., polylactic acid, polylactide, polylactide-co-glycolide, polycapro-lactone, polyhydroxybutyrate), polyorthoesters and polyanhydrides. These formulations may be administered *via* surgical incision into the subcutaneous tissue, muscular tissue or directly into specific organs.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of co-solvents and/or solubility-enhancing agents such as surfactants, micelle structures and cyclodextrins.

In one embodiment, the compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid plugs, solid microparticulates, semi-solid and liquid (including multiple phases or dispersed systems) such as tablets; soft or hard capsules containing

multi- or nano-particulates, liquids, emulsions or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Formulations suitable for oral administration may also be designed to deliver the compounds of the invention in an immediate release manner or in a rate-sustaining manner, wherein the release profile can be delayed, pulsed, controlled, sustained, or delayed and sustained or modified in such a manner which optimises the therapeutic efficacy of the said compounds. Means to deliver compounds in a rate-sustaining manner are known in the art and include slow release polymers that can be formulated with the said compounds to control their release.

Examples of rate-sustaining polymers include degradable and non-degradable polymers that can be used to release the said compounds by diffusion or a combination of diffusion and polymer erosion. Examples of rate-sustaining polymers include hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, xanthum gum, polymethacrylates, polyethylene oxide and polyethylene glycol.

Liquid (including multiple phases and dispersed systems) formulations include emulsions, solutions, syrups and elixirs. Such formulations may be presented as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Liang and Chen, Expert Opinion in Therapeutic Patents, 2001, **11 (6)**, 981-986.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.01 mg and 1000 mg, or between 0.1 mg and 250 mg, or between 1 mg and 50 mg depending, of course, on the mode of administration.

The total dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having

a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Examples

In these examples the following abbreviations and definitions are used:

aq	Aqueous solution
CDI	Carbonyl diimidazole
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	Ethyl Acetate
HATU	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V)
HBTU	O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluorophosphate
hrs	Hours
HOBt	Hydroxybenzotriazole
LCMS	Liquid chromatography mass spectrometry
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
MS	Mass spectrum
NMR	Nuclear magnetic resonance spectrum – NMR spectra were recorded at a frequency of 400MHz unless otherwise indicated
Pet. Ether	Petroleum ether fraction boiling at 60-80°C
Ph	Phenyl
SWFI	Sterile water for injection
rt	room temperature
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

^{1}H NMR spectra were recorded on a Bruker (400MHz) spectrometer with reference to deuterium solvent and at rt.

Molecular ions were obtained using LCMS which was carried out using a Chromolith Speedrod RP-18e column, 50 x 4.6 mm, with a linear gradient 10% to 90% 0.1% HCO_2H/MeCN into 0.1% HCO_2H/H_2O over 13 min, flow rate 1.5 mL/min, or using Agilent, X-Select, acidic, 5-95% MeCN/water over 4 min. Data was collected using a Thermofinnigan Surveyor MSQ mass spectrometer with electospray ionisation in conjunction with a Thermofinnigan Surveyor LC system.

Where products were purified by flash chromatography, 'silica' refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Merck silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Reverse phase preparative HPLC purifications were carried out using a Waters 2525 binary gradient pumping system at flow rates of typically 20 mL/min using a Waters 2996 photodiode array detector. Automated FC refers to a Biotage purification system with UV directed sample collection using either SNAP ultra or ZIP Sphere cartridges.

All solvents and commercial reagents were used as received.

Chemical names were generated using automated software such as the Autonom software provided as part of the ISIS Draw package from MDL Information Systems or the Chemaxon software provided as a component of MarvinSketch or as a component of the IDBS E-WorkBook.

General Methods:

Alkylation

Performed with K_2CO_3 unless otherwise stated in either DMF, MeCN or acetone at between rt and 80 °C.

Saponification

Performed using either $LiOH.H_2O$ in THF/water or NaOH in methanol or ethanol at reflux.

Amide formation

Method A: To the carboxylic acid component (1 eq) in DCM (and DMF if required) at 0 °C was added HOBt (1.2 eq) and EDC (1.4 eq). The reaction mixture was stirred for 10 min then Et_3N (5 eq) and the amine component (1 eq) were added and the reaction stirred at rt. The reaction was diluted with $CHCl_3$

(50 mL) and washed with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* and then purified by automated FC.

Method B: The carboxylic acid component (1 eq), the amine component (1 eq) and HATU (1.1 eq) were suspended in anhydrous DCM (and DMF if required) and Et_3N (6 eq) added. The reaction mixture was stirred at rt. The solvent was removed under vacuum. The residue was purified by automated FC.

Method C: To the carboxylic acid component (1 eq) in DCM (and DMF if required) was added HBTU (1.2 eq), Et_3N (5 eq) and the amine component (1 eq) and the reaction stirred at rt. The reaction was diluted with $CHCl_3$ (50 mL) and washed with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated and then purified by automated FC.

Intermediates ("B" ring):

A1. 2-((*E*)-2-Dimethylamino-vinyl)-terephthalonitrile ester

Methylterephthalonitrile (1.42g, 9.99mmol) and Bredereck's reagent (3.48g, 19.98mmol) were dissolved in DMF (15mL). The reaction mixture was heated at 75 °C under nitrogen for 72hrs after which time the solvent was removed *in vacuo*. Trituration with Pet. Ether gave a bright yellow solid identified as 2-((E)-2-dimethylamino-vinyl)-terephthalonitrile ester (1.88g, 0.95mmol, 95% yield).

^{1}H NMR (CD_3OD) δ: 3.20 (6H, s), 5.34 (1H, d, J = 13.4Hz), 7.21 (1H, dd, J = 8.0Hz, 1.4Hz), 7.9 (1H, d, 13.4Hz), 7.61 (1H, d, J = 8.0Hz), 7.94 (1H, d, J =1.2Hz)

A2. 1-Amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile

2-((*E*)-2-Dimethylamino-vinyl)-terephthalonitrile ester (1.85g, 9.38mmol) was dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (5mL) and 2,4-dimethoxybenzylamine (2.35g, 14.07mmol) was added. The reaction mixture was heated at 75 °C under nitrogen. After 3hrs the reaction mixture was cooled and diethyl ether/ Pet. Ether (15:85) was added. The yellow solid was filtered off, dried *in vacuo,* and identified as 1-amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile (2.65g, 8.38mmol, 89% yield)

$[MH]^+$ = 320

^{1}H NMR (CD_3OD) δ: 3.85 (3H, s), 3.92 (3H, s), 5.02 (2H, s), 6.39 (1H, d, J = 7.4Hz), 6.57 (1H, dd, J = 8.4Hz, 2.4Hz), 6.66 (1H, d, J = 2.4Hz), 7.18 (1H, d, J = 8.4Hz), 7.24(1H, d, J = 7.4Hz), 7.72 (1H, dd, J = 8.5Hz, 1.4Hz), 7.93 (1H,s), 8.45 (1H, d, J = 8.5 Hz)

A3. 1-Amino-isoquinoline-6-carbonitrile

1-Amino-2-(2,4-dimethoxy-benzyl)-1,2-dihydro-isoquinoline-6-carbonitrile (1.6g, 5.0mmol) was dissolved in anisole (17mL) and trifluoroacetic acid (20mL). The reaction mixture was heated at 105°C under nitrogen for 12hrs after which time the reaction mixture was cooled, diethyl ether/Pet. Ether (3:7) was added, the resultant solid was filtered off, dried *in vacuo* and identified as 1-amino-isoquinoline-6-carbonitrile (770mg, 4.54mmol, 91%).

$[MH]^+ = 170$.

^1H NMR (CD_3OD) δ: 7.23 - 7.25 (1H, d, J = 6.9Hz), 7.65 (1H, d, J = 6.8Hz), 8.11 (1H, dd, J = 8.7Hz, 1.6Hz), 8.33 (1H, s), 8.45 (1H, d, J = 8.7Hz).

A4. (1-Amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester

1-Amino-isoquinoline-6-carbonitrile (200mg, 1.18mmol) was dissolved in methanol (20mL). This solution was cooled to 0°C. Nickel (II) chloride hexahydrate (28mg, 0.12mmol) and di-tertbutyl dicarbonate (516g, 2.36mmol) were added followed by sodium borohydride (313g, 8.22mmol) portionwise. The reaction mixture was stirred at 0 °C to room temp for 3 days. The MeOH was removed by evaporation. The residue was dissolved in $CHCl_3$ (70mL), washed with sat $NaHCO_3$ (30 mL), water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil identified as (1-amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester (110mg, 0.4mmol, 34% yield).

$[MH]^+ = 274$.

A5. 6-Aminomethyl-isoquinolin-1-ylamine hydrochloride

(1-Amino-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester (110mg, 0.40mmol) was dissolved in 4M HCl in dioxane (40mL). After 18 hrs at rt the solvent was removed *in vacuo* to give a pale brown solid identified as 6-aminomethyl-isoquinolin-1-ylamine hydrochloride (67mg, 0.39mmol, 96% yield).

$[MH]^+ = 174$.

B1. 3-Chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile

5-Cyano-7-azaindole (1.0 g, 6.99 mmol) was dissolved in dry DMF (5 mL). To this solution was added N-chlorosuccinimide (1.12 g, 8.38 mmol) at 40 °C. The reaction mixture was stirred at 55 °C for 5 hrs and cooled to rt and left stirring for 2 days. The mixture was diluted with water (40 mL) and stirred for a further 18 hrs. The solid was filtered off and dried to give 3-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (1.1 g, 89% yield).

$[MH]^+ = 178.2$

B2. (3-Chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester

3-Chloro-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (1.0 g, 5.63 mmol) was dissolved in methanol (150 mL). This solution was cooled to 0 °C. Nickel (II) chloride hexahydrate (134 mg, 0.56 mmol) and di-tertbutyl dicarbonate (2.46 g, 11.3 mmol) were added followed by sodium borohydride (1.49 g, 39.4 mmol) portionwise. The reaction mixture was allowed to warm to rt and stirred for 18 hrs. The MeOH was removed *in vacuo*. The residue was dissolved in $CHCl_3$ (70 mL), washed with sat. aq. $NaHCO_3$ (30 mL), water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3% MeOH, 97% $CHCl_3$ to give (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester (870 mg, 55% yield).

$[MH]^+$ = 282.2

B3. C-(3-Chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine

(3-Chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-carbamic acid tert-butyl ester (870 mg, 3.09 mmol) was dissolved in 4M HCl in dioxan (150 mL). After one hour at rt the solvent was removed *in vacuo* to give C-(3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl)-methylamine (650 mg, 97% yield).

C1. 4-Bromo-5-fluoro-2-methylbenzamide

To dry THF (25 mL, 305 mmol) at rt was added 4-bromo-5-fluoro-2-methylbenzoic acid (5.43 g, 23.30 mmol) followed by CDI (4.91 g, 30.3 mmol) which was added portionwise at rt. The solution was left to stir at rt for 3 hrs. Ammonium hydroxide (10 mL, 90 mmol) was then added. The resulting reaction mixture was left to stir at rt overnight. The solvent was then concentrated under reduced pressure at 40 °C to 15 mL and the resulting solution was slowly quenched into water (100 mL). An off white solid precipitated and was filtered under reduced pressure, washed with water (50 mL) and isohexanes. The product was dried in a vacuum oven to afford 4-bromo-5-fluoro-2-methylbenzamide (4.92 g, 86 % yield) used directly in the next step without purification.

$[MH]^+$ = 232.0/234.2

C2. (*E*)-4-Bromo-N-((dimethylamino)methylene)-5-fluoro-2-methylbenzamide

In dry THF (30 mL, 366 mmol) was dissolved 4-bromo-5-fluoro-2-methylbenzamide (4.92 g, 21.20 mmol), to which 1,1-dimethoxy-N,N-dimethylmethanamine (3.19 mL, 23.32 mmol) were added. The reaction was heated at 60 °C over two nights. The reaction mixture was evaporated under reduced pressure to give (*E*)-4-bromo-N-((dimethylamino)methylene)-5-fluoro-2-methylbenzamide (6.0 g, 97% yield) identified as the desired product.

$[MH]^+$ = 287/289

C3. 6-Bromo-7-fluoro-2H-isoquinolin-1-one

(*E*)-4-Bromo-N-((dimethylamino)methylene)-5-fluoro-2-methylbenzamide (6.0 g, 20.90 mmol) was dissolved in dry THF (30 mL, 366 mmol) to which potassium tert-butoxide (2.66 g, 22.99 mmol) was added at rt. The solution was warmed to 60 °C for 3 days. The reaction mixture was cooled and then quenched into 1M citric acid (200 mL), a solid precipitated and was filtered under reduced pressure, washed with water and dried in a vacuum oven at 40 °C for 3 hrs. Flash column chromatography on silica eluting with ethyl acetate-isohexane, in gradient steps up to 60% ethyl acetate gave 6-bromo-7-fluoro-2H-isoquinolin-1-one (560 mg, 10.2% yield).

$[MH]^+$ = 242/244

C4. 6-Bromo-1-chloro-7-fluoro-isoquinoline

The following typical chlorination procedure was used

To dry toluene (typically 13 mL per gram of starting material) was added the appropriate pyridinone starting material (1 eq) and diisopropylaime (3 eq) followed by neat phosphoryl trichloride (3 eq). The suspension was heated to 130 °C overnight. The reaction mixture was allowed to cool to rt and then quenched into water and then further diluted with water. The mixture was extracted with EtOAc, the combined organics were washed with sodium carbonate solution, followed by brine, dried over magnesium sulphate, filtered and evaporated *in vacuo* at 45 °C to dryness. The crude material was purified by trituration or flash column chromatography.

Following the typical chlorination procedure, 6-bromo-7-fluoro-2H-isoquinolin-1-one (0.560 g, 2.129 mmol) was converted to 6-bromo-1-chloro-7-fluoro-isoquinoline (460 mg, 82 % yield).

$[MH]^+$ = 259.8/261.8/263.8

C5. 6-bromo-7-fluoroisoquinolin-1-amine

The following typical amination procedure was used

A mixture of the appropriate chloroisoquinoline (1 eq), ammonium acetate (15 eq) and phenol (15 eq) were heated to 140 °C overnight. After cooling, the reaction mixture was partitioned between 2N NaOH and DCM. The organic layer was collected and the aqueous extracted with further DCM. The organics were phase separated using a phase separating cartridge and concentrated *in vacuo.* The crude material was purified using flash column chromatography eluting with 1% ammonia in methanol/DCM.

6-Bromo-1-chloro-7-fluoroisoquinoline (460 mg, 1.78 mmol) was converted using the typical amination procedure to 6-bromo-7-fluoroisoquinolin-1-amine (23.8 mg, 5.5% yield).

$[MH]^+$ = 240.8/242.8

C6. 1-amino-7-fluoroisoquinoline-6-carbonitrile

The following typical cyanation procedure was used

To a stirred solution of dicyanozinc (1 eq) and the appropriate arylbromide (1 eq) in DMF was added $Pd(Ph_3P)_4$ (0.1 eq). The reaction was heated to 100 °C overnight. The reaction was quenched into ice-water (30 mL), the resulting solid filtered, washed with water and dried under reduced pressure. The crude material was purified by SXC cartridge eluting with neat methanol (150 mL) followed by 1% ammonia/methanol (250 mL).

6-Bromo-7-fluoroisoquinolin-1-amine (23.8 mg, 0.099 mmol) was converted using the typical cyanation procedure to 1-amino-7-fluoroisoquinoline-6-carbonitrile (13.3 mg, 64.8 % yield).

$[MH]^+ = 188$

C7. tert-butyl ((1-amino-7-fluoroisoquinolin-6-yl)methyl)carbamate

The following typical nitrile reduction procedure was used

To dry methanol was added the appropriate aryl nitrile (1 eq) followed by nickel chloride hexahydrate (0.1 eq) and di-tert-butyl dicarbonate (2 eq). The mixture was cooled in an ice-salt bath to -5 °C and sodium borohydride (7 eq) was added portionwise maintaining the reaction temperature at approximately 0 °C. The reaction was left stirring at 0 °C and slowly allowed to warm to rt overnight. The solvent was removed *in vacuo* at 40 °C. The residue was taken up with chloroform (30 mL) and washed with sodium hydrogen carbonate (15 mL). The crude material was purified by flash column chromatography eluting with (1% ammonia-methanol)-DCM.

Following the typical nitrile reduction procedure 1-amino-7-fluoroisoquinoline-6-carbonitrile (13 mg, 0.063 mmol) was converted to tert-butyl ((1-amino-7-fluoroisoquinolin-6-yl)methyl)carbamate (12 mg, 64.6% yield).

$[MH]^+ = 292$

C8. 6-(Aminomethyl)-7-fluoroisoquinolin-1-amine dihydrochloride

To a flask containing tert-butyl ((1-amino-7-fluoroisoquinolin-6-yl)methyl)carbamate (12 mg, 0.040 mmol) was added dry hydrochloric acid (6M in 2-propanol) (47.1 µl, 0.283 mmol). The reaction was stirred at rt overnight. Solvent was removed under reduced pressure to give a dark yellow oil which was tritutrated with ether to give 6-(aminomethyl)-7-fluoroisoquinolin-1-amine dihydrochloride (10.7 mg, 98% yield).

$[MH]^+ = 192$

D1. *tert*-Butyl pivaloyloxycarbamate

tert-Butyl hydroxycarbamate (15.0 g, 113 mmol) was dissolved in acetonitrile (300 mL). Pivalic anhydride (25.4 mL, 124 mmol) was added as a steady stream and the resulting mixture heated to reflux overnight. After 18 hrs, the reaction mixture was allowed to cool to rt, then concentrated under vacuum. The residue was partitioned between EtOAc (350 mL) and $NaHCO_3$ (200 mL). The layers were separated and the organic fraction washed with $NaHCO_3$ (3 x 100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford *tert*-butyl pivaloyloxycarbamate (26.38 g, 97 mmol, 86 % yield).

D2. O-Pivaloylhydroxylamine trifluoromethanesulfonate

tert-Butyl pivaloyloxycarbamate (26.38 g, 97 mmol) was dissolved in dry diethyl ether (237 mL). The reaction mixture was cooled to 0 °C and then triflic acid (8.80 mL, 99 mmol) was added (vigorous evolution of gas noted). The mixture was stirred at 0 °C for 5 min and then allowed to warm to rt. After 1 hour iso-hexanes (250 mL) was added and the mixture stirred for 10 min. The resulting solid was filtered, washed with hexanes (3 x 50 mL) and then dried in the vacuum oven overnight to afford O-pivaloylhydroxylamine trifluoromethanesulfonate (24.83 g, 91% yield).

D3. 4-Bromo-3-methoxybenzoyl chloride

4-Bromo-3-methoxybenzoic acid (0.50 g, 2.164 mmol) was suspended in dry DCM (5.01 mL). Oxalyl chloride (0.227 mL, 2.60 mmol) was added drop-wise over 5 min. Dry DMF (1 drop) was added and gas evolved. The resulting mixture was stirred at ambient temperature. Dissolution slowly occurred over 45 min. After a total of 1.5 hrs, solvents were removed under vacuum to afford 4-bromo-3-methoxybenzoyl chloride (539 mg).

D4. 4-Bromo-3-methoxy-N-(pivaloyloxy)benzamide

To a dry flask under an atmosphere of nitrogen was added O-pivaloylhydroxylamine trifluoromethanesulfonate (547 mg, 1.944 mmol) dissolved in EtOAc (5.5 mL). Water (5.5 mL) and then sodium carbonate (458 mg, 4.32 mmol) were added. The resulting mixture was cooled to 0 °C and then a solution of 4-bromo-3-methoxybenzoyl chloride (539 mg, 2.16 mmol) in EtOAc (5.5 mL) was added in one portion. The reaction was stirred at 0 °C. After 1.5 hrs the reaction mixture was diluted with EtOAc (10 mL) and quenched with water (5 mL) and $NaHCO_3$ (15 mL). The layers were separated and the aqueous was extracted with EtOAc (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Multiple triturations from iso-hexanes afforded 4-bromo-3-methoxy-N-(pivaloyloxy)benzamide (378 mg, 47.7 % yield).

$[MH]^+$ = 330.1/332.1

D5. 6-Bromo-7-methoxyisoquinolin-1(2H)-one

Vinyl acetate (62.8 µL, 0.681 mmol) was added to a N_2 degassed solution of $[CpRhCl_2]_2$ (5.62 mg, 9.09 µmol), caesium acetate (52.3 mg, 0.273 mmol) and 4-bromo-3-methoxy-N-(pivaloyloxy)benzamide (150 mg, 0.454 mmol) in anhydrous MeOH (1.5 mL) in a sealed vial under a N_2 atmosphere. The reaction was allowed to stir at 50 °C for 1 hour, forming a precipitate. The reaction was cooled to rt and stirred over a weekend. The reaction mixture was filtered, washing with a small quantity of MeOH to afford 6-bromo-7-methoxyisoquinolin-1(2H)-one (73 mg, 63% yield) identified as desired product.

$[MH]^+$ = 254.0/256.0

D6. (1-Amino-7-methoxy-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester

6-Bromo-7-methoxyisoquinolin-1(2H)-one was converted to (1-Amino-7-methoxy-isoquinolin-6-ylmethyl)-carbamic acid tert-butyl ester using typical chlorination, amination, cyanation and nitrile reduction procedures.

$[MH]^+$ = 304.1

D7. 6-Aminomethyl-7-methoxy-isoquinolin-1-ylamine dihydrochloride

A suspension of tert-butyl ((1-amino-7-methoxyisoquinolin-6-yl)methyl)carbamate (120 mg, 0.396 mmol) hydrochloric acid, 6M in 2-propanol (462 µL, 2.77 mmol) was heated at 40 °C for 1 hour. The mixture was allowed to stir for a further 45 min at rt then treated with diethyl ether (2.5 mL) and the solid filtered and dried under vacuum to afford 6-(aminomethyl)-7-methoxyisoquinolin-1-amine dihydrochloride (102.5 mg, 89 % yield).

$[MH]^+$ = 204.0

E1. 4-Bromo-3-fluoro-N-hydroxy-benzamide

4-Bromo-3-fluorobenzoic acid (5.0 g, 22.83 mmol) was dissolved in dry DMF (10 mL) at ambient temperature and CDI (5.55 g, 34.2 mmol) was added portionwise, vigorous effervescence was observed. On completion of the addition the reaction solidified. Further dry DMF (6 mL) was added and the resultant slurry was left to stir at rt for 3 hrs. Neat hydroxylamine hydrochloride (3.17 g, 45.7 mmol) was added, forming a solution (some effervescence/heat noted). The mixture was allowed to stir over a weekend. The reaction mixture was quenched into water (200 mL) resulting in an off white precipitate,

which was filtered and washed with water, then dried under vacuum overnight to afford 4-bromo-3-fluoro-N-hydroxy-benzamide (3.14 g, 58.2% yield).

$[MH]^+$ = 234.1/236.1

E2. 4-Bromo-N-(2,2-dimethyl-propionyloxy)-3-fluoro-benzamide

To anhydrous MeCN (25 mL) was suspended 4-bromo-3-fluoro-N-hydroxybenzamide (3.14 g, 13.42 mmol). Pivalic anhydride (2.75 mL, 13.42 mmol) was added and the resulting mixture was heated at reflux for 3 hrs. The reaction mixture was cooled to rt and poured into saturated aq. $NaHCO_3$ (100 mL) then extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by automated flash chromatography loading in DCM and eluting with a gradient of 0 to 30% EtOAc/Iso-Hexanes to afford 4-bromo-N-(2,2-dimethyl-propionyloxy)-3-fluoro-benzamide (2.56 g, 58.2% yield) as a white powder.

$[MH]^+$ = 318.0/320.0

E3. 6-Aminomethyl-5-fluoro-isoquinolin-1-ylamine

6-Aminomethyl-5-fluoro-isoquinolin-1-ylamine was prepared in 6 steps from 4-bromo-N-(2,2-dimethyl-propionyloxy)-3-fluoro-benzamide using procedures described above.

$[MH]^+$ = 192

F. 3-Aminomethyl-[1,7]naphthyridin-8-ylamine dihydrochloride

3-Aminomethyl-[1,7]naphthyridin-8-ylamine dihydrochloride was prepared in 8 steps from 5-bromo-3-methylpicolinic acid using procedures described above.

$[MH]^+$ = 175

G1. 4-Bromo-3-methoxy-2-methyl-benzoic acid methyl ester

A solution of methyl 4-bromo-3-hydroxy-2-methylbenzoate (1.0 g, 4.08 mmol) in dry MeCN (7 mL) was treated with potassium carbonate (0.677 g, 4.90 mmol), then iodomethane (0.762 mL, 12.24 mmol) and the mixture heated at 50 °C for 5 hrs. Solvents were removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and water (20 mL). The aqueous layer was extracted with further EtOAc (2 x 20

mL) and the combined organics washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated to give 4-bromo-3-methoxy-2-methyl-benzoic acid methyl ester (974 mg, 91 % yield).

$[MH]^+$ = 259.0//261.0

G2. 4-Bromo-3-methoxy-2-methyl-benzoic acid

A solution of methyl 4-bromo-3-methoxy-2-methylbenzoate (974 mg, 3.76 mmol) in THF (3 mL) and MeOH (0.5 mL) was treated with lithium hydroxide (180 mg, 7.52 mmol) and water (1 mL). The mixture was warmed at 50 °C for 1.5 hrs. Solvents were removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and water (15 mL, containing 1 mL 2N NaOH). The aqueous layer was collected and acidified to pH 5 with 1M HCl, precipitating a white powder which was filtered and dried overnight under vacuum to afford 4-bromo-3-methoxy-2-methyl-benzoic acid (805 mg, 87 % yield).

$[MH]^+$ = 244.9/246.9

G3. 6-Aminomethyl-5-methoxy-isoquinolin-1-ylamine dihydrochloride

6-Aminomethyl-5-methoxy-isoquinolin-1-ylamine dihydrochloride was prepared in 8 steps from 4-bromo-3-methoxy-2-methyl-benzoic acid using procedures described above.
$[MH]^+$ = 204.0

H1. 4-Bromo-2-methoxy-6-methyl-phenylamine

To a stirred solution of 2-methoxy-6-methylaniline (15.44 g, 113 mmol) in MeOH (30 mL) and acetic acid (20 mL) at 0 °C was added a solution of bromine (5.80 mL, 113 mmol) in acetic acid (20 mL) dropwise. After half of the bromine was added the reaction mixture had solidfied due to precipitation. Additional acetic acid (30 mL) was added and stirring continued. After addition was complete the reaction allowed to stir for 4 hrs. The reaction mixture was filtered to give a light brown filter cake that was washed with additional acetic acid (30 mL) and then isohexanes (50 mL). The solid was in EtOAc (300 mL) and then washed with NaOH (2M, 200 mL). The organics were washed with brine (200 mL), dried over magnesium sulfate, filtered and solvent removed *in vacuo* to give 4-bromo-2-methoxy-6-methyl-phenylamine (20.14g, 81% yield).

$[MH]^+$ = 216/218

H2. 4-Bromo-2-methoxy-6-methylbenzonitrile

To a stirred suspension of 4-bromo-2-methoxy-6-methylaniline (7 g, 32.4 mmol) in conc. HCl (20 mL) and water (80 g of crushed ice) at 0 °C in a 3 necked round bottom flask was added sodium nitrite (2.347 g, 34.02 mmol) portionwise over 10 min. The internal temperature was maintained at 0 °C for a further 30 min. The reaction mixture was neutralised with solid sodium carbonate until a basic pH was measured. This diazonium solution was diluted with toluene (60 mL) and added to a cooled 0 °C solution of copper cyanide (3.482 g, 38.91 mmol) and sodium cyanide (4.76 g, 97.2 mmol) in water (30 mL) with vigorous stirring. The reaction was held at 0 °C and allowed to warm to rt after 1 hour. The reaction mixture was diluted with toluene (100 mL). The organic layer was extracted and washed with brine (200 mL), dried over magnesium sulfate, filtered and solvent removed *in vacuo* to afford 4-bromo-2-methoxy-6-methylbenzonitrile (7.02 g, 77 % yield).

H3. 4-Bromo-2-methoxy-6-methylbenzamide

To a stirred solution of 4-bromo-2-methoxy-6-methylbenzonitrile (7.05 g, 31.2 mmol) in MeOH (50 mL) was added sodium hydroxide (1.247 g, 31.2 mmol) and heated to 90 °C overnight. The reaction was charged with additional solid sodium hydroxide (3.74 g, 94 mmol) and MeOH (50 mL) and then heated to 100 °C for 3 days. The reaction mixture was concentrated to remove MeOH and the product extracted with DCM (150 mL). The organics were washed with brine (100 mL) and then dried over magnesium sulfate, filtered and solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica eluting with 0-100% EtOAc in isohexanes to afford 4-bromo-2-methoxy-6-methylbenzamide (1.227 g, 15% yield).

$[MH]^+$ = 244.0/246.0

H4. 6-Aminomethyl-8-methoxy-isoquinolin-1-ylamine dihydrochloride

6-Aminomethyl-8-methoxy-isoquinolin-1-ylamine dihydrochloride was prepared in 6 steps from 4-bromo-2-methoxy-6-methylbenzamide using procedures described above.

$[MH]^+$ = 204.2

J1. (4-Chloro-benzyl)-(2,2-dimethoxy-1-methyl-ethyl)-amine

4-Chlorobenzylamine (2.0 g, 14.12 mmol) was dissolved in 1,2-dichloroethane (100 mL). Pyruvic aldehyde dimethyl acetal (1.835 g, 15.54 mmol) was added followed by sodium triacetoxyborohydride (4.49 g, 21.19 mmol). The reaction mixture was stirred at rt for 18 hrs after which time the solvent was removed *in vacuo* to afford (4-chloro-benzyl)-(2,2-dimethoxy-1-methyl-ethyl)-amine (1.80 g, 45% yield).
$[MH]^+ = 244$

J2. 6-Chloro-3-methyl-isoquinoline

(4-Chloro-benzyl)-(2,2-dimethoxy-1-methyl-ethyl)-amine (1.25 g, 16.55 mmol) was added dropwise to chlorosulphonic acid (100 mL) at -10 °C over a period of 10 min. The reaction mixture was then stirred at 100 °C for 10 min after which time the reaction mixture was cooled and poured into ice and neutralised (to pH7) with 33% NaOH. Care was taken that temperature did not rise above 35 °C. The reaction mixture was extracted with chloroform (3 x 100 mL). The combined organics were washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3% MeOH, 97% chloroform to give 6-chloro-3-methyl-isoquinoline (750 mg, 82% yield)

J3. 3-Bromomethyl-6-chloro-isoquinoline

6-Chloro-3-methyl-isoquinoline (750 mg, 4.22 mmol) was dissolved in 1,2-dichloroethane (70 mL). To this solution was added N-bromosuccinimide (901 mg, 5.07 mmol) and azobisisobutyronitrile (69 mg, 0.42 mmol). The reaction was heated at reflux for 5 hrs. The reaction was diluted with DCM, brine was added and the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography eluting with petroleum ether:ethyl acetate afforded 3-bromomethyl-6-chloro-isoquinoline (980 mg, 90% yield).
$[MH]^+ = 255/257$

J4. 3-Azidomethyl-6-chloro-isoquinoline

3-Bromomethyl-6-chloro-isoquinoline (980 mg, 3.820 mmol) was dissolved in DMF (20 mL). Sodium azide (126 mg, 1.95 mmol) was added. The reaction mixture was stirred at rt for 18 hrs after which time the reaction mixture was diluted with EtOAc (100 mL). The solution was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography (silica), eluting with 85%Pet Ether 60-80, 15% EtOAc afforded 3-azidomethyl-6-chloro-isoquinoline (570 mg, 68%).
$[MH]^+ = 219$

J5. C-(6-Chloro-isoquinolin-3-yl)-methylamine

3-Azidomethyl-6-chloro-isoquinoline (300 mg, 1.37 mmol) was dissolved in ethanol (50 mL) and acetic acid (1 mL). Zinc powder (180 mg, 2.74 mmol) was added portionwise. The reaction mixture was stirred at rt for 18 hrs. The mixture was through Celite and the residue washed with ethanol (50 mL). The filtrates were evaporated *in vacuo*, dissolved in $CHCl_3$ (150 mL), washed with sat $NaHCO_3$ (30 mL), water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give C-(6-chloro-isoquinolin-3-yl)-methylamine (264 mg, 99% yield)

$[MH]^+ = 193$

Intermediates (other):

I. 1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one

4-(Chloromethyl)benzylalcohol (5.0 g, 31.93 mmol) was dissolved in acetone (150 mL). 2-hydroxypyridine (3.64 g, 38.3 mmol) and potassium carbonate (13.24 g, 95.78 mmol) were added and the reaction mixture was stirred at 50 °C for 3 hrs after which time the solvent was removed *in vacuo* and the residue taken up in chloroform (100 mL). This solution was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent 3%MeOH / 97% $CHCl_3$, to give a white solid identified as 1-(4-hydroxymethyl-benzyl)-1H-pyridin-2-one (5.30g, 24.62mmol, 77% yield).

$[M+Na]^+ = 238$

II-1. 1-(4-Chloromethyl-benzyl)-1H-pyridin-2-one

1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (8.45 g, 39.3 mmol), dry DCM (80 mL) and triethylamine (7.66 ml, 55.0 mmol) were cooled in an ice bath. Methanesulfonyl chloride (3.95 ml, 51.0 mmol) was added and stirred in ice bath for 15 min. The ice bath was removed and stirring continued at rt temperature overnight. The reaction mixture was partitioned between DCM (100 mL) and saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with further DCM (2 x 50 mL) and the combined organics washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give 1-(4-chloromethyl-benzyl)-1H-pyridin-2-one (8.65 g, 36.6 mmol, 93 % yield) as a pale yellow solid.

$[MH]^+ = 234.1$

II-2. 1-(4-Bromomethyl-benzyl)-1H-pyridin-2-one

1-(4-Hydroxymethyl-benzyl)-1H-pyridin-2-one (2.30 g, 6.97 mmol) was dissolved in DCM (250 mL). To this solution was added phosphorous tribromide (5.78 g, 21.37 mmol) The reaction mixture was stirred at rt for 18 hrs and diluted with $CHCl_3$ (250 mL). The filtrate was washed with sat. $NaHCO_3$ (aq) (30 mL), water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid which was identified as 1-(4-bromomethyl-benzyl)-1H-pyridin-2-one (2.90 g, 10.43 mmol, 98%).

$[MH]^+ = 277.7$

V. [4-(4-Methyl-pyrazol-1-ylmethyl)-phenyl]-methanol

4-(Chloromethyl)benzylalcohol (5.47 g, 34.9 mmol) was dissolved in acetone (50 mL). 4-Methylpyrazole (2.86 g, 34.9 mmol) and potassium carbonate (5.07 g, 36.7 mmol) were added and the reaction mixture was stirred at rt for 18 hrs and at 60 °C for 30 hrs after which time the solvent was removed *in vacuo* and the residue taken up in EtOAc (100 mL). This solution was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent gradient of 10 to 80% EtOAc in iso-Hexane, fractions combined and evaporated *in vacuo* to give a white solid identified as [4-(4-methyl-pyrazol-1-ylmethyl)-phenyl]-methanol (3.94 g, 18.90 mmol, 54% yield).

$[MH]^+ = 203$

VI. 1-(4-Chloromethyl-benzyl)-4-methyl-1H-pyrazole

[4-(4-Methyl-pyrazol-1-ylmethyl)-phenyl]-methanol (2.03 g, 10.04 mmol) and triethylamine (1.13 g, 11.54 mmol) was dissolved in DCM (40 mL). To this solution was added methanesulphonyl chloride (1.26 g, 11.04 mmol) dropwise. The reaction mixture was stirred at rt for 18 hrs and diluted with $CHCl_3$ (250 mL). The mixture was washed with saturated NH_4Cl (30 mL), water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica), eluent gradient of 0 to 60% EtOAc in iso-Hexane, fractions combined and evaporated *in vacuo* to give a white solid identified as 1-(4-chloromethyl-benzyl)-4-methyl-1H-pyrazole (1.49 g, 6.62 mmol, 60% yield).

$[MH]^+ = 221, 223$

X. Methyl 5-methoxy-3-oxopentanoate

CDI (3.24 g, 20.0 mmol) was added portionwise to a stirred suspension of 3-methoxypropanoic acid (1.81 ml, 19.2 mmol) in anhydrous MeCN (80 mL). The mixture was allowed to stir at rt for 1.5 hrs. A powdered mixture of magnesium chloride (1.57 g, 16.5 mmol) and methyl potassium malonate (4.5 g, 28.8 mmol) was added portionwise (note CO_2 gas evolved). The mixture was allowed to stir at rt. Volatiles were removed *in vacuo* and hydrochloric acid (2M, 105 mL) was added. The solution was stirred at rt for 1 hr and extracted with DCM (3 x 100 mL). The organics were dried over magnesium sulfate, filtered and solvent removed *in vacuo* to afford methyl 5-methoxy-3-oxopentanoate (2.69 g, 87% yield).

XI. (Z)-Methyl 2-((dimethylamino)methylene)-5-methoxy-3-oxopentanoate

A stirred mixture of methyl 5-methoxy-3-oxopentanoate (2.69 g, 16.8 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (2.68 ml, 20.2 mmol) was left overnight at rt. Reaction mixture was reduced *in vacuo* and azetroped with toluene (30 mL) to afford crude (Z)-methyl 2-((dimethylamino)methylene)-5-methoxy-3-oxopentanoate which was used without further purification.

XII. Methyl 3-(2-methoxyethyl)-1H-pyrazole-4-carboxylate

To a stirred solution of (Z)-methyl 2-((dimethylamino)methylene)-5-methoxy-3-oxopentanoate (3.62 g, 16.82 mmol) in ethanol (50 mL) was added hydrazine hydrate (1.89 ml, 25.2 mmol) and heated to reflux for 4 hrs. Reaction mixture cooled to rt and diluted with EtOAc (200 mL), washed with $NaHCO_3$ (aq, 200 mL), then brine (2 x 100 mL), dried over magnesium sulfate, filtered and solvent removed *in vacuo* to give methyl 3-(2-methoxyethyl)-1H-pyrazole-4-carboxylate (2.42 g, 77% yield).

$[MH]^+ = 185.1$

XV. 4-Bromomethyl-2-fluoro-benzoic acid

2-Fluoro-4-(hydroxymethyl)benzoic acid (500 mg, 2.94 mmol) was dissolved in dry DCM (20 mL), under an atmosphere of N_2 and PBr_3 (276 µL, 2.94 mmol) was added. Anhydrous DMF (4 mL) was added and the reaction stirred for 2 hrs at rt. The reaction mixture was quenched with dilute $NaHCO_3$ (sat diluted to 10%) (50 mL). After stirring for 15 mins, until bubbling ceased, the layers were separated and the aqueous adjusted to pH =0 using 2M HCl. The precipitate was collected by vaccum filtration, washed with water and dried in an oven to afford 4-bromomethyl-2-fluoro-benzoic acid (420mg, 61% yield).

XVI. (4-Bromomethyl-2-fluoro-phenyl)-methanol

4-Bromomethyl-2-fluoro-benzoic acid (420 mg, 1.80 mmol) was dissolved in anhydrous THF (20 mL) and cooled to -20°C. To this solution was added triethylamine (0.75 mL, 5.41 mmol) and isobutyl chloroformate (0.283 mL, 2.16 mmol). The reaction mixture was stirred at -20°C for 1 hour and then poured into a solution of sodium borohydride (341 mg, 9.01 mmol) in water (2 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 18 hrs. The reaction mixture was diluted with EtOAc (200 mL) and the layers separated. The organic layer was washed with 0.3M $KHSO_4$ (50 mL), water (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The solid was purified by flash column chromatography on silica, eluting with EtOAc/Pet Ether (85:15) to give (4-bromomethyl-2-fluoro-phenyl)-methanol.

XVII. (2-Fluoro-4-pyrazol-1-ylmethyl-phenyl)-methanol

(4-Bromomethyl-2-fluoro-phenyl)-methanol (108 mg, 0.49 mmol) and pyrazole (37 mg, 0.54 mmol) were taken up in MeCN (10 mL). K_2CO_3 (136 mg, 0.99 mmol) was added and the reaction was heated to 50 °C. Volatiles were removed *in vacuo*. EtOAc (60 mL) and water (20 mL) were added. The organic layer was dried, filtered and evaporated *in vacuo*. Purified by automated FC eluting in step gradients up to 50% EtOAc in pet ether to afford (2-fluoro-4-pyrazol-1-ylmethyl-phenyl)-methanol (94 mg, 94% yield).

$[MH]^+ = 206.7$

XVIII. 1-(4-Bromomethyl-3-fluoro-benzyl)-1H-pyrazole

(2-Fluoro-4-pyrazol-1-ylmethyl-phenyl)-methanol (94 mg, 0.46 mmol) was dissolved in dry DCM (5 mL) under an atmosphere of N_2. PBr_3 (43 µL, 0.46 mmol) was added and the reaction stirred for 1 hour at rt. The reaction mixture was quenched with dilute $NaHCO_3$ (sat diluted to 10%) (10 mL) The layers were separated and the organic washed with water (10 mL) and brine (10 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1-(4-bromomethyl-3-fluoro-benzyl)-1H-pyrazole (80 mg, 65% yield).

$[MH]^+ = 206.7$

XX. Ethyl 3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

A solution of diethyl 2-(ethoxymethylene)malonate (40 g, 185 mmol) in absolute ethanol (400 mL) was treated with hydrazine hydrate (8.99 ml, 185 mmol) dropwise. After approximately 20 min, 2N NaOH (25 mL) was added slowly (reaction in an ice-bath), then water (25 mL). The ice-bath was removed and the mixture stirred at rt for 1.5 hrs. The ethanol was removed *in vacuo* and the aqueous layer diluted with water (25 mL) and partitioned over EtOAc (100 mL). The aqueous layer was collected and cooled in an ice-bath. The pH was adjusted to 5 with 1M HCl, forming a precipitate. The precipitate was filtered, washing with water and dried *in vacuo* in the presence of $CaCl_2$ to afford ethyl 3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (22.31 g, 76% yield).

$[MH]^+ = 157.1$

XXI. Ethyl 1-acetyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate

Acetic anhydride (13.50 ml, 143 mmol) was added to a suspension of ethyl 3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (22.30 g, 143 mmol) in acetic acid (185 mL). The mixture was stirred at rt overnight. Solvents were removed *in vacuo*. The remaining solid was triturated from water (200 mL) and filtered, washing with water. The product was dried *in vacuo* in the presence of $CaCl_2$ to afford ethyl 1-acetyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (27.39 g, 94 % yield).

$[MH]^+ = 199.2$

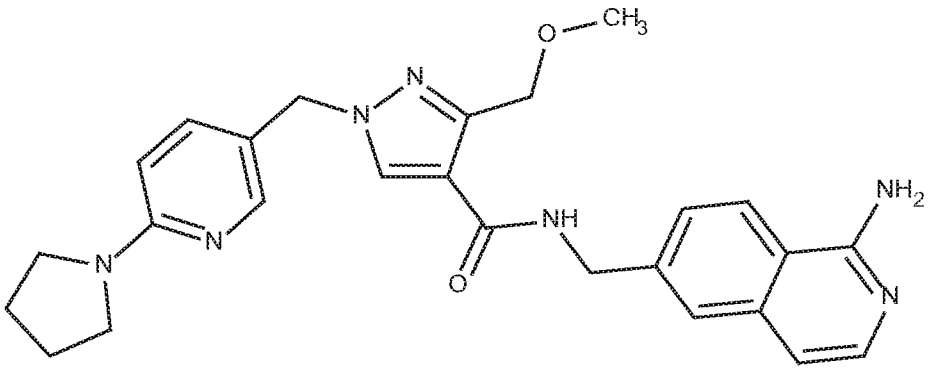
XXII. Ethyl 3-(2-methoxyethoxy)-1H-pyrazole-4-carboxylate

To a stirred solution of ethyl 1-acetyl-3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2.0 g, 10.09 mmol) in DMF (10 mL) was added 1-bromo-2-methoxyethane (0.948 ml, 10.09 mmol) and K_2CO_3 (1.395 g, 10.09 mmol) and heated to 70 °C for 5 hrs. Reaction mixture cooled to rt and extracted with EtOAc (100 mL) and washed with water (100 mL). Organic phase was dried over magnesium sulfate, filtered and solvent removed *in vacuo*. Material taken up into MeOH (20 mL) and K_2CO_3 (1.395 g, 10.09 mmol) added and stirred at rt overnight. The mixture was diluted with water (30 mL) and product extracted with EtOAc (2 x 50 mL). The organics were washed with brine (20 mL), dried over magnesium sulfate, filtered and solvent removed *in vacuo* to afford ethyl 3-(2-methoxyethoxy)-1H-pyrazole-4-carboxylate (700 mg, 25.9 % yield). $[MH]^+ = 215.2$

Examples:

Example 1.

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride



Methyl 1-((6-fluoropyridin-3-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate

To a stirred solution of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (758 mg, 4.45mmol); CAS no. 318496-66-1 (synthesised according to the method described in WO 2012/009009) and 5-(chloromethyl)-2-fluoropyridine (778 mg, 5.34 mmol) in DMF (8 mL) was added K_2CO_3 (1231 mg, 8.91 mmol) and left at rt overnight. Reaction mixture diluted with EtOAc (150 mL) and washed with brine (2 x 100 mL), dried over magnesium sulfate, filtered and solvent removed. The crude product was purified by automated FC 0-60% (3:1 EtOAc: MeCN) in isohexanes) to afford:

Isomer 1: methyl 1-((6-fluoropyridin-3-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylate (348 mg, 27.4%).

MH^+ = 280.1

Isomer 2: methyl 1-((6-fluoropyridin-3-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate (749 mg, 59.0%)

MH^+ = 280.1

1-((6-Fluoropyridin-3-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid

General saponification method with lithium hydroxide afforded title compound (309 mg, 46.1%).

MH^+ = 266.1

3-(Methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxylic acid

A solution of 1-((6-fluoropyridin-3-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid (305 mg, 1.15 mmol) in anhydrous dioxanes (1 mL) was treated with pyrrolidine (236 µl, 2.87 mmol) and the mixture heated at 100 °C overnight. Solvents were removed under vacuum. The mixture was partitioned between EtOAc (10 mL) and water (10 mL, containing 2N NaOH to pH14). The aqueous layer was extracted with further EtOAc (3 x 15 mL) and the combined organics discarded. The aqueous layer was adjusted to pH 4/5 with 1M HCl. The aqueous layer was purified by SCX (10 g), washing with MeOH, eluting with 1% NH_3/MeOH to afford 3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxylic acid (336 mg, 0.882 mmol, 77% yield).

MH^+ = 317.2

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride

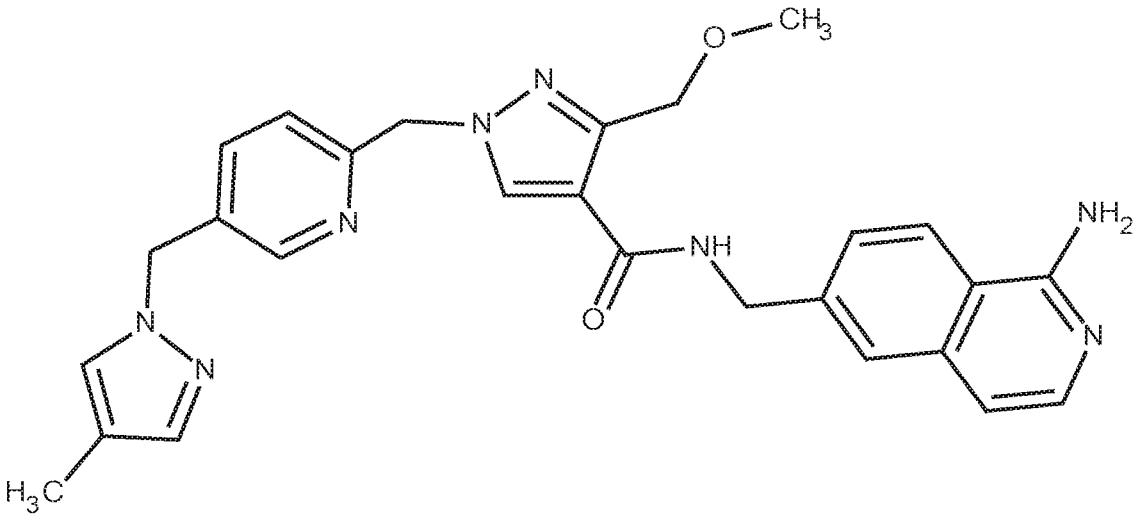
Amide formed using amide formation method A. The product was treated with 4M HCl in dioxanes to afford the HCl salt of the title compound (90 mg, 0.164 mmol, 16.9% yield).

MH^+ = 472.3

^1H NMR (d6-DMSO): δ 1.90-2.08 (4H, m), 3.22 (3H, s), 3.49-3.56 (4H, m), 4.56 (2H, s), 4.60 (2H, d, J = 5.9Hz), 5.31 (2H, s), 7.05 (1H, d, J = 9.4Hz), 7.19 (1H, d, J = 7.0Hz), 7.64-7.73 (2H, m), 7.80 (1H, s), 7.88(1H, d, J = 8.7Hz), 8.07 (1H, s), 8.37 (1H, s), 8.58 (1H, d, J = 8.6Hz), 8.70 (1H, t, J = 5.9Hz), 9.14 (2H,br s), 13.34 (1H, br s), 13.73 (1H, br s).

Example 2.

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide



5-(Chloromethyl)-2-methylpyridine

A solution of (6-methylpyridin-3-yl)methanol (5.04 g, 40.9 mmol) and triethylamine (7.99 ml, 57.3 mmol) in anhydrous DCM (85 mL) was cooled in an ice-bath before the addition of methanesulfonyl chloride (4.12 ml, 53.2 mmol) dropwise. On completion of the addition the ice-bath was removed and the mixture stirred at rt overnight. The reaction mixture was partitioned between DCM (100 mL) and sat. aq. $NaHCO_3$ (150 mL). The aqueous layer was extracted with further DCM (2 x 50 mL) and the combined organics dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 5-(chloromethyl)-2-methylpyridine (5.12 g, 87 % yield) which was used without further purification.

MH^+ = 141.9

2-Methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine

To a stirred solution of 4-methyl-1H-pyrazole (3.60 ml, 43.4 mmol) and 5-(chloromethyl)-2-methylpyridine (5.12 g, 36.2 mmol) in MeCN (75 mL) under N_2 was added potassium carbonate (7.50 g, 54.2 mmol) and the suspension stirred at 80 °C overnight. The volatiles were removed *in vacuo*. The residue was partitioned between EtOAc (150 mL) and water (150 mL). The aqueous was extracted with EtOAc (2 x 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography eluting with a gradient of 50 to 100% EtOAc/Iso-Hexanes to afford 2-methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine (2.58 g, 37.7 % yield).

MH^+ = 188.0

2-Methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine-1-oxide

A solution of 2-methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine (0.50 g, 2.67 mmol) in chloroform (15 mL) was treated portionwise with 3-chlorobenzoperoxoic acid (1.11 g, 3.20 mmol). The mixture was allowed to stir at rt for 2 hrs. The reaction was cooled in an ice-bath and treated with 2N NaOH (5 mL) with vigorous stirring. The ice-bath was removed and the mixture allowed to stir for 20 minutes, forming a suspension and water (5 mL) added. The layers were allowed to separate and the organic collected. The aqueous was extracted with chloroform (2 x 20 mL) and the combined organics dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 2-methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine1-oxide (467 mg, 84% yield).

MH^+ = 204

(5-((4-Methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl acetate

A solution of 2-methyl-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine 1-oxide (467 mg, 2.30 mmol) in acetic anhydride (9770 µl, 103 mmol) was heated to 95 °C (bath temperature) and the mixture allowed to stir for 2 hrs. Solvents were removed *in vacuo* and the residue purified by flash chromatography, loading in dichloromethane, eluting with a gradient of 50 to 100% EtOAc/Iso-Hexanes to afford (5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl acetate (410 mg, 61.8 % yield).

MH^+ = 246.0

(5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methanol

A solution of (5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl acetate (410 mg, 1.42 mmol) in MeOH (8 mL) was treated with a solution of potassium carbonate (471 mg, 3.41 mmol) in water (2 mL) and the mixture stirred at rt for 2 hrs. The MeOH was removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and water (8 mL). Sat. aq. NH_4Cl was added to ~pH 9 and the organic layer collected. The aqueous was extracted with further EtOAc (2 x 20 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford (5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methanol (262 mg, 82 % yield).

MH^+ = 203.9

2-(Chloromethyl)-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine

Prepared using procedure for 1-(-chloromethyl-benzyl)-4-methyl-1H-pyrazole

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide

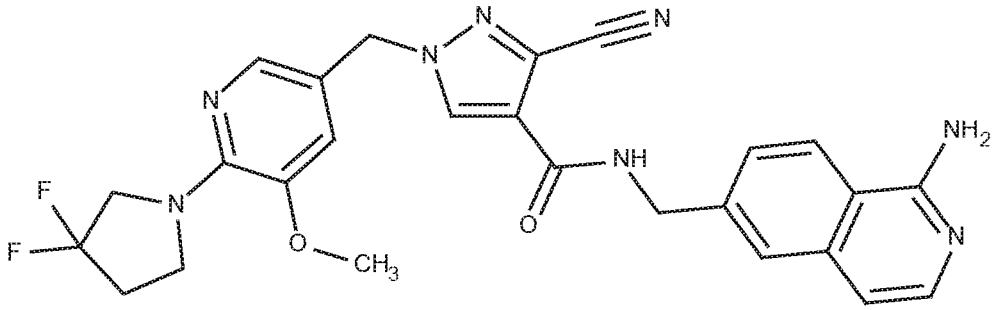
Prepared from 2-(chloromethyl)-5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridine, methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate and 6-aminomethyl-isoquinolin-1-ylamine hydrochloride using general methods (core alkylation, saponification and amide formation method B).

MH^+ = 497.2

^{1}H NMR (d6-DMSO): δ 1.98 (3H, s), 3.21 (3H, s), 4.56 (2H, s), 4.60 (2H, d, J = 5.9Hz), 5.29 (2H, s), 5.43 (2H, s), 7.17-7.28 (3H, m), 7.60 (1H, s), 7.62-7.75 (3H, m), 7.81 (1H, s), 8.37 (1H, s), 8.45 (1H, d, J = 2.3Hz), 8.56 (1H, d, J = 8.6Hz), 8.68 (1H, t, J = 5.9Hz), 9.11 (2H, brs), 13.28 (1H, s)

Example 3.

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



(6-Chloro-5-methoxy-pyridin-3-yl)-methanol

To a stirred solution of 6-chloro-5-methoxy-nicotinic acid methyl ester (0.5 g, 2.48 mmol) in anhydrous THF (20 mL) cooled to 0 °C under nitrogen, was added $LiAlH_4$ (104 mg, 2.73 mmol). The reaction was allowed to warm to rt. The reaction was cooled to 0 °C and quenched with water. Potassium sodium tartrate (Rochelle's salt) was added and the mixture was filtered through Celite and washed with EtOAc (20 mL). The filtrate was separated and the aqueous extracted with EtOAc (20 mL). The combined organic layers were washed with brine (50 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by automated FC (EtOAc/petrol) to afford (6-chloro-5-methoxy-pyridin-3-yl)-methanol (710 mg, 82% yield)

$[MH]^+$ = 173.7

5-Bromomethyl-2-chloro-3-methoxy-pyridine

(6-Chloro-5-methoxy-pyridin-3-yl)-methanol (710 mg, 4.09 mmol) was dissolved in anhydrous DCM (15 mL), under an atmosphere of N_2. PBr_3 (384 mL, 4.09mmol) was added and the reaction stirred at rt. The reaction mixture was quenched with a dilute aqueous solution of $NaHCO_3$ (10%, 10 mL). The layers were separated and the organic layer washed with water (10 mL) and brine (10 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by automated FC eluting with (EtOAc/Petrol) to afford 5-bromomethyl-2-chloro-3-methoxy-pyridine (851 mg, 88% yield).

$[MH]^+$ = 238.0

1-(6-Chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyano-1H-pyrazole-4-carboxylic acid ethyl ester

3-Cyano-1H-pyrazole-4-carboxylic acid ethyl ester (139.7mg, 0.85mmol) was taken up in DMF and treated with potassium carbonate (233.8mg, 1.69mmol). 5-Bromomethyl-2-chloro-3-methoxy-pyridine (200 mg, 0.85 mmol) was added and reaction stirred at rt overnight. Diluted with DCM (30 mL) and washed with water (10 mL). The organic layer was washed with $NaHCO_3$ (1 x 10ml), brine (10 ml), dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by automated FC (EtOAc/petrol) to afford 1-(6-chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyano-1H-pyrazole-4-carboxylic acid ethyl ester (157mg, 68% yield).

$[MH]^+$ = 321.1

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid ethyl ester

To a suspension of 1-(6-chloro-5-methoxy-pyridin-3-ylmethyl)-3-cyano-1H-pyrazole-4-carboxylic acid ethyl ester (41 mg, 0.13 mmol) in 1,4-dioxane (1 mL) was added 3,3-dilfuoropyrrolidine hydrochloride salt (73.4 mg, 0.51 mmol) and Et_3N (142.5 mL, 1.02 mmol). The reaction was heated at 125 °C. The reaction mixture was concentrated and purified by automated FC to afford 3-cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid ethyl ester (40 mg, 80% yield).

$[MH]^+$ = 391.9

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid

To 3-cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid ethyl ester (40 mg, 0.10 mmol) dissolved in THF (10 mL) was added lithium hydroxide monohydrate (12 mg, 0.13 mmol) in water (1 mL). The reaction mixture was stirred at 50 °C. NaOH (41 mg, 1.02 mmol) was added and continued stirring at 50 °C for 6h. The reaction was concentrated to dryness *in vacuo* and acidified with 2M HCl to ~pH = 4-5. The aqueous layer was washed with 10% 2-propanol in chloroform

(10 x 10 mL). The combined organics were dried and concentrated *in vacuo* to afford 3-cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid.

$[MH]^+$ = 364

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

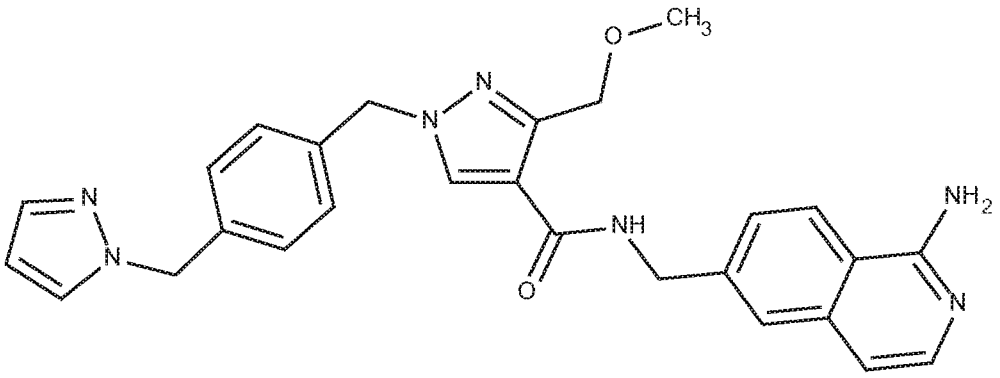
Prepared from 3-cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid and 6-aminomethyl-isoquinolin-1-ylamine hydrochloride using amide formation method A.

$[MH]^+$ = 519.0

^{1}H NMR (d6-DMSO): δ 2.42 (2H, dd, J = 14.4, 7.3 Hz), 3.73 (2H, t, J = 7.2 Hz), 3.75 (3H, s), 3.93 (2H, t, J = 13.7 Hz), 4.61 (2H, d, J = 5.8 Hz), 5.38 (2H, s), 7.21-7.24 (1H, m), 7.25 (1H, d, J = 1.8 Hz), 7.65 (1H, d, J = 7.0 Hz), 7.70 (1H, dd, J = 8.6, 1.7 Hz), 7.82-7.83 (2H, m), 8.46 (1H, s), 8.50 (1H, d, J = 8.7 Hz), 8.92 (2H, br.s), 9.11 (1H, t, J = 5.9 Hz), 12.82 (1H, br.s)

Example 4.

3-Methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



Methyl 1-(4-((1H-pyrazol-1-yl)methyl)benzyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate

To a stirred suspension of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (470 mg, 2.76 mmol) and 1-(4-(chloromethyl)benzyl)-1H-pyrazole (571 mg, 2.76 mmol) in DMF (2.5 mL) was added potassium carbonate (763 mg, 5.52 mmol) and the mixture stirred at rt overnight. The reaction was diluted with EtOAc (30 mL) and water (25 mL) containing brine (25 mL). The aqueous layer was extracted with further EtOAc (2 x 30 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography loading in dichloromethane, eluting with a gradient of 0 to 100% EtOAc/Iso-Hexanes holding at 70% to elute methyl 1-(4-((1H-pyrazol-1-

yl)methyl)benzyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylate (232 mg, 21.0 % yield) then 85% to elute methyl 1-(4-((1H-pyrazol-1-yl)methyl)benzyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate (494 mg, 52.0 % yield).

$[MH]^+$ = 341.1

3-Methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

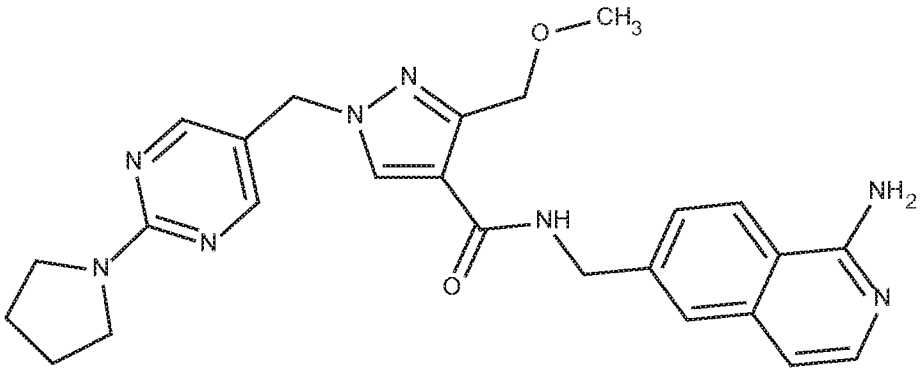
Prepared from methyl 1-(4-((1H-pyrazol-1-yl)methyl)benzyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate and 6-aminomethyl-isoquinolin-1-ylamine hydrochloride using general methods (saponification and amide formation method B).

$[MH]^+$ = 482.3

^{1}H NMR (d6-DMSO): δ 3.21 (3H, s), 4.56 (2H, s), 4.59 (2H, d, J = 5.8Hz), 5.26-5.34 (4H, m), 6.25 (1H, t, J = 2.1Hz), 7.17-7.22 (3H, m), 7.25 (2H, d, J = 8.2Hz), 7.44 (1H, d, J = 1.8Hz), 7.63-7.72 (2H, m), 7.79 (1H, s), 7.81 (1H, d, J = 2.3Hz), 8.31 (1H, s), 8.55 (1H, d, J = 8.6Hz), 8.66 (1H, t, J = 5.9Hz), 9.12 (2H, brs), 13.29 (1H, s)

Example 8

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide



Route A

5-Bromomethyl-2-chloro-pyridine

2-Chloro-5-methylpyrimidine (3.0 g, 23.3 mmol) was dissolved in 1,2-dichloroethane (120 mL). To this solution was added N-bromosuccinimide (4.98 g, 28.0 mmol) and azobisisobutyronitrile (1.15 g, 7.00 mmol). The reaction was stirred at 95 °C. After 18 hrs at 95 °C the reaction mixture was diluted with

$CHCl_3$ (150 mL), this solution was washed with sat. $NaHCO_3$ (1x50 mL), water (1x50 mL), brine (1x50 mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluent 15% EtOAc, 85% Pet. Ether, fractions combined and evaporated in vacuo to give a yellow oil identified as 5-bromomethyl-2-chloro-pyridine (1.64 g, 34%).

MH^+ = 207.8

1-(2-Chloro-pyrimidin-5-ylmethyl)-3-methoxymethyl-1H-pyrazole-4-carboxylic acid methyl ester

To a stirred solution of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (2.01g, 11.83mmol); CAS no. 318496-66-1 (synthesised according to the method described in WO 2012/009009) and 5-bromomethyl-2-chloro-pyridine (2.70 g, 13.1 mmol) in DMF (8 mL) was added K_2CO_3 (3.27 g, 23.7 mmol) and left at rt overnight. Reaction mixture diluted with EtOAc (150 mL) and washed with brine (2 x 100 mL), dried over magnesium sulfate, filtered and solvent removed. The crude product was purified by automated FC 0-60% (1:1 EtOAc: MeCN) in Pet. Ether to afford Isomers 1 and 2:

Isomer 1: 1-(2-Chloro-pyrimidin-5-ylmethyl)-5-methoxymethyl-1H-pyrazole-4-carboxylic acid methyl ester (420 mg, 12%); MH^+ = 296.7

Isomer 2: 1-(2-Chloro-pyrimidin-5-ylmethyl)-3-methoxymethyl-1H-pyrazole-4-carboxylic acid methyl ester (638 mg, 18%); MH^+ = 296.7

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester

A solution of 1-(2-chloro-pyrimidin-5-ylmethyl)-3-methoxymethyl-1H-pyrazole-4-carboxylic acid methyl ester (418 mg, 1.41 mmol) in anhydrous dioxane (1 mL) was treated with pyrrolidine (1.2 mL, 14.1 mmol) and the mixture heated at 100 °C overnight. Solvents were removed under vacuum. The residue was purified by automated FC 0-60% EtOAc in Pet. Ether to afford 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester (290 mg, 0.88 mmol, 62% yield).

MH^+ = 331.9

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid

General saponification method with sodium hydroxide afforded title compound (250mg, 0.79mmol, 90%).

MH^+ = 317.9

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Amide formed using amide formation method A. Purified by flash chromatography (silica), eluent 15% methanol, 84% dichloromethane, 1% NH_4OH, fractions combined and evaporated in vacuo to give a white solid identified as 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (163 mg, 0.35 mmol, 44% yield).

MH^+ = 473.0

^1H NMR (DMSO): 1.88-1.94 (4H, m), 3.22 (3H, s), 3.44-3.45 (4H, m), 4.53 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.15 (2H, s), 6.82 (2H, br.s), 6.87 (1H, d, J = 5.9 Hz), 7.39 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.75 (1H, d, J = 5.9 Hz), 8.15 (1H, d, J = 8.3 Hz), 8.23 (1H, s), 8.38 (2H, s), 8.46 (1H, t, J = 5.8 Hz)

Route B

Ethyl 2-(pyrrolidin-1-yl)pyrimidine-5-carboxylate

Ethyl-2-chloropyrimidine-5-carboxylate (300 g, 1.6 mol) was stirred in 1,4-dioxane (3000 mL) in an ice/water bath. Pyrrolidine (375 mL, 4.5 mol) was added and the mixture stirred for 3 hrs at rt. The reaction mixture was concentrated and separated between ethyl acetate (4000 mL) and water (4000 mL). The organics were washed with water (2000 mL) and saturated brine (3000 mL), dried over sodium sulfate, filtered and concentrated. The product was dried in the vacuum oven at approximately 45 °C to give a yellow solid identified as ethyl 2-(pyrrolidin-1-yl)pyrimidine-5-carboxylate (328 g, 92% yield).

MH^+ = 221.9

(2-(Pyrrolidin-1-yl)pyrimidin-5-yl)methanol

To a stirred solution of ethyl 2-(pyrrolidin-1-yl)pyrimidine-5-carboxylate (100 g, 0.45 moles) in dry DCM (1000 mL) under N_2 at 0 °C was added a solution of diisobutylaluminium hydride in hexanes (1.0M solution, 950 mL, 0.95 moles). Water (40 mL) was carefully added to the reaction mixture followed by a 15% aq. solution of sodium hydroxide (40 mL) and finally water (100 mL). Sodium sulfate (~200 g) was added and the mixture was stirred at rt for a further 18 hrs. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give a pale yellow solid identified as (2-(pyrrolidin-1-yl)pyrimidin-5-yl)methanol (81.0 g, 100% yield)

MH^+ = 180.1

Acetic acid 2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl ester

To a stirred solution of (2-(pyrrolidin-1-yl)pyrimidin-5-yl)methanol (89.1 g, 0.50 moles) in dry DCM (900 mL) at 20 °C was added 4-(dimethylamino)pyridine (3.05 g, 0.025 moles) followed by acetic anhydride (50.8 g, 0.50 moles). The mixture was stirred at ambient temperature for a further 18 hrs. Water (700 mL) was added and the aqueous phase was extracted with DCM (500 mL) and the combined organics

were dried (Na_2SO_4) and concentrated in vacuo to give a pale yellow solid identified as acetic acid 2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl ester (110 g, 100% yield).

MH^+ = 221.8

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester

Acetic acid 2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl ester (112.3 g, 0.51 mol) and methyl-3-(methoxymethyl)-1*H*-pyrazole-4-carboxylate (CAS no. 318496-66-1, synthesised according to the method described in WO 2012/009009) (86.3 g, 0.51 mol) were combined in acetonitrile (1500 mL). Trimethylsilyl trifluoromethanesulfonate (110.3 mL, 0.61 mol) was added. The mixture was heated to 65-70 °C for 3 hrs and then allowed to cool. The reaction mixture was concentrated and separated between EtOAc (1500 mL) and saturated aqueous sodium hydrogen carbonate (1000 mL). The organics were washed with saturated aqueous sodium hydrogen carbonate (750 mL), washed with saturated brine (1000 mL), dried over sodium sulfate, filtered and concentrated to give a brown solid. The solid was dissolved in hot methanol. The solution was cooled to approximately 10 °C and stirred for 1 hour. The solid produced was filtered. The filtrate was concentrated to yield a beige solid identified as a mixture of 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester and 5-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester (94 g).

MH^+ = 332.0

3-(Methoxymethyl)-1-((2-(pyrrolidin-1-yl)pyrimidin-5-yl)methyl)-1H-pyrazole-4-carboxylic acid

A mixture of 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester and 5-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid methyl ester (94 g) was stirred in methanol (188 mL) and water (200 mL). Potassium hydroxide (23.9 g, 0.43 mol) in water (82 mL) was added. The mixture was heated to 55-60 °C for 1 hour and allowed to cool. The majority of the methanol was removed under reduced pressure. The remaining mixture was diluted with water (250 mL) and stirred and cooled in an ice/water bath. Glacial acetic acid (18 mL, 0.31 mol) was added and the mixture stirred for 1 hour. The solid produced was collected by filtration. The filtrates were cooled in an ice/water bath and glacial acetic acid (23 mL, 0.40 mol) was added. After 1 hour the solid produced was collected on top of the previous filter cake. The combined solids were washed with cold ethanol and dried *in vacuo*. The solid was dissolved in hot ethanol and cooled to rt. The solid produced was filtered and washed with cold ethanol (2 × 150 mL). The solid was dissolved in hot ethanol and cooled to rt. The solid product produced was filtered, washed with cold

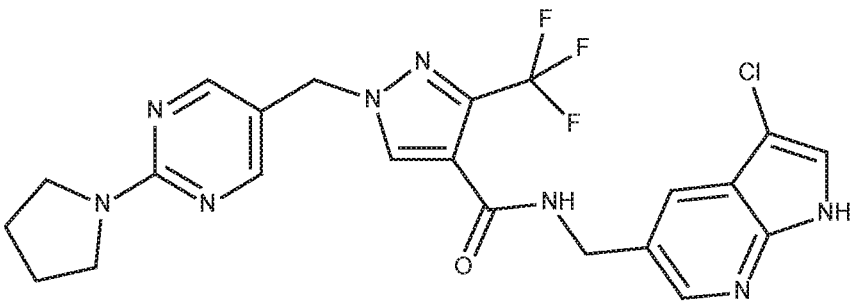
ethanol and *tert*-butyl methyl ether and dried *in vacuo* to afford a white, solid identified as 3-(methoxymethyl)-1-((2-(pyrrolidin-1-yl)pyrimidin-5-yl)methyl)-1H-pyrazole-4-carboxylic acid (49 g). MH^+ = 317.7

3-Methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

1,1'-Carbonyldiimidazole (26.1g, 0.161 mole) was added to a suspension of 3-(methoxymethyl)-1-((2-(pyrrolidin-1-yl)pyrimidin-5-yl)methyl)-1H-pyrazole-4-carboxylic acid (51.1g, 0.161 mole) in N-methylpyrrolidinone (200 mL) and stirred for 3 hrs to give the acylimidazol eintermediate. 6-(Aminomethyl)isoquinolin-1-amine dihydrochloride (47.5 g, 0.193 mole) was suspended in N-methylpyrrolidinone (240 mL) and heated to 55 °C – 60 °C. Triethylamine (102 mL, 0.73 mole) was added and the mixture was stirred for 1 hour, cooled and stirred for a further 1.5 hrs. The acylimidazolide intermediate formed above was added in one portion and stirred for 18hrs. The reaction mixture was poured into water (5000 mL) and stirred for 1.5 hrs. The solid was collected by filtration, washed with water (2 × 250 mL), cold acetonitrile (250 mL) and *tert*-butyl methyl ether (250 mL) and dried *in vacuo* to give a white solid identified as 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide (70.8 g, 93% yield). MH^+ = 473.0

Example 64.

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide



1-(2-Chloro-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Ethyl 3-trifluoromethyl-1H-pyrazole-4-carboxylate (1.25 g, 6.01 mmol) was dissolved in DMF (20 mL). 5-Bromomethyl-2-chloro-pyridine (1.50 g, 7.21 mmol) and cesium carbonate (2.94 g, 9.01 mmol) were added and the reaction mixture was stirred at rt for 3 hrs after which time the reaction mixture was

diluted with EtOAc (100 mL), was washed with water (1x30mL), brine (1x30mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluent 60% Pet. Ether, 40% EtOAc to give a yellow oil identified as 1-(2-chloro-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (710 mg, 35%).

MH^+ = 375.8 (MH^+ + MeCN)

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester

1-(2-Chloro-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (700 mg, 2.09 mmol) was dissolved in anhydrous dioxanes (25 mL) and pyrrolidine (10 mL) and the reaction mixture was stirred at 80 °C for 18 hrs after which time the reaction mixture was evaporated in vacuo. The residue was purified by flash chromatography (silica), eluent 3%MeOH, 97% $CHCl_3$ to give a yellow solid identified as 1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid ethyl ester (760 mg, 99% yield).

MH^+ = 369.0

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid

General saponification method with lithium hydroxide afforded 1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (596 mg, 85% yield).

MH^+ = 341.8

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (596 mg, 1.75 mmol) was dissolved in DCM (50 mL) and DMF (2.5 mL). This solution was cooled to 0 °C. 5-Aminomethyl azaindole (308 mg, 2.10 mmol) was added followed by HOBt (260 mg, 1.92 mmol) and triethylamine (530 mg, 5.24 mmol). EDC (402 mg, 2.1 mmol) was added. After 18 hrs at 0 °C to rt reaction mixture was diluted with chloroform (200 mL), washed with $NaHCO_3$ (1x30mL), water (1x30mL), brine (1x30mL) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluent 6%MeOH, 94% $CHCl_3$ to give a white solid identified as 1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (620 mg, 75% yield).

MH^+ = 470.9

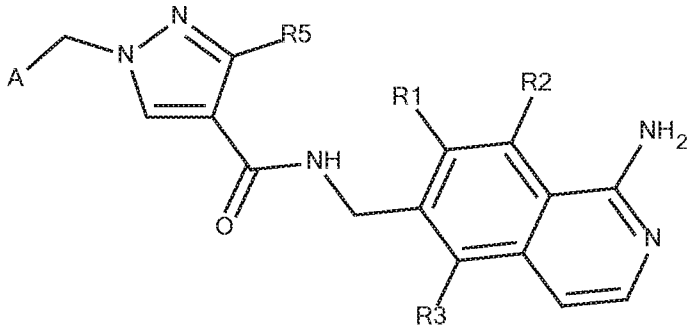
1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide

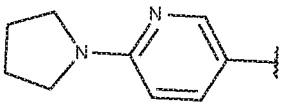
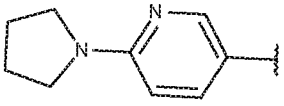
1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (500 mg, 1.06 mmol) was dissolved in acetonitrile (50 mL). To this solution was added N-chlorosuccinimide (149 mg, 1.12 mmol). The reaction mixture was stirred at reflux for 7 hrs. The solvent was removed in vacuo and the residue taken up in EtOAc (100 mL), washed with sat. $NaHCO_3$ (1x20mL), water (1x20mL), brine (1x20mL), dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by flash chromatography (silica), eluent 6%MeOH, 94% $CHCl_3$. The resulting material was dissolved in chloroform (100 mL) and this solution was washed with sat. $NaHCO_3$ (1x20mL), water (1x20mL), brine (1x20mL), dried (Na_2SO_4) and evaporated in vacuo to give a white solid identified as 1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide (430 mg, 80% yield).

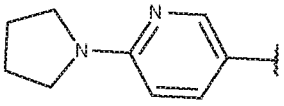
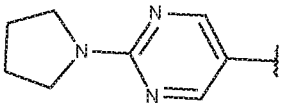
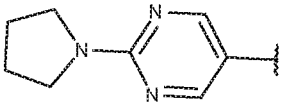
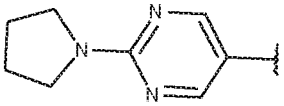
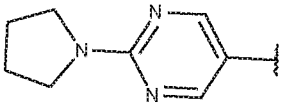
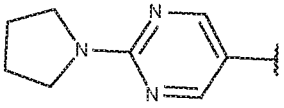
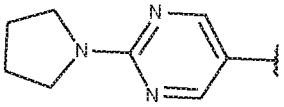
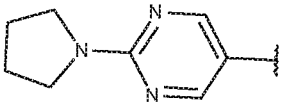
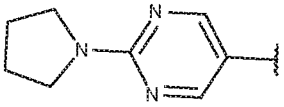
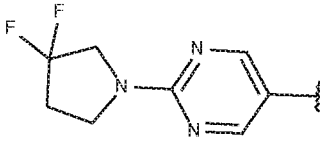
$MH^+ = 505.0$

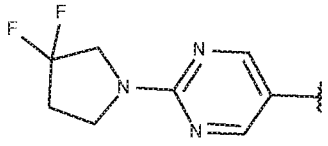
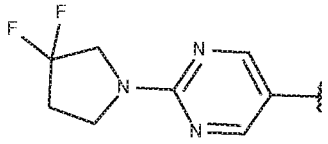
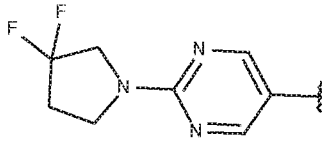
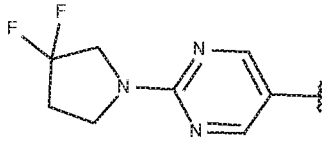
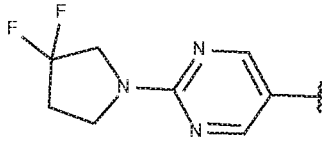
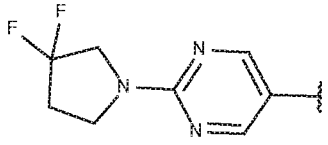
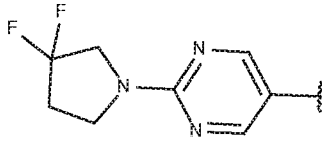
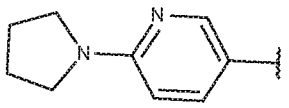
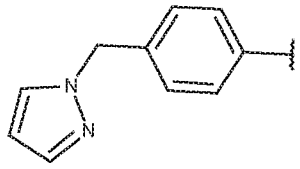
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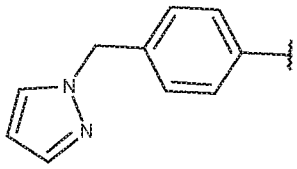
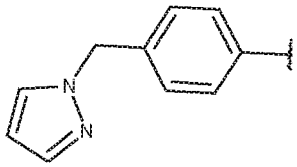
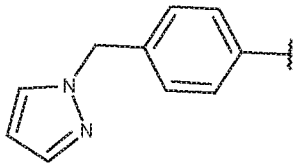
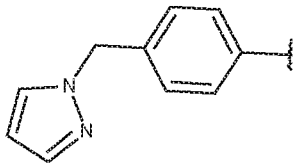
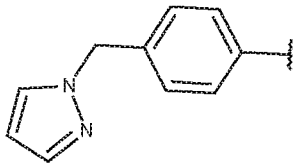
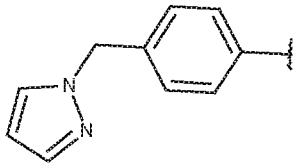
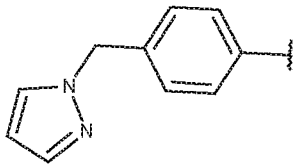
Table 1

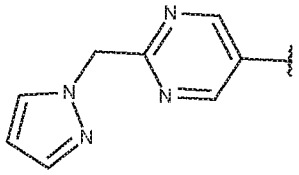
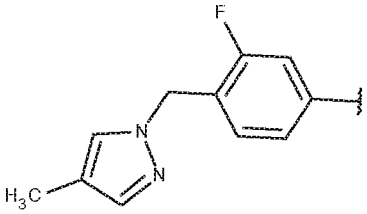
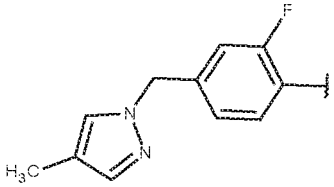
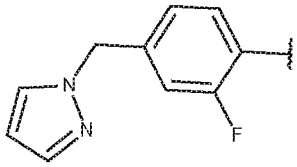
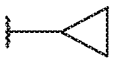
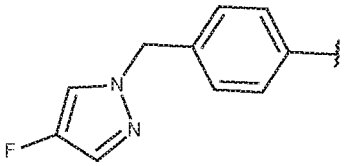
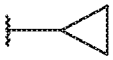
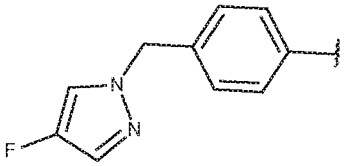
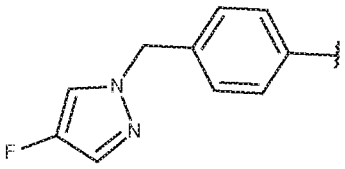


Example number	A	R1	R2	R3	R5	Free Base MW
5		H	H	CH_3	CH_2OMe	485.6
6		H	H	F	CH_2OMe	489.5

Example number	A	R1	R2	R3	R5	Free Base MW
7		H	H	OMe	CH_2OMe	501.6
8		H	H	H	CH_2OMe	472.5
9		H	H	CH_3	CH_2OMe	486.6
10		H	H	F	CH_2OMe	490.5
11		H	H	OMe	CH_2OMe	502.6
12		CH_3	H	H	CH_2OMe	486.6
13		OMe	H	H	CH_2OMe	502.6
14		F	H	H	CH_2OMe	490.5
15		H	OMe	H	CH_2OMe	502.6
16		H	H	H	CH_2OMe	508.5

Example number	A	R1	R2	R3	R5	Free Base MW
17		H	H	CH_3	CH_2OMe	522.6
18		H	H	F	CH_2OMe	526.5
19		H	H	OMe	CH_2OMe	538.5
20		OMe	H	H	CH_2OMe	538.5
21		CH_3	H	H	CH_2OMe	522.6
22		F	H	H	CH_2OMe	526.5
23		H	OMe	H	CH_2OMe	538.5
24		H	H	H	CH_2CH_2OMe	485.6
25		H	H	CH_3	CH_2OMe	495.6

Example number	A	R1	R2	R3	R5	Free Base MW
26		H	H	F	CH_2OMe	499.5
27		H	H	OMe	CH_2OMe	511.6
28		OMe	H	H	CH_2OMe	511.6
29		F	H	H	CH_2OMe	499.5
30		CH_3	H	H	CH_2OMe	495.6
31		H	OMe	H	CH_2OMe	511.6
32		H	H	H	$CH_2OCH_2CH_3$	495.6

Example number	A	R1	R2	R3	R5	Free Base MW
34		H	H	H	CF_3	507.5
35		H	H	H	CH_2OMe	513.6
36		H	H	H	CH_2OMe	513.6
37		H	H	H		495.6
38		H	H	H		495.6
39		H	H	H	CH_2OMe	499.5
40		H	H	CH_3	CH_2OMe	513.6

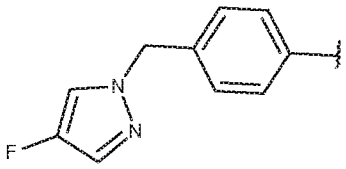
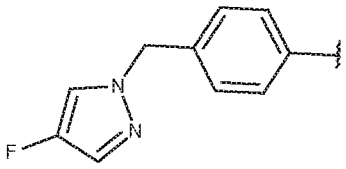
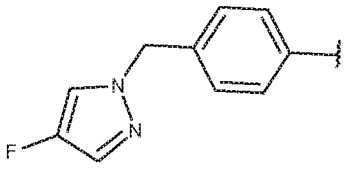
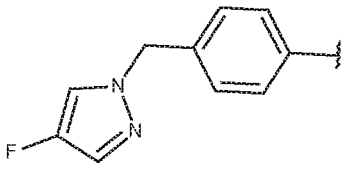
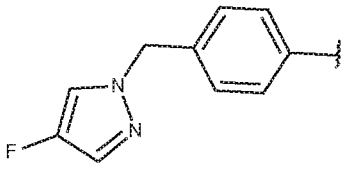
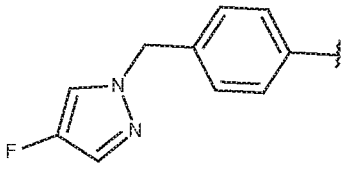
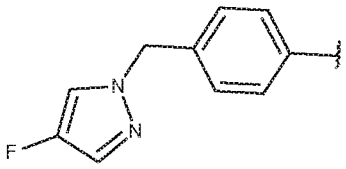
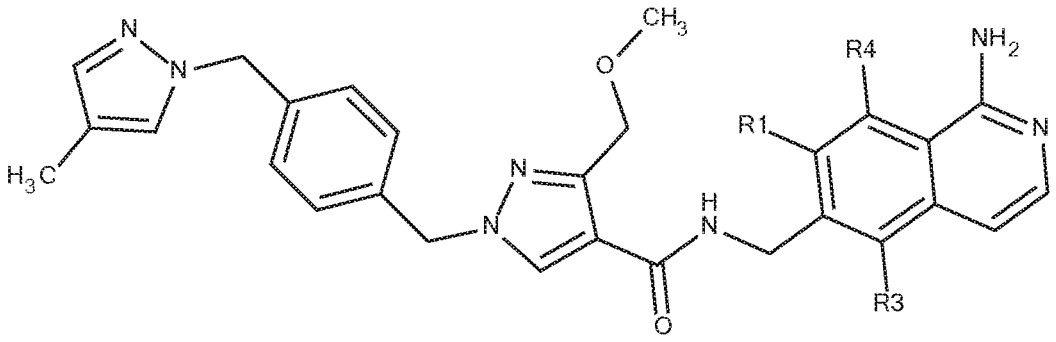
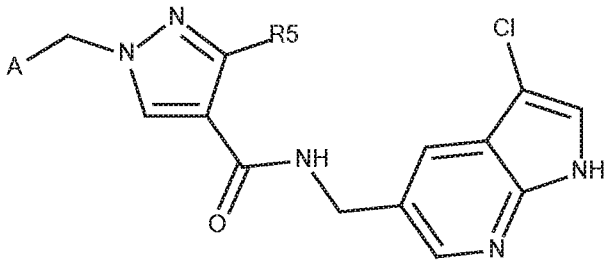
Example number	A	R1	R2	R3	R5	Free Base MW
41		H	H	F	CH_2OMe	517.5
42		H	H	OMe	CH_2OMe	529.6
43		OMe	H	H	CH_2OMe	529.6
44		F	H	H	CH_2OMe	517.5
45		H	OMe	H	CH_2OMe	529.6
46		CH_3	H	H	CH_2OMe	513.6
47		H	H	H	CF_3	523.5

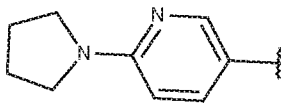
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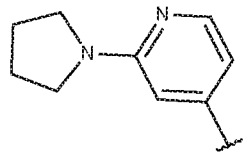
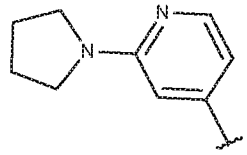
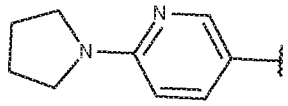
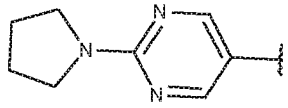
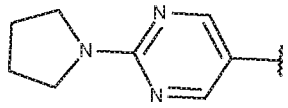
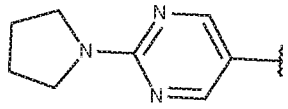
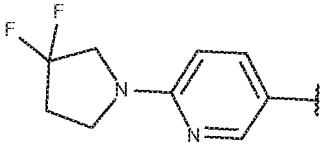
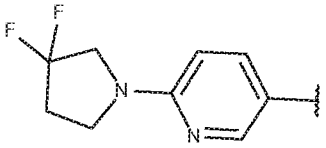
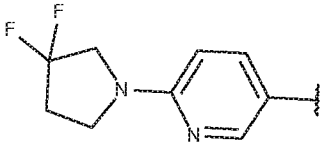


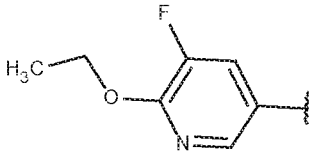
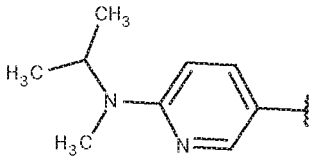
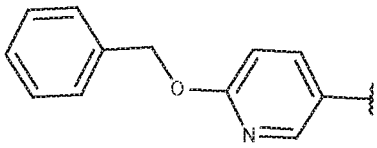
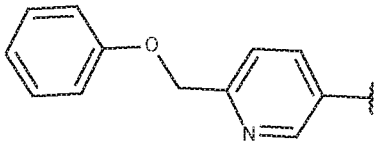
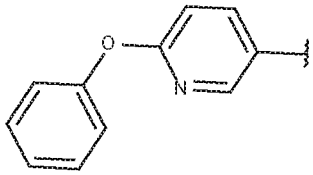
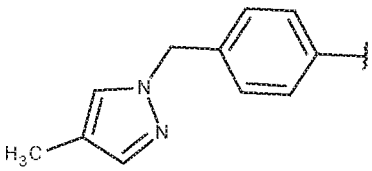
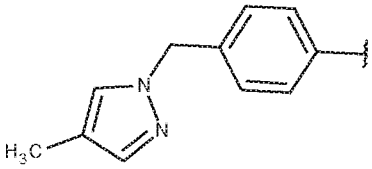
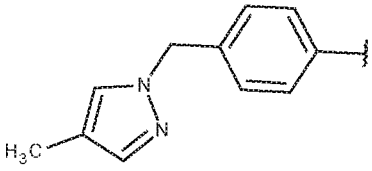
Example Number	R1	R3	R4	Free Base MW
48	F	H	H	513.6
49	OMe	H	H	525.6
50	H	F	H	513.6
51	H	OMe	H	525.6
52	H	H	OMe	525.6
53	H	CH_3	H	509.6
54	CH_3	H	H	509.6

Table 3



Example Number	A	R5	Free Base MW
55		CF_3	503.9

Example Number	A	R5	Free Base MW
56		CF_3	503.9
57		NH_2	450.9
59		CN	460.9
63		NH_2	451.9
64		CF_3	504.9
65		CH_2OMe	481.0
66		CF_3	539.9
67		NH_2	486.9
68		CH_2OMe	515.9

Example Number	A	R5	Free Base MW
69		CF_3	496.8
70		CF_3	505.9
71		NH_2	487.0
72		NH_2	487.0
73		NH_2	472.9
74		CH_2OMe	504.0
75		CN	484.9
76		NH_2	474.9

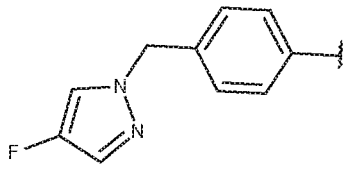
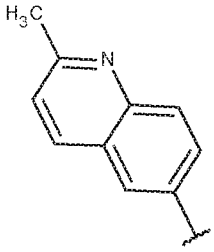
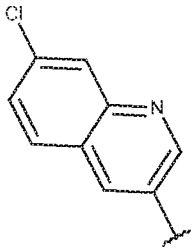
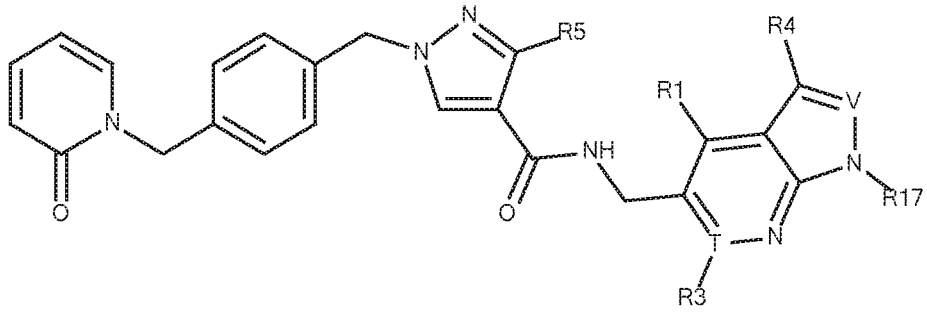
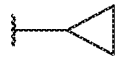
Example Number	A	R5	Free Base MW
78		CH_2OMe	508.0
79		CH_2OMe	474.9
80		CH_2OMe	495.4

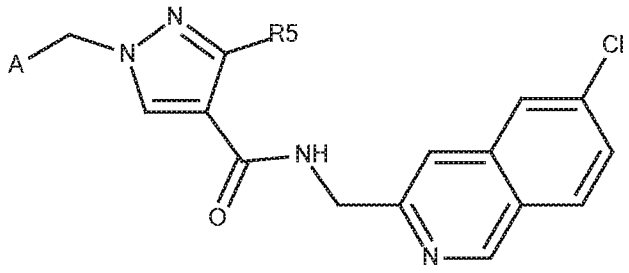
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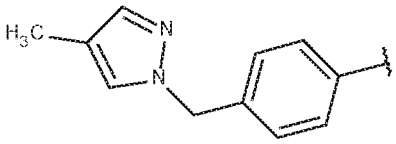
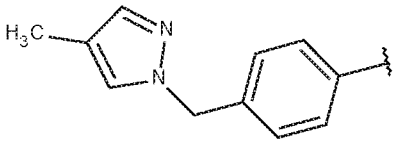
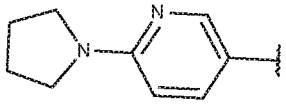
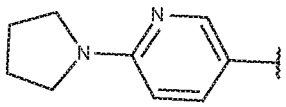


Example Number	R5	R1	R3	R4	R17	T	V	Free Base MW
81	NH_2	H	H	Cl	H	C	CH	487.0
82	NH_2	H	H	Cl	H	C	N	487.9
83		H	H	CN	H	C	CH	503.6

Example Number	R5	R1	R3	R4	R17	T	V	Free Base MW
84	CH_2OMe	H	H	F	H	C	CH	500.5
85	CF_3	CH_3	H	H	H	C	CH	520.5
86	CF_3	H	H	H	CH_3	C	N	521.5
87	CH_2OMe	H	absent	Cl	H	N	CH	517.0

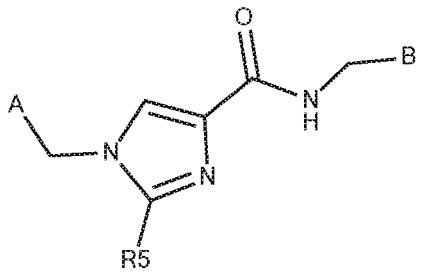
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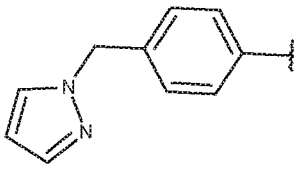
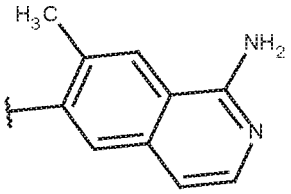
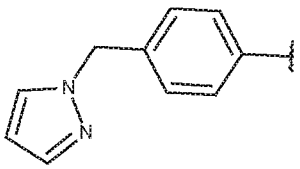
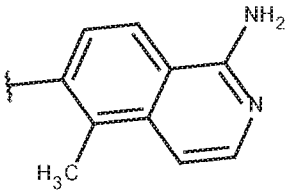
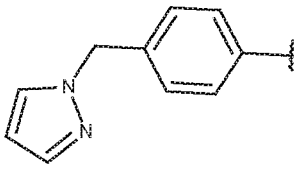
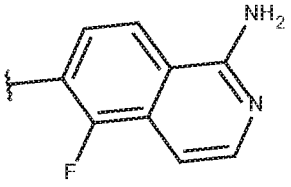
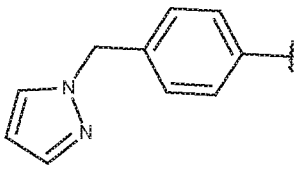
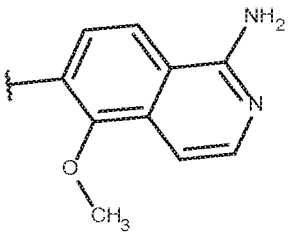
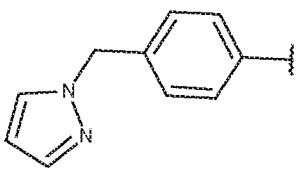
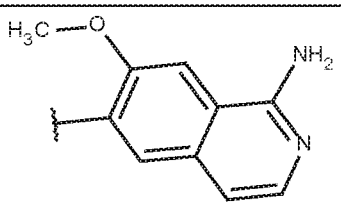


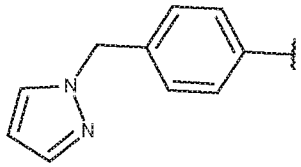
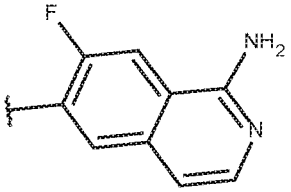
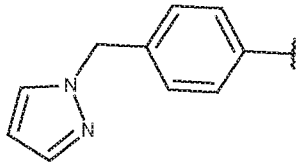
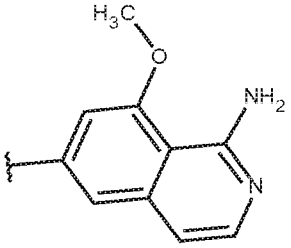
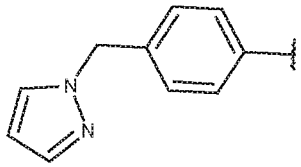
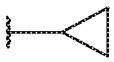
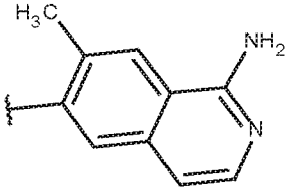
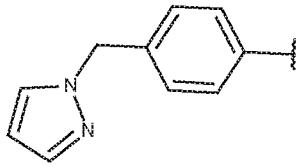
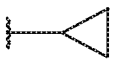
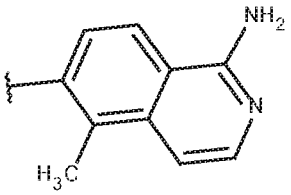
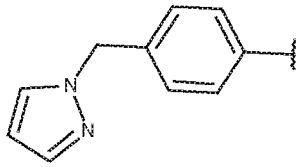
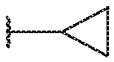
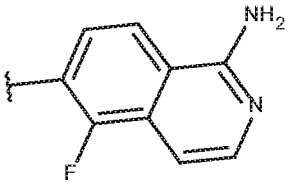
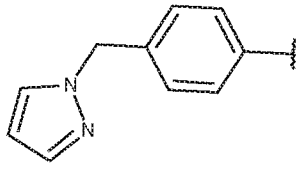
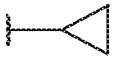
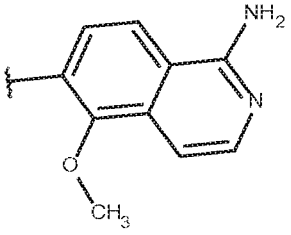
Example Number	A	R5	Free Base MW
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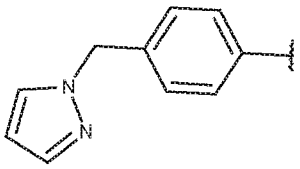
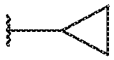
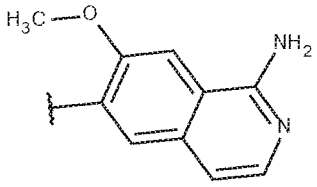
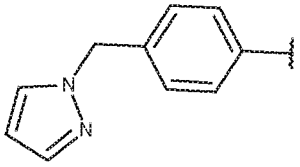
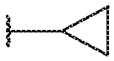
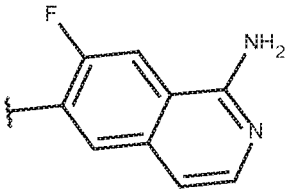
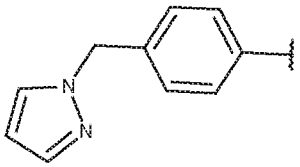
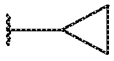
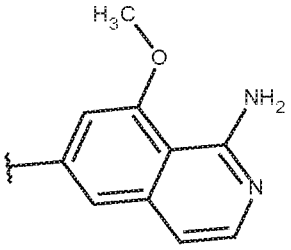
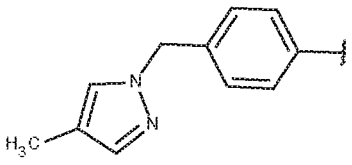
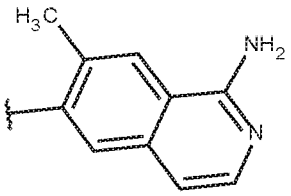
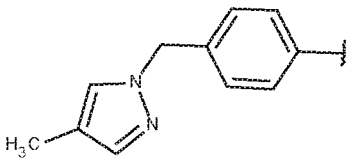
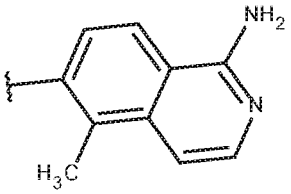
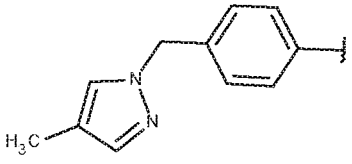
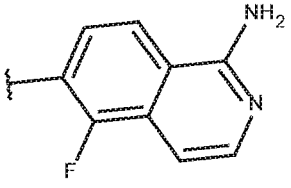
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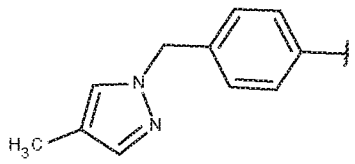
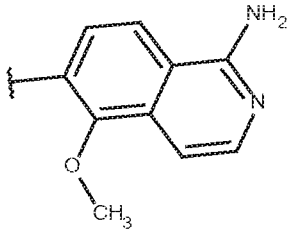
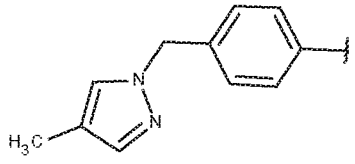
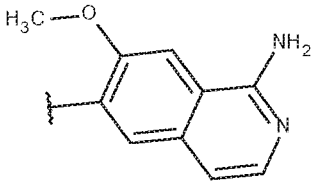
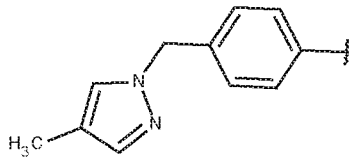
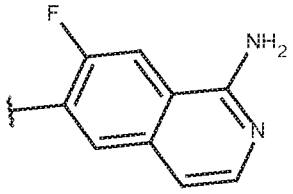
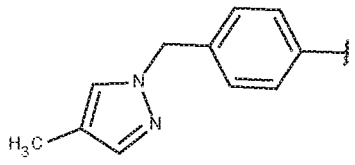
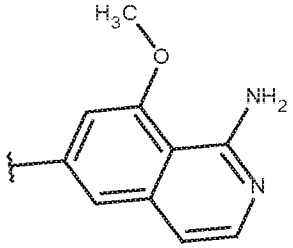
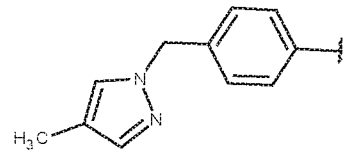
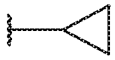
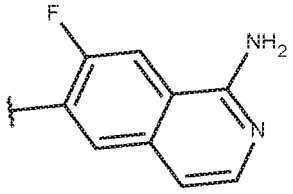
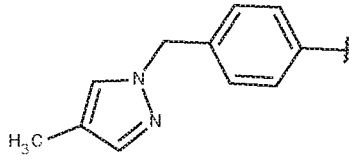
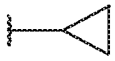
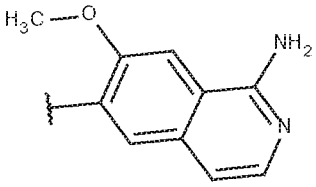
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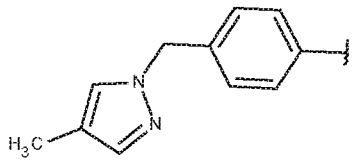
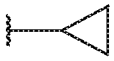
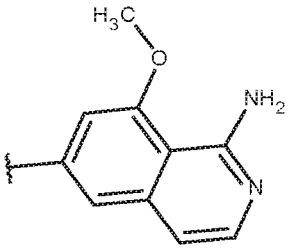
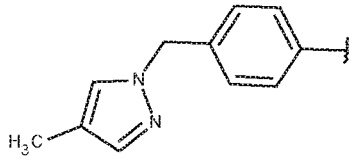
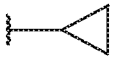
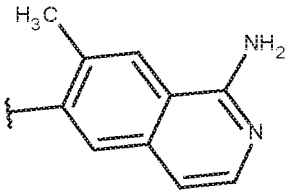
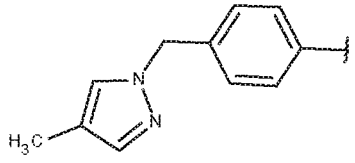
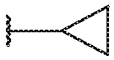
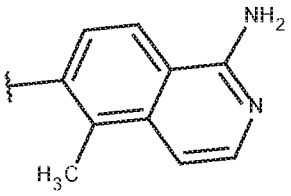
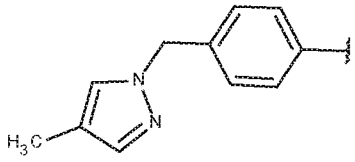
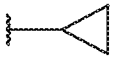
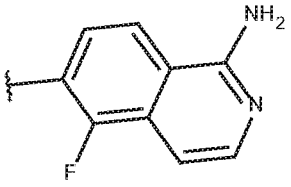
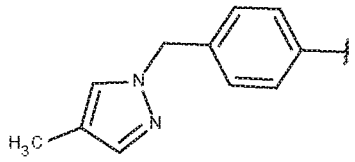
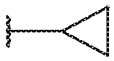
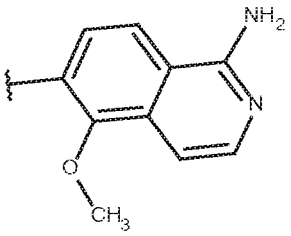
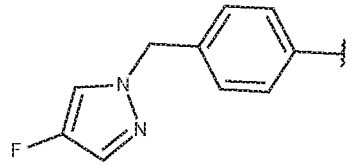
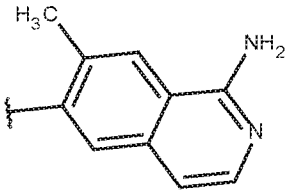


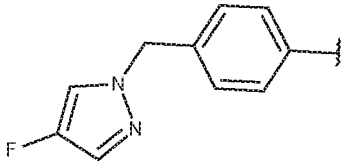
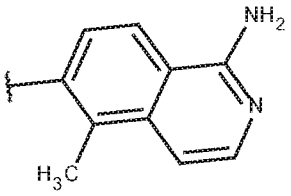
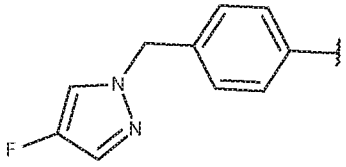
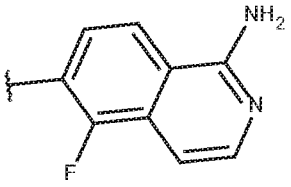
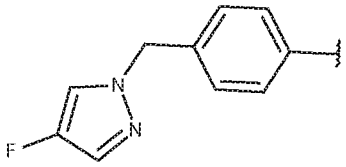
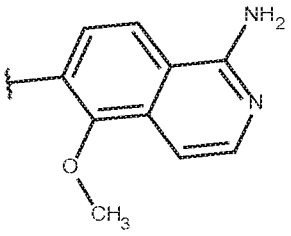
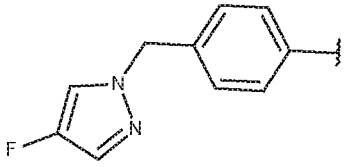
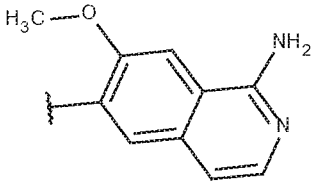
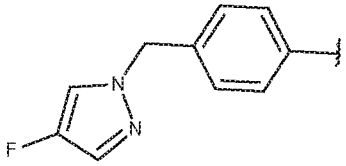
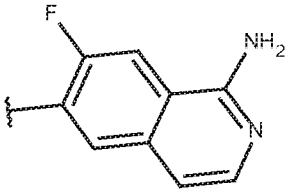
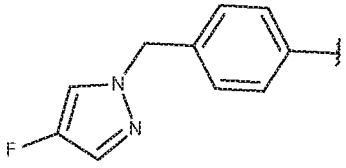
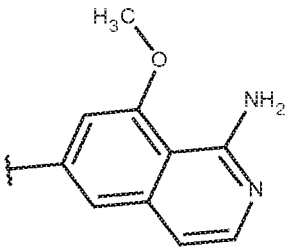
Example number	A	R5	B	Free Base MW
106		CH_3		465.5
107		CH_3		465.5
108		CH_3		469.5
109		CH_3		481.5
110		CH_3		481.5

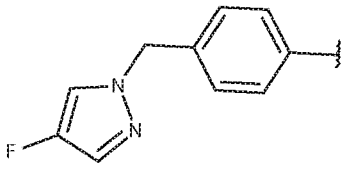
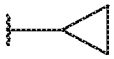
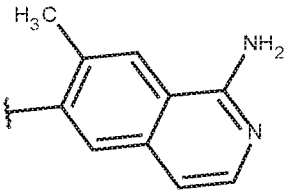
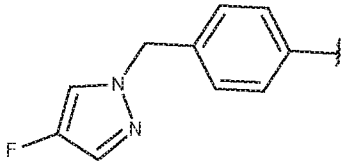
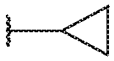
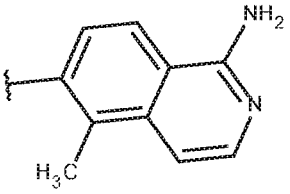
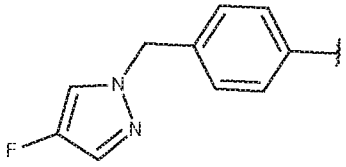
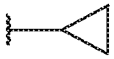
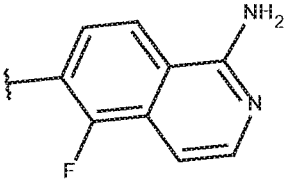
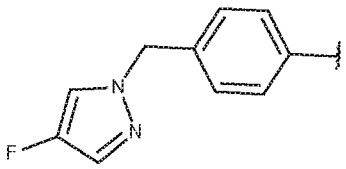
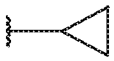
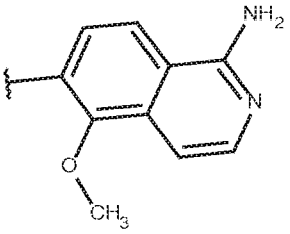
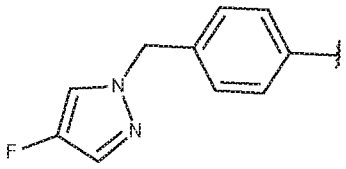
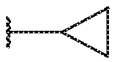
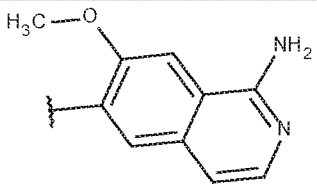
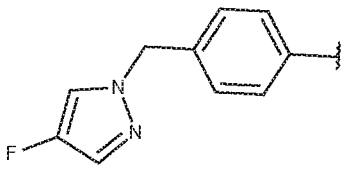
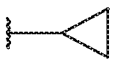
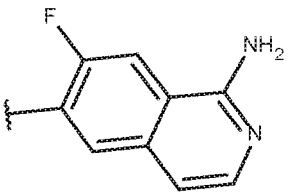
Example number	A	R5	B	Free Base MW
111		CH_3		469.5
112		CH_3		481.5
113				491.6
114				491.6
115				495.6
116				507.6

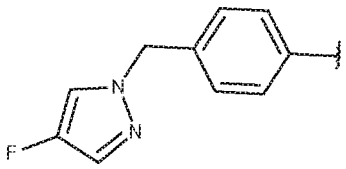
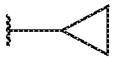
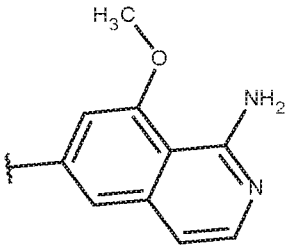
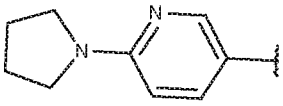
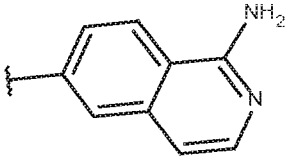
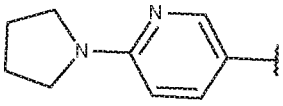
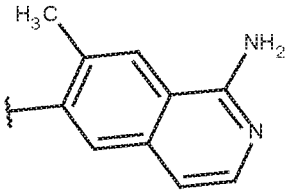
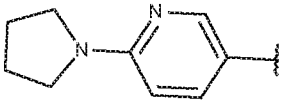
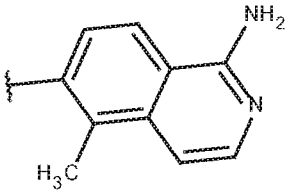
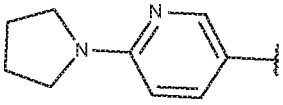
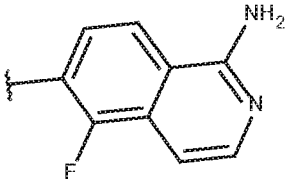
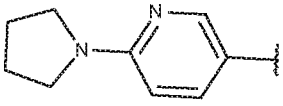
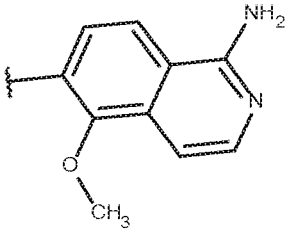
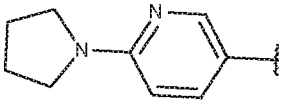
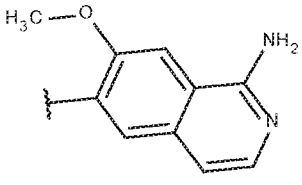
Example number	A	R5	B	Free Base MW
117				507.6
118				495.6
119				507.6
120		CH_3		479.6
121		CH_3		479.6
122		CH_3		483.5

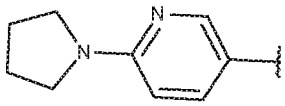
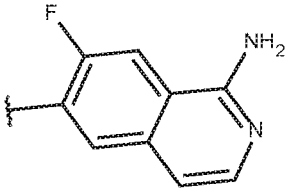
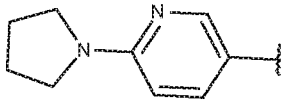
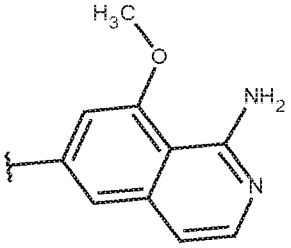
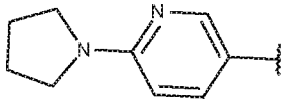
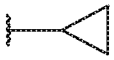
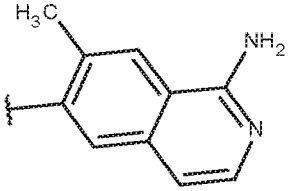
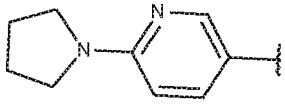
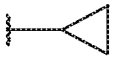
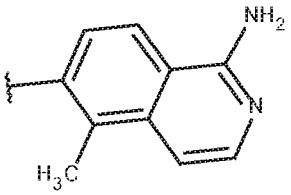
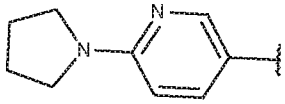
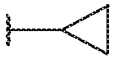
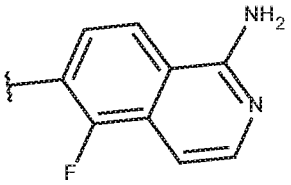
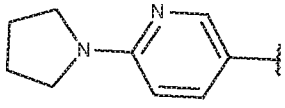
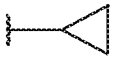
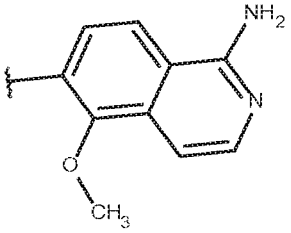
Example number	A	R5	B	Free Base MW
123		CH_3		495.6
124		CH_3		495.6
125		CH_3		483.5
126		CH_3		495.6
127				509.6
128				521.6

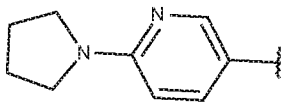
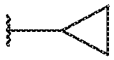
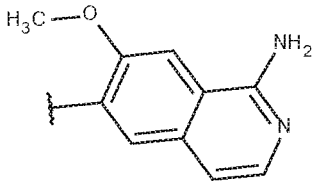
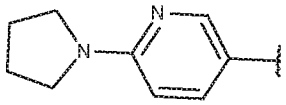
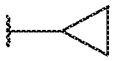
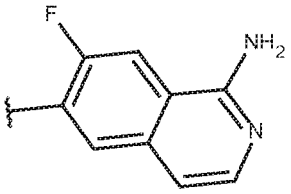
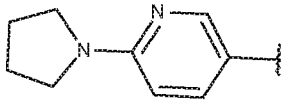
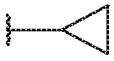
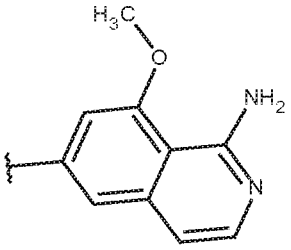
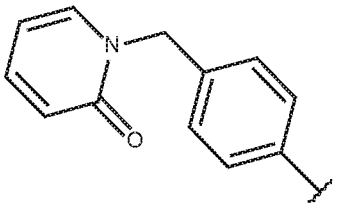
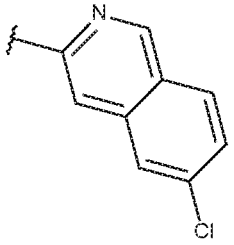
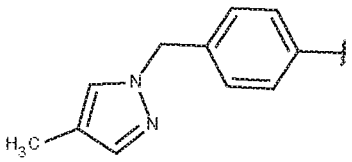
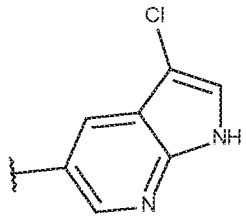
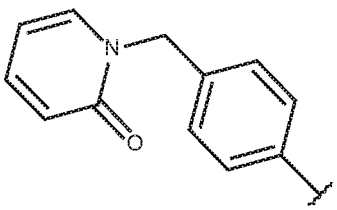
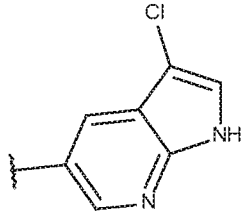
Example number	A	R5	B	Free Base MW
129				521.6
130				505.6
131				505.6
132				509.6
133				521.6
134		CH_3		483.5

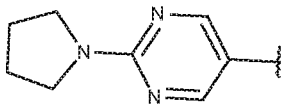
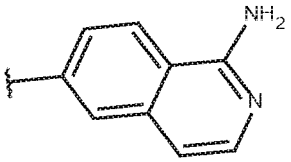
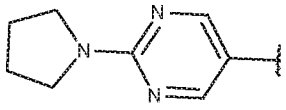
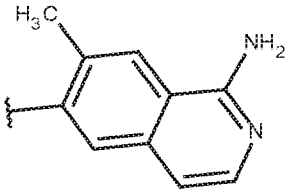
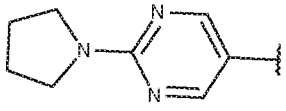
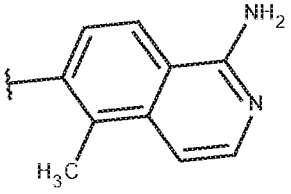
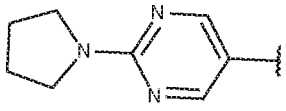
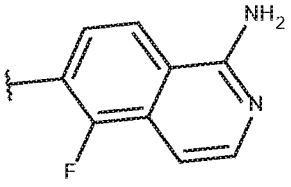
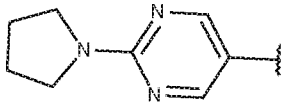
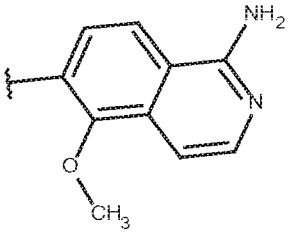
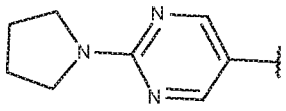
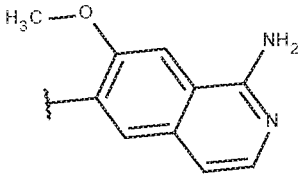
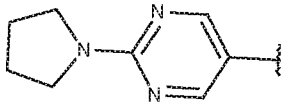
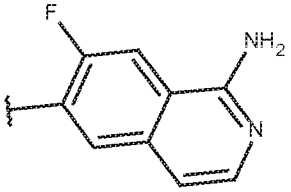
Example number	A	R5	B	Free Base MW
135		CH_3		483.5
136		CH_3		487.5
137		CH_3		499.5
138		CH_3		499.5
139		CH_3		487.5
140		CH_3		499.5

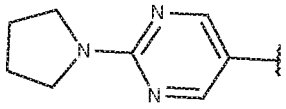
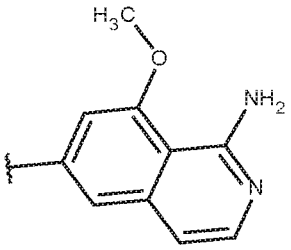
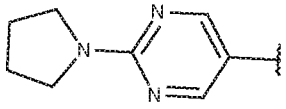
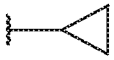
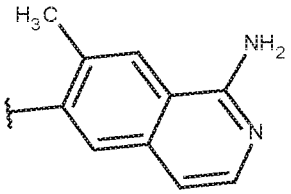
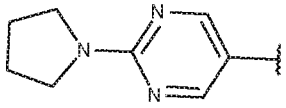
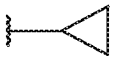
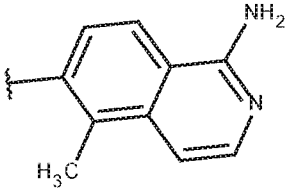
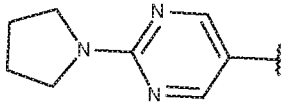
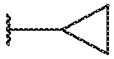
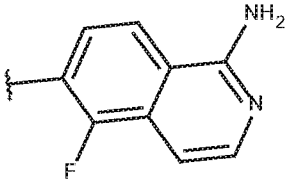
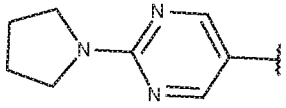
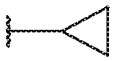
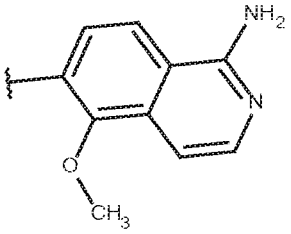
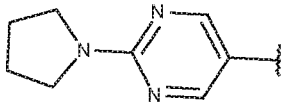
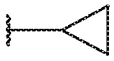
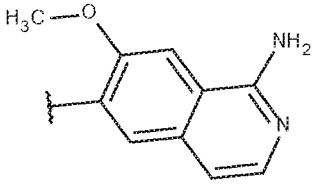
Example number	A	R5	B	Free Base MW
141				509.6
142				509.6
143				513.5
144				525.6
145				525.6
146				513.5

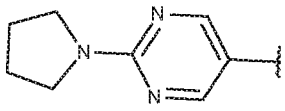
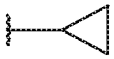
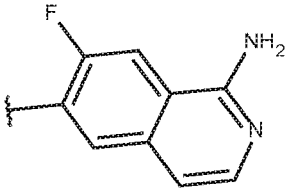
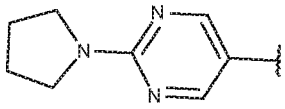
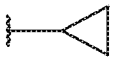
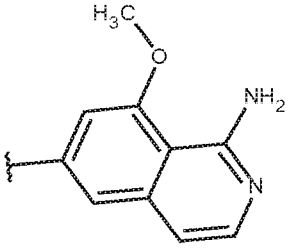
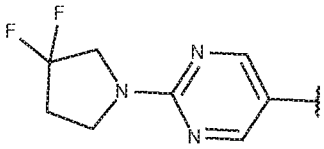
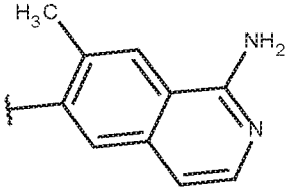
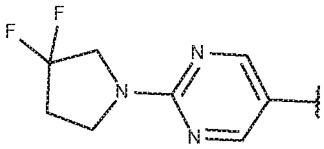
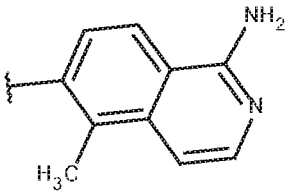
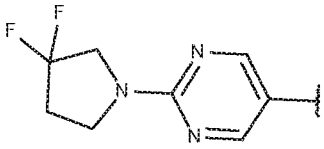
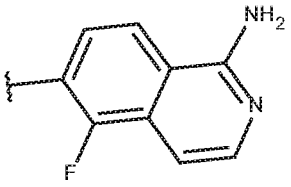
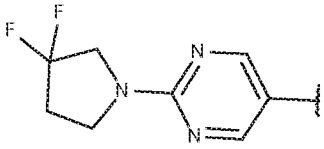
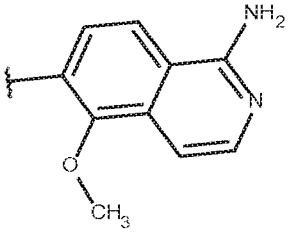
Example number	A	R5	B	Free Base MW
147				525.6
148		CH_3		441.5
149		CH_3		455.6
150		CH_3		455.6
151		CH_3		459.5
152		CH_3		471.6
153		CH_3		471.6

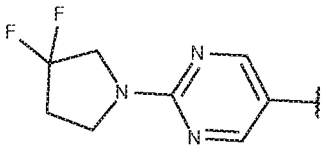
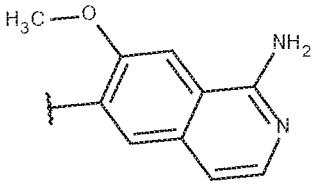
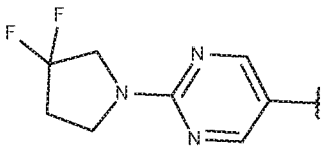
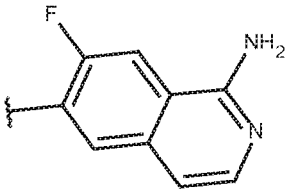
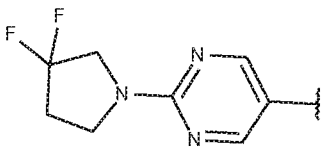
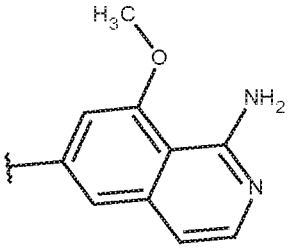
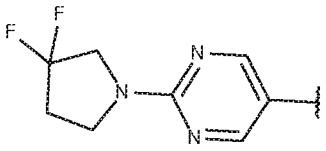
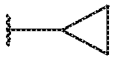
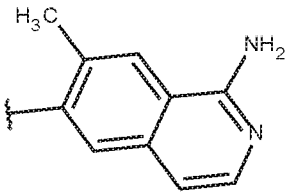
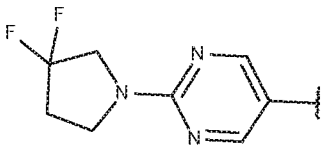
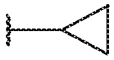
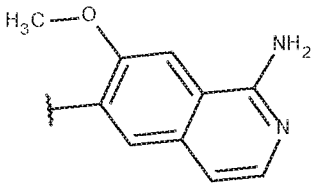
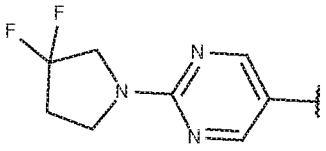
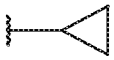
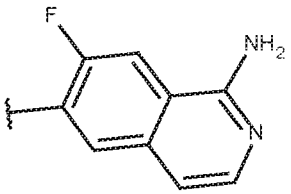
Example number	A	R5	B	Free Base MW
154		CH_3		459.5
155		CH_3		471.6
156				481.6
157				481.6
158				485.6
159				497.6

Example number	A	R5	B	Free Base MW
160				497.6
161				485.6
162				497.6
163		CH_3		498.0
164		CH_3		474.0
165		CH_3		487.0

Example number	A	R5	B	Free Base MW
166		CH_3		442.5
167		CH_3		456.5
168		CH_3		456.5
169		CH_3		460.5
170		CH_3		472.5
171		CH_3		472.5
172		CH_3		460.5

Example number	A	R5	B	Free Base MW
173		CH_3		472.5
174				482.6
175				482.6
176				486.5
177				498.6
178				498.6

Example number	A	R5	B	Free Base MW
179				486.5
180				498.6
181		CH_3		492.5
182		CH_3		492.5
183		CH_3		496.5
184		CH_3		508.5

Example number	A	R5	B	Free Base MW
185		CH_3		508.5
186		CH_3		496.5
187		CH_3		508.5
188				518.6
189				534.6
190				522.5

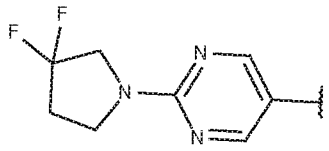
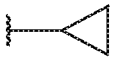
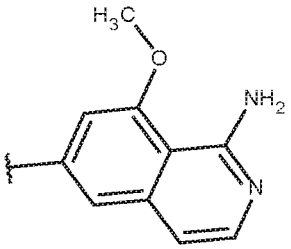
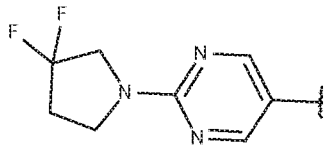
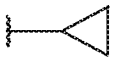
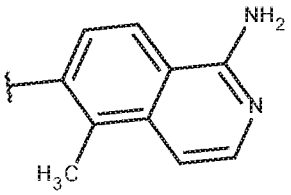
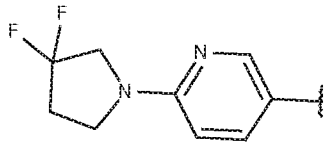
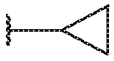
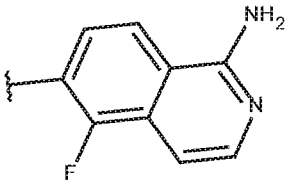
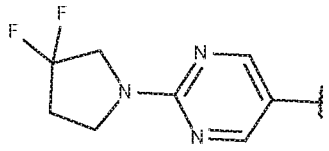
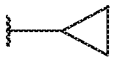
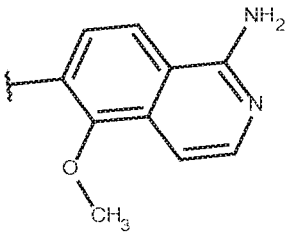
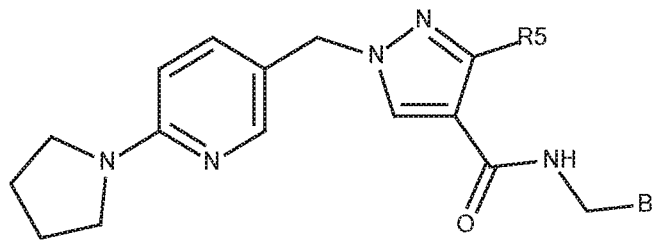
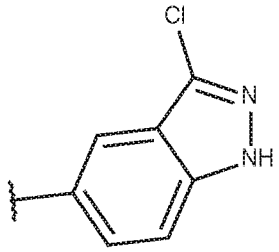
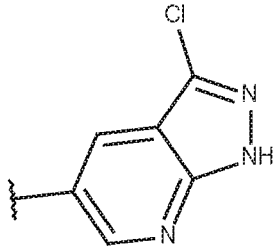
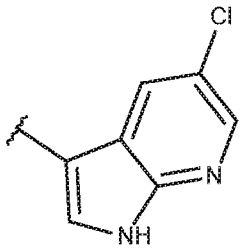
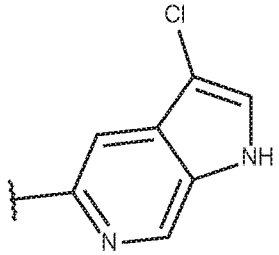
Example number	A	R5	B	Free Base MW
191				534.6
192				518.6
193				521.5
194				534.6

Table 7



Example Number	R5	B	Free Base MW
196	NH_2		450.9
197	CF_3		504.9
199	CF_3		503.9
201	CF_3		503.9

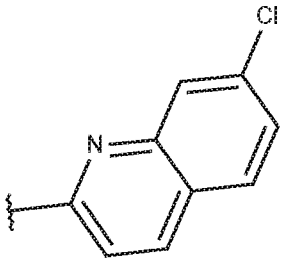
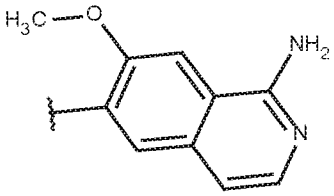
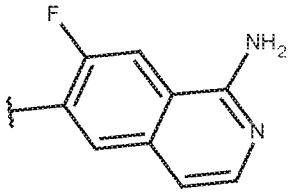
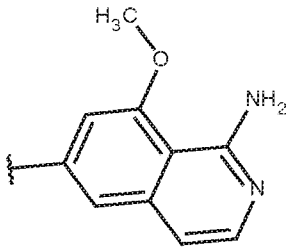
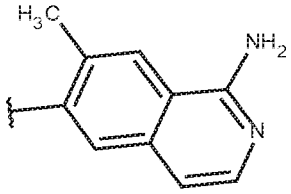
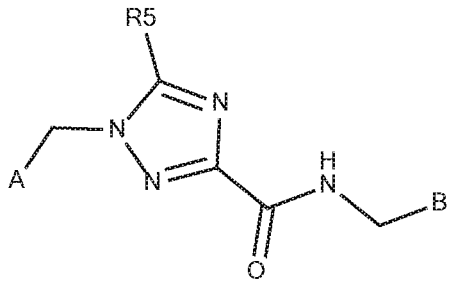
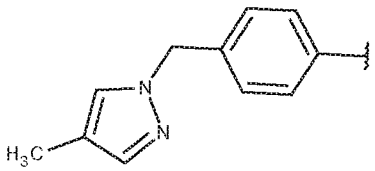
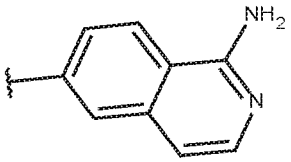
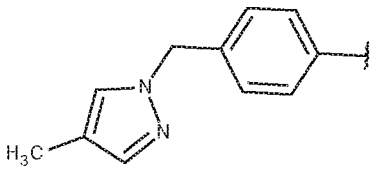
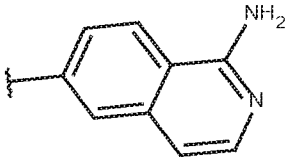
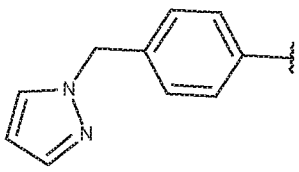
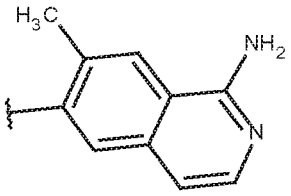
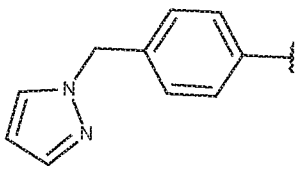
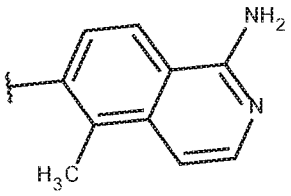
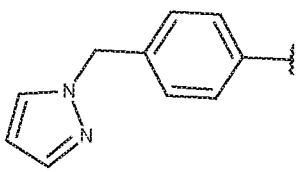
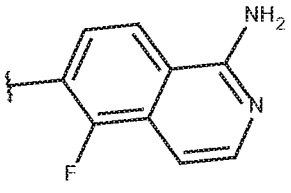
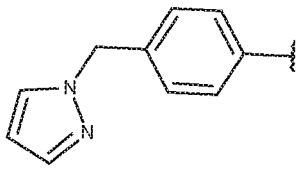
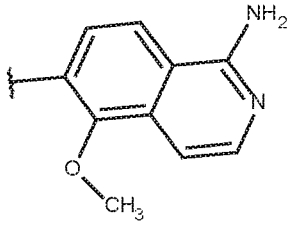
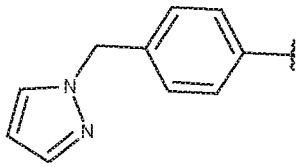
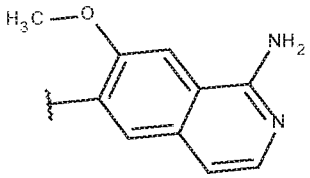
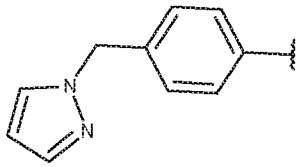
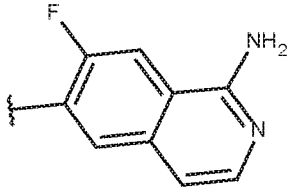
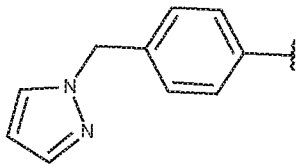
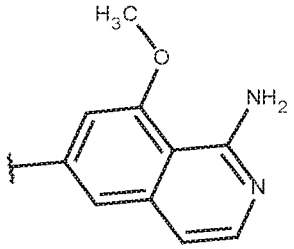
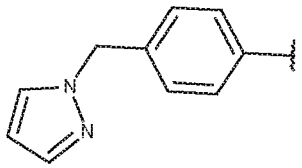
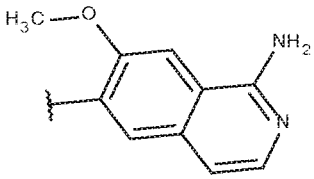
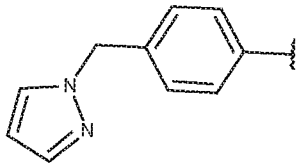
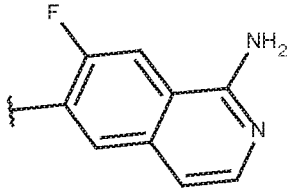
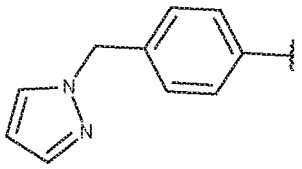
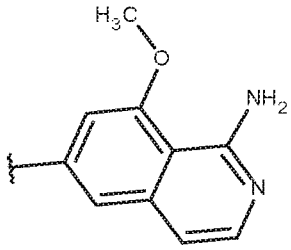
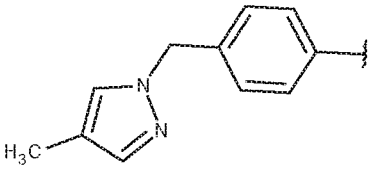
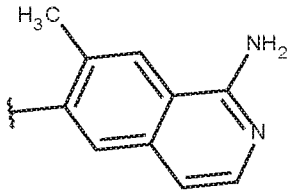
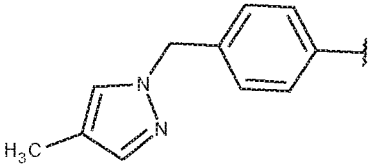
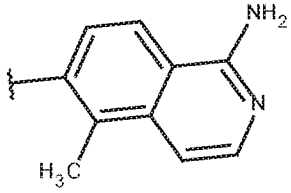
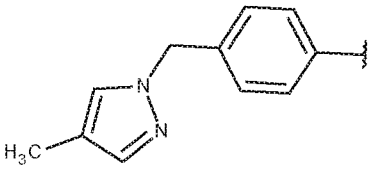
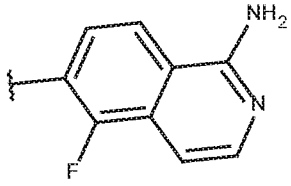
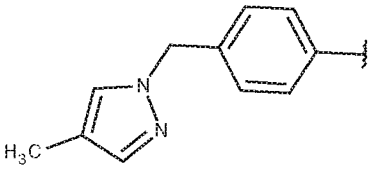
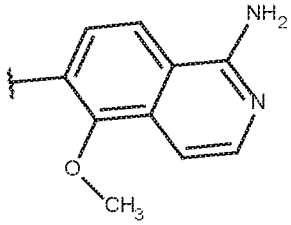
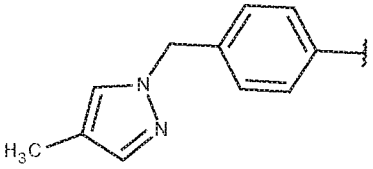
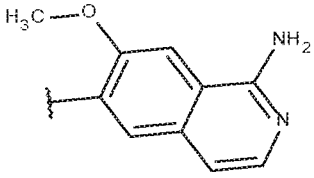
Example Number	R5	B	Free Base MW
202	NH_2		461.9
203	CH_2OMe		501.6
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206	CH_2OMe		485.6

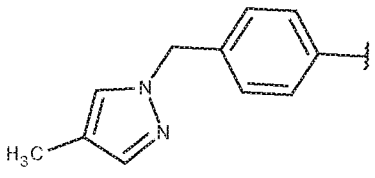
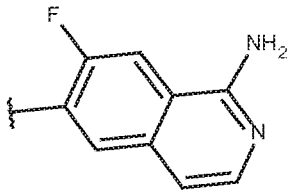
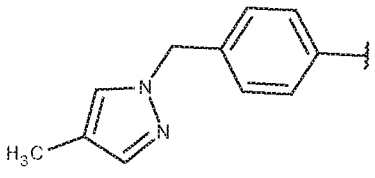
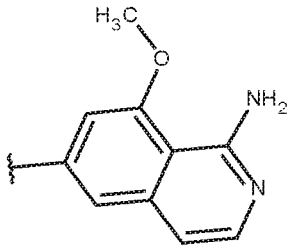
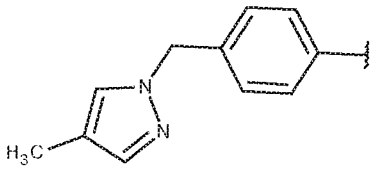
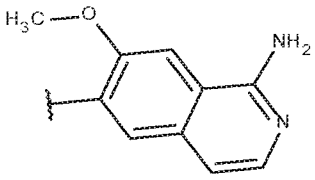
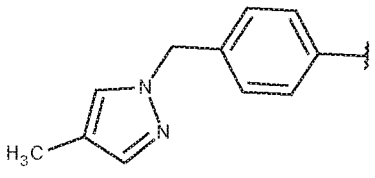
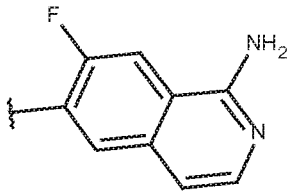
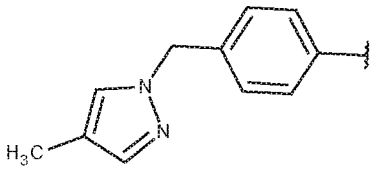
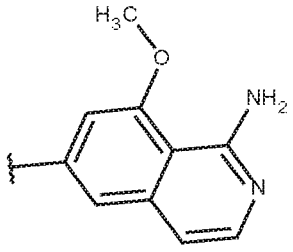
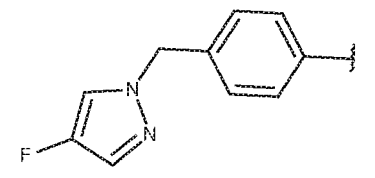
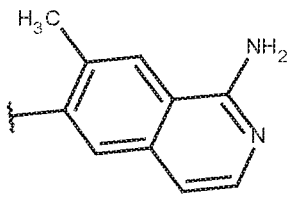
Table 8

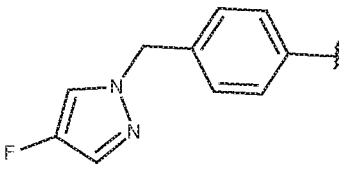
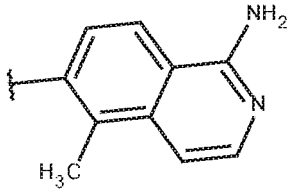
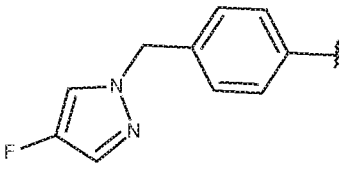
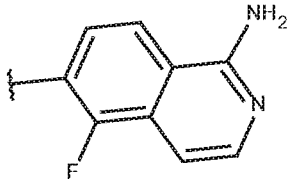
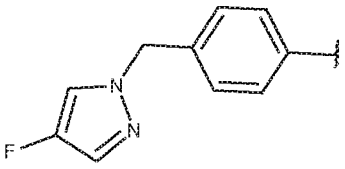
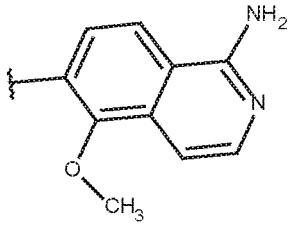
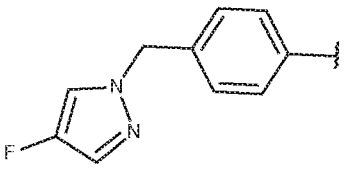
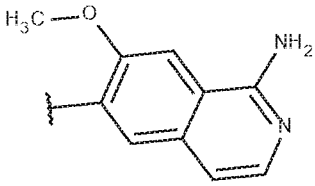
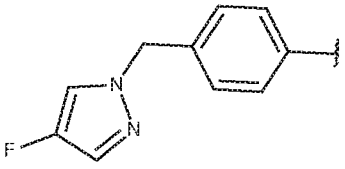
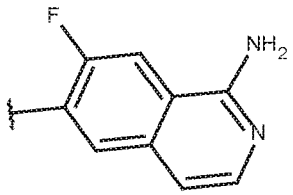
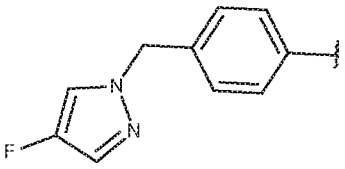
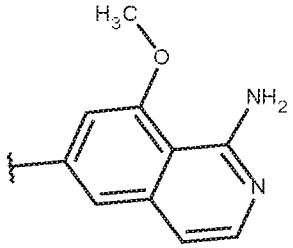


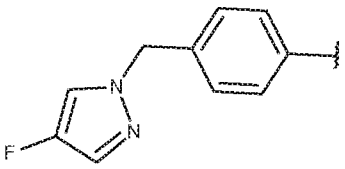
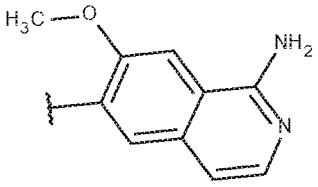
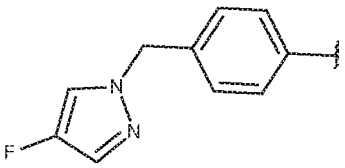
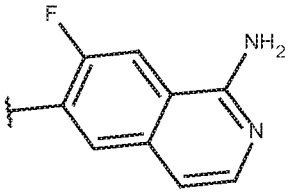
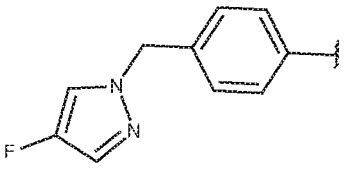
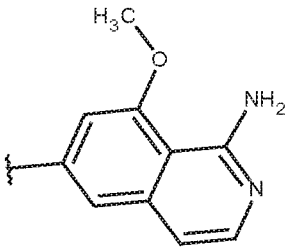
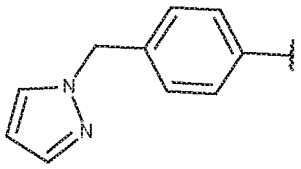
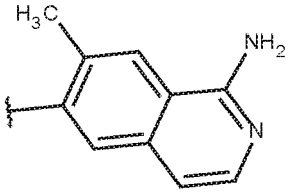
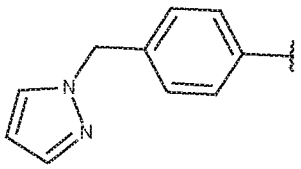
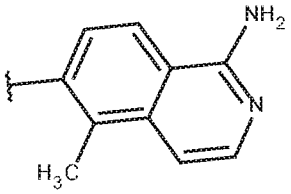
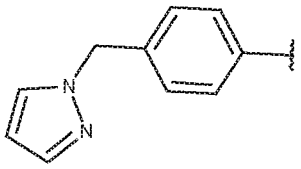
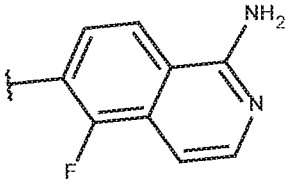
Example number	A	R5	B	Free Base MW
207		CH_3		466.5
208		CH_2OMe		496.6
209		CH_3		466.5
210		CH_3		466.5
211		CH_3		470.5

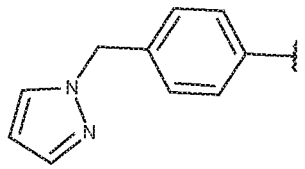
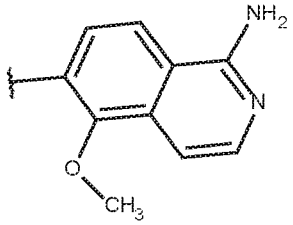
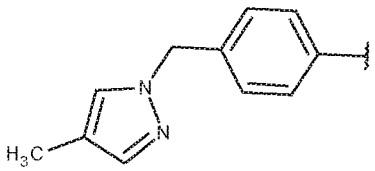
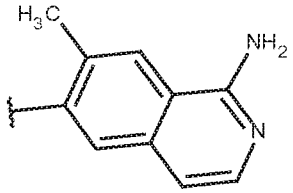
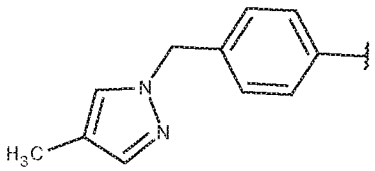
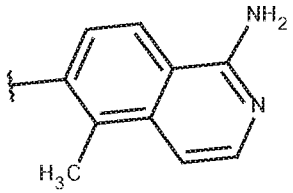
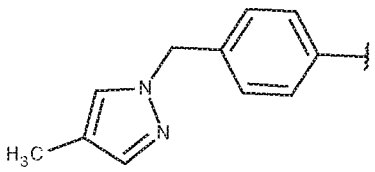
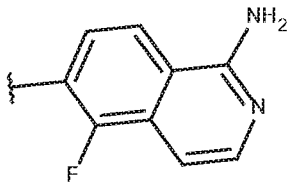
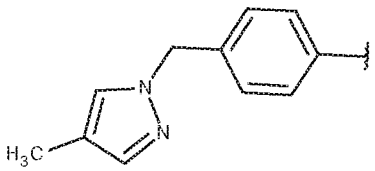
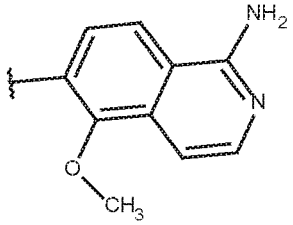
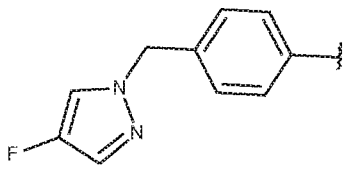
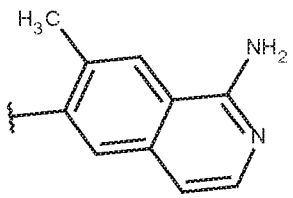
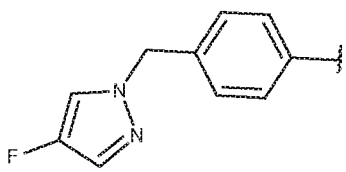
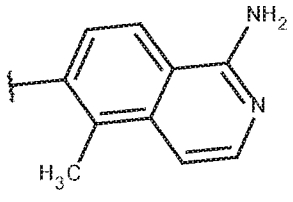
Example number	A	R5	B	Free Base MW
212		CH_3		482.5
213		CH_3		482.5
214		CH_3		470.5
215		CH_3		482.5
216		CH_2OMe		512.6
217		CH_2OMe		500.5

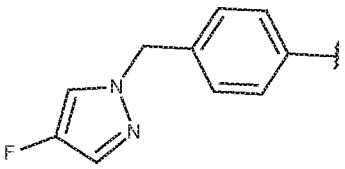
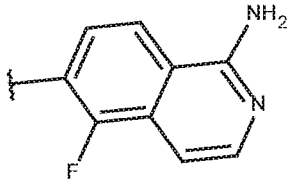
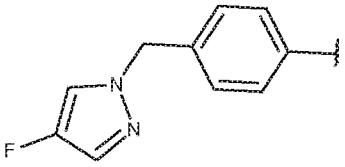
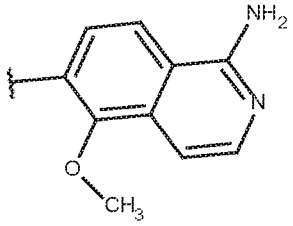
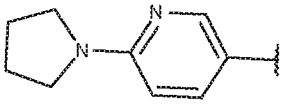
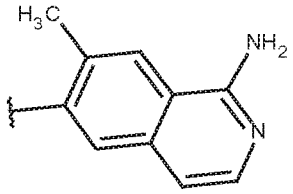
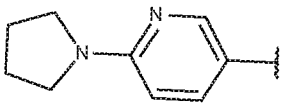
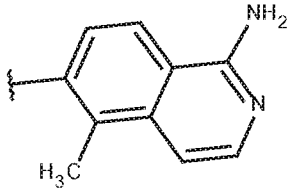
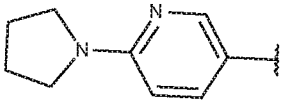
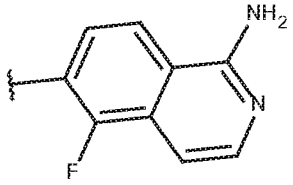
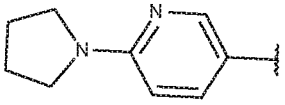
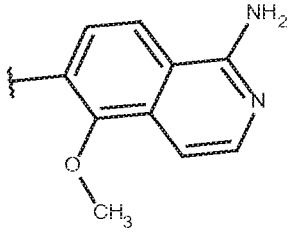
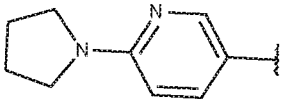
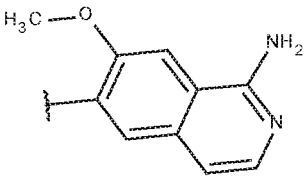
Example number	A	R5	B	Free Base MW
218		CH_2OMe		512.6
219		CH_3		480.6
220		CH_3		480.6
221		CH_3		484.5
222		CH_3		496.6
223		CH_3		496.6

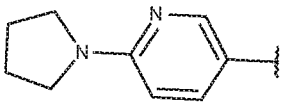
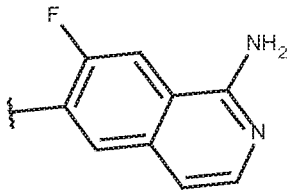
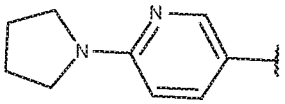
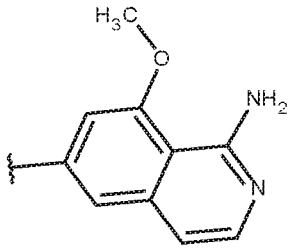
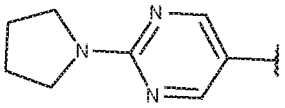
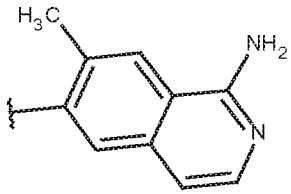
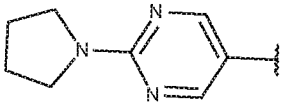
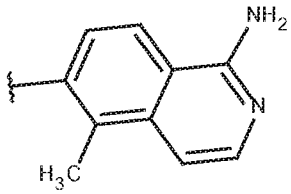
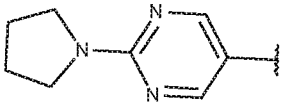
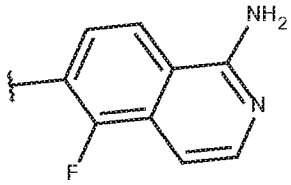
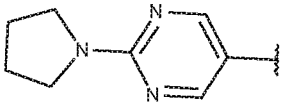
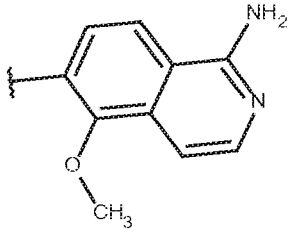
Example number	A	R5	B	Free Base MW
224		CH_3		484.5
225		CH_3		496.6
226		CH_2OMe		526.6
227		CH_2OMe		514.6
228		CH_2OMe		526.6
229		CH_3		484.5

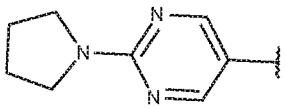
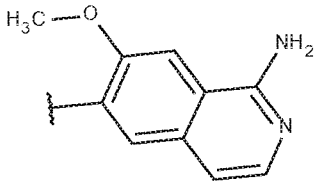
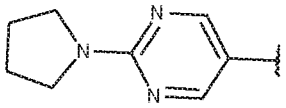
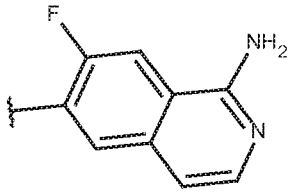
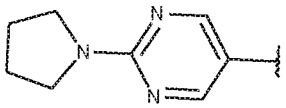
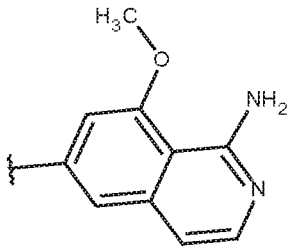
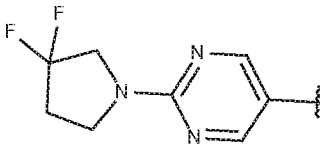
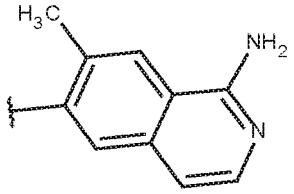
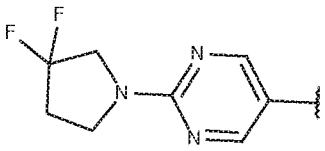
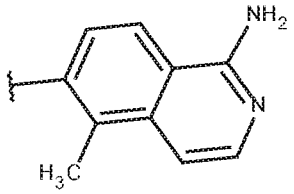
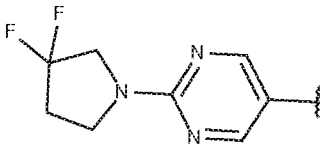
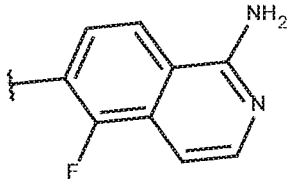
Example number	A	R5	B	Free Base MW
230		CH_3		484.5
231		CH_3		488.5
232		CH_3		500.5
233		CH_3		500.5
234		CH_3		488.5
235		CH_3		500.5

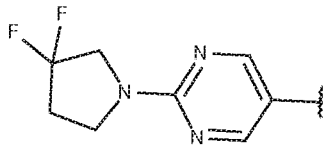
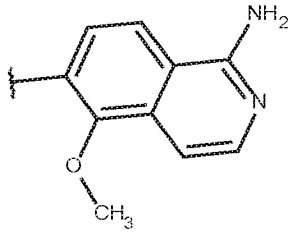
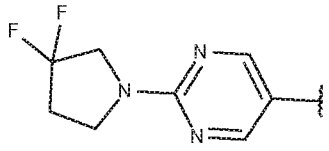
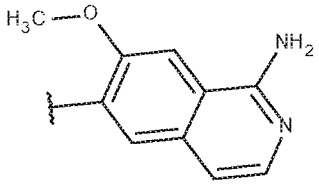
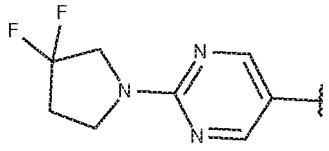
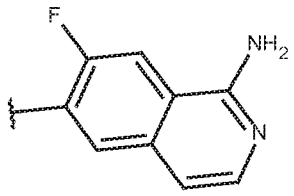
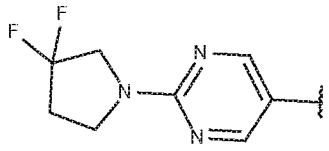
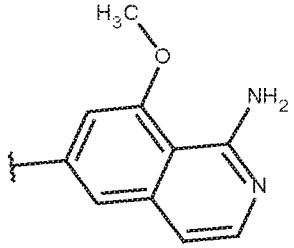
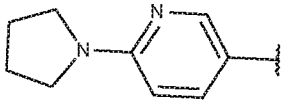
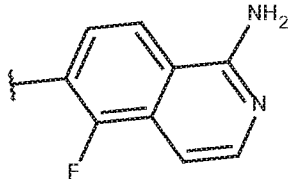
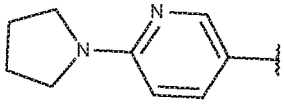
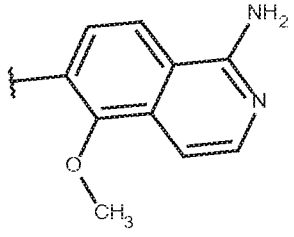
Example number	A	R5	B	Free Base MW
236		CH_2OMe		530.6
237		CH_2OMe		518.5
238		CH_2OMe		530.6
239		CH_2OMe		496.6
240		CH_2OMe		496.6
241		CH_2OMe		500.5

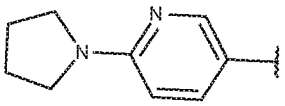
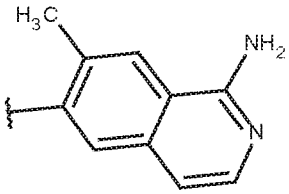
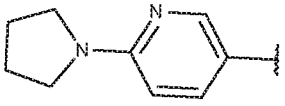
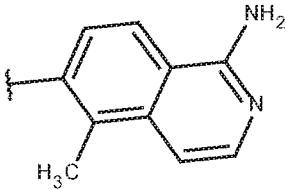
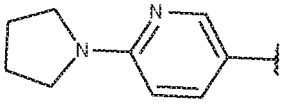
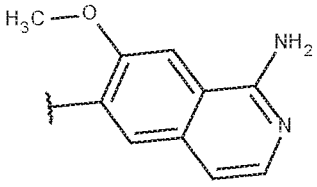
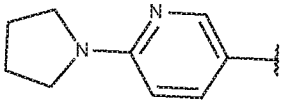
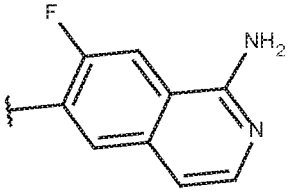
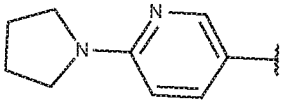
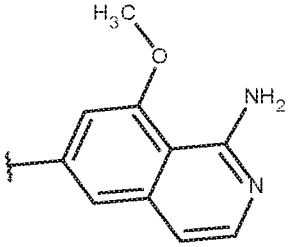
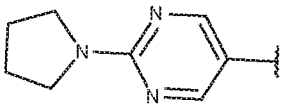
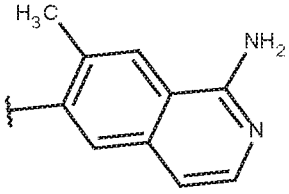
Example number	A	R5	B	Free Base MW
242		CH_2OMe		512.6
243		CH_2OMe		510.6
244		CH_2OMe		510.6
245		CH_2OMe		414.6
246		CH_2OMe		526.6
247		CH_2OMe		514.6
248		CH_2OMe		514.6

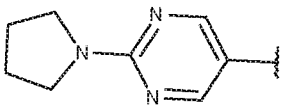
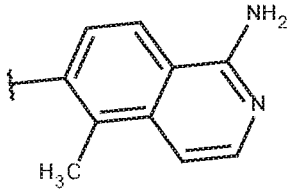
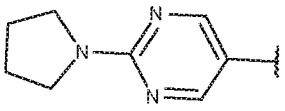
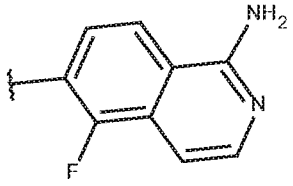
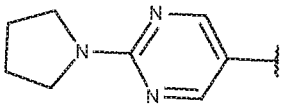
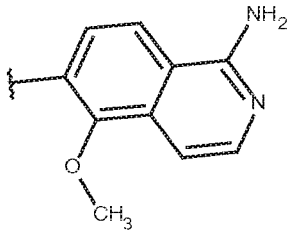
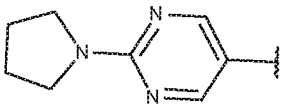
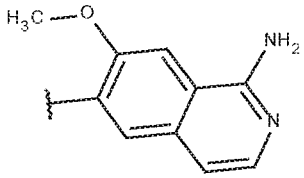
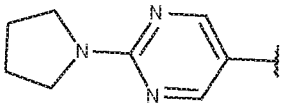
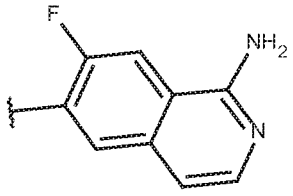
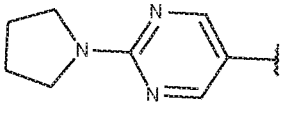
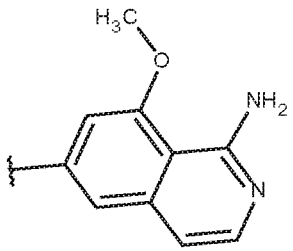
Example number	A	R5	B	Free Base MW
249		CH_2OMe		518.5
250		CH_2OMe		530.6
251		CH_2OMe		486.6
252		CH_2OMe		486.6
253		CH_2OMe		490.5
254		CH_2OMe		502.6
255		CH_2OMe		502.6

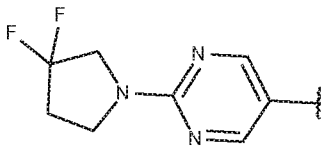
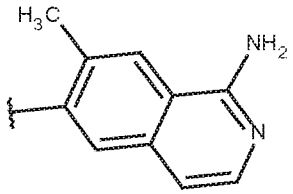
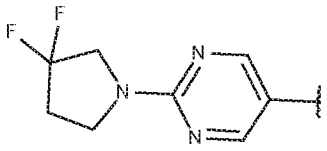
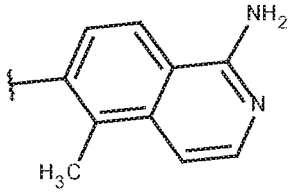
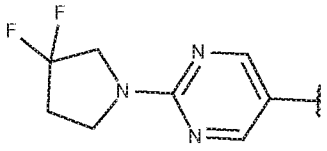
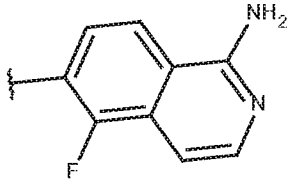
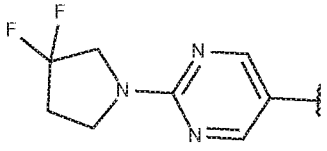
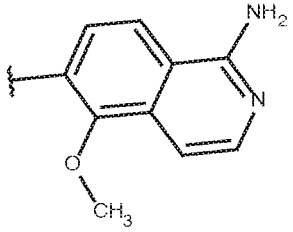
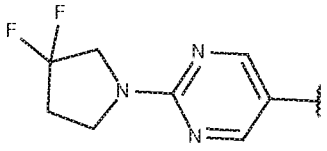
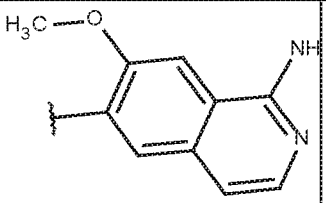
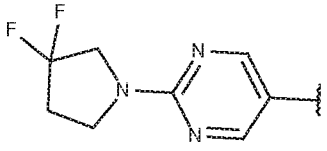
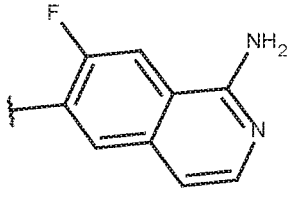
Example number	A	R5	B	Free Base MW
256		CH_2OMe		490.5
257		CH_2OMe		502.6
258		CH_2OMe		487.6
259		CH_2OMe		487.6
260		CH_2OMe		491.5
261		CH_2OMe		503.6

Example number	A	R5	B	Free Base MW
262		CH_2OMe		503.6
263		CH_2OMe		491.5
264		CH_2OMe		503.6
265		CH_2OMe		523.5
266		CH_2OMe		523.5
267		CH_2OMe		527.4

Example number	A	R5	B	Free Base MW
268		CH_2OMe		539.5
269		CH_2OMe		539.5
270		CH_2OMe		527.5
271		CH_2OMe		539.5
272		CH_3		460.5
273		CH_3		472.5

Example number	A	R5	B	Free Base MW
274		CH_3		456.5
275		CH_3		456.5
276		CH_3		472.5
277		CH_3		460.5
278		CH_3		472.5
279		CH_3		457.5

Example number	A	R5	B	Free Base MW
280		CH_3		457.5
281		CH_3		461.5
282		CH_3		473.5
283		CH_3		473.5
284		CH_3		461.5
285		CH_3		473.5

Example number	A	R5	B	Free Base MW
286		CH_3		493.5
287		CH_3		493.5
288		CH_3		497.5
289		CH_3		509.5
290		CH_3		509.5
291		CH_3		497.5

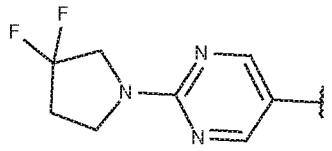
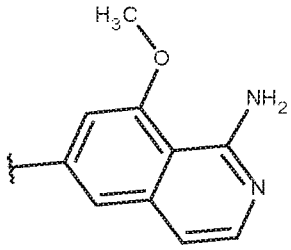
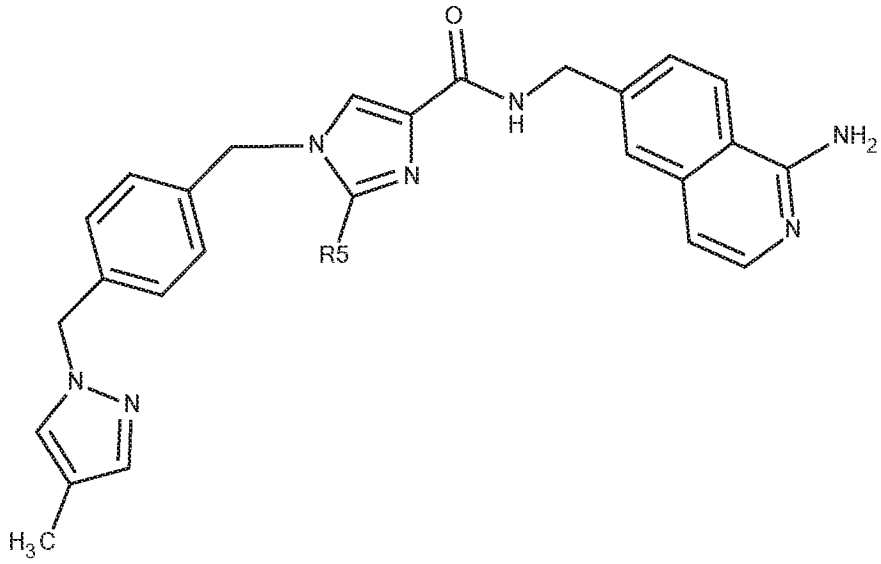
Example number	A	R5	B	Free Base MW
292		CH_3		509.5

Table 9



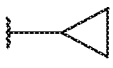
Example number	R5	Free Base MW
293		491.6

Table 10: Compound names

Example Number	Name
5	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
6	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
7	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
8	3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
9	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
10	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
11	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
12	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
13	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
14	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
15	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
16	1-[2-(3,3-difluoro-pyrrolidin-1-yl)-pyrimidin-5-ylmethyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
17	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide

Example Number	Name
18	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
19	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
20	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
21	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
22	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
23	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
24	3-(2-methoxy-ethyl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
25	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
26	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
27	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
28	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
29	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
30	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
31	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide
32	3-ethoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide

Example Number	Name
34	N-[(1-aminoisoquinolin-6-yl)methyl]-1-{[2-(pyrazol-1-ylmethyl)pyrimidin-5-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
35	N-[(1-aminoisoquinolin-6-yl)methyl]-1-({3-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
36	N-[(1-aminoisoquinolin-6-yl)methyl]-1-({2-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
37	3-cyclopropyl-1-(2-fluoro-4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
38	3-cyclopropyl-1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
39	1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
40	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
41	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
42	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
43	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
44	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
45	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
46	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
47	N-[(1-aminoisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide
48	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide

Example Number	Name
49	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
50	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
51	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
52	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
53	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
54	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
55	1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
56	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyridin-4-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
57	3-amino-N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyridin-4-yl]methyl}pyrazole-4-carboxamide
59	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-3-cyano-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
63	3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
64	1-(2-Pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-3-trifluoromethyl-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
65	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide
66	N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
67	3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide

Example Number	Name
68	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide
69	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-[(6-ethoxy-5-fluoropyridin-3-yl)methyl]-3-(trifluoromethyl)pyrazole-4-carboxamide
70	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-({6-[isopropyl(methyl)amino]pyridin-3-yl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide
71	3-amino-1-{[6-(benzyloxy)pyridin-3-yl]methyl}-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1H-pyrazole-4-carboxamide
72	3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-{[6-(phenoxymethyl)pyridin-3-yl]methyl}-1H-pyrazole-4-carboxamide
73	3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-[(6-phenoxypyridin-3-yl)methyl]-1H-pyrazole-4-carboxamide
74	3-methoxymethyl-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
75	3-cyano-1-[4-(4-methyl-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (3-chloro-1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)-amide
76	3-amino-N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
78	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide
79	N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-[(2-methylquinolin-6-yl)methyl]pyrazole-4-carboxamide
80	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-[(7-chloroquinolin-3-yl)methyl]-3-(methoxymethyl)pyrazole-4-carboxamide
81	3-amino-N-[(3-chloro-1H-indol-5-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
82	3-amino-N-[(3-chloro-1H-indazol-5-yl)methyl]-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
83	N-({3-cyano-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-cyclopropyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide

Example Number	Name
84	N-({3-fluoro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
85	N-({4-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide
86	N-({1-methylpyrazolo[3,4-b]pyridin-5-yl}methyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide
87	N-({3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl}methyl)-3-(methoxymethyl)-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
102	3-amino-N-[(6-chloroisoquinolin-3-yl)methyl]-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
103	N-[(6-chloroisoquinolin-3-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide
104	N-[(6-chloroisoquinolin-3-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
105	N-[(6-chloroisoquinolin-3-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
106	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
107	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
108	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
109	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
110	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
111	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
112	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide

Example Number	Name
113	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
114	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
115	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
116	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
117	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
118	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
119	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide
120	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
121	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
122	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
123	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
124	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
125	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
126	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
127	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide

Example Number	Name
128	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
129	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
130	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
131	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
132	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
133	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
134	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
135	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
136	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
137	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
138	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
139	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
140	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide
141	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
142	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide

Example Number	Name
143	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{{4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
144	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{{4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
145	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{{4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
146	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{{4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
147	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{{4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
148	2-methyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide
149	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
150	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
151	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
152	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
153	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
154	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
155	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
156	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
157	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide

Example Number	Name
158	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
159	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
160	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
161	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
162	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
163	N-[(6-chloroisoquinolin-3-yl)methyl]-2-methyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
164	N-({3-chloro-1H-pyrrolo[2,3-b]pyridin-5-yl}methyl)-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
165	N-({5-chloro-7H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-2-methyl-1-({4-[(2-oxopyridin-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide
166	N-[(1-aminoisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
167	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
168	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
169	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
170	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
171	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
172	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide

Example Number	Name
173	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
174	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
175	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
176	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
177	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
178	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
179	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
180	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
181	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
182	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
183	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
184	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
185	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
186	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide
187	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide

Example Number	Name
188	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
189	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
190	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
191	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
192	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
193	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide
194	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide
196	3-amino-N-[(3-chloro-1H-indazol-5-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
197	N-({3-chloro-1H-pyrazolo[3,4-b]pyridin-5-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
199	N-({5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
201	N-({3-chloro-1H-pyrrolo[2,3-c]pyridin-5-yl}methyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide
202	3-amino-N-[(7-chloroquinolin-2-yl)methyl]-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
203	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
204	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
205	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide

Example Number	Name
206	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide
207	N-[(1-aminoisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
208	N-[(1-aminoisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
209	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
210	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
211	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
212	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
213	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
214	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
215	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
216	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
217	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
218	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
219	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
220	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide

Example Number	Name
221	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
222	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
223	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
224	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
225	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
226	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
227	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
228	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
229	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
230	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
231	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
232	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
233	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
234	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide
235	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide

Example Number	Name
236	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
237	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
238	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
239	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
240	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
241	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
242	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide
243	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
244	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
245	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
246	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide
247	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
248	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
249	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
250	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide

Example Number	Name
251	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
252	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
253	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
254	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
255	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
256	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
257	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
258	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
259	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
260	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
261	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
262	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
263	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
264	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
265	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide

Example Number	Name
266	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
267	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
268	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
269	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
270	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
271	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide
272	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
273	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
274	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
275	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
276	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
277	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
278	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide
279	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
280	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide

Example Number	Name
281	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
282	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
283	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
284	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
285	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide
286	N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
287	N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
288	N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
289	N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
290	N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
291	N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
292	N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide
293	N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide

Table 11: ^{1}H NMR data (solvent d6 DMSO) and mass spectroscopy data of examples

Example Number	Chemical shift	$[M+H]^+$
8	1.88-1.94 (4H, m), 3.22 (3H, s), 3.44-3.45 (4H, m), 4.53 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.15 (2H, s), 6.82 (2H, br.s), 6.87 (1H, d, J = 5.9 Hz), 7.39 (1H, d, J = 8.6 Hz), 7.54 (1H, s), 7.75 (1H, d, J = 5.9 Hz), 8.15 (1H, d, J = 8.3 Hz), 8.23 (1H, s), 8.38 (2H, s), 8.46 (1H, t, J = 5.8 Hz)	473.0
9	1.87 - 1.99 (4H, m), 2.57 (3H, s), 3.21 (3H, s), 3.43 -3.55 (4H, m), 4.54 (2H, s), 4.61 (2H, d, J = 5.6 Hz), 5.20 (2H, s), 7.37 (1H, d, J = 7.4 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.71 (1H, s), 8.30 (1H, s), 8.37 - 8.49 (3H, m), 8.50 - 8.58 (1H, m), 9.07 (2H, s), 13.32 (1H, s)	487.9
12	1.88-1.98 (4H, m), 2.49 (3H, s), 3.22 (3H, s), 3.42-3.55 (4H, m), 4.54-4.59 (4H, m), 5.21 (2H, s), 7.17 (1H, d, J = 7.0 Hz), 7.61 (1H, dd, J = 7.0, 4.5 Hz), 7.71 (1H, s), 8.33 (1H, s), 8.42-8.48 (3H, m), 8.54 (1H, t, J = 5.7 Hz), 9.04 (2H, br s), 13.29 (1H, s)	487.1
13	1.89-1.96 (4H, m), 3.23 (3H, m), 3.45-3.56 (4H, m), 4.01 (3H, s), 4.51 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.22 (2H, s), 7.18 (1H, d, J = 6.9 Hz), 7.56 (1H, dd, J = 6.9, 5.0 Hz), 7.70 (1H, s), 8.08 (1H, s), 8.34 (1H, s), 8.46-8.54 (3H, m), 9.05 (2H, br s), 13.41 (1H, s)	503.1
16	2.53-2.57 (2H, m), 3.23 (3H, s), 3.71 (2H, t, J = 7.4 Hz), 3.89 (2H, t, J = 13.2 Hz), 4.56 (2H, s), 4.60 (2H, d, J = 5.8 Hz), 5.23 (2H, s), 7.20 (1H, d, J = 6.9 Hz), 7.63 - 7.71 (2H, m), 7.79 (1H, s), 8.29 (1H, s), 8.48 (2H, s), 8.51 (1H, d, J = 8.6 Hz), 8.63 (1H, t, J = 5.9 Hz), 8.90 (2H, s), 13.07 (1H, s)	509.3
17	2.52 - 2.55 (2H, m), 2.56 (3H, s), 3.21 (3H, s), 3.71 (2H, t, J = 7.4 Hz), 3.89 (2H, t, J = 13.2 Hz), 4.54 (2H, s), 4.61 (2H, d, J = 5.7 Hz), 5.22 (2H, s), 7.37 (1H, d, J = 7.4 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 7.2 Hz), 8.30 (1H, s), 8.42 (1H, d, J = 8.7 Hz), 8.47 (2H, s), 8.52 (1H, t, J = 5.7 Hz), 9.08 (2H, s), 13.34 (1H, s)	523.3
24	1.83 - 2.05 (4H, m), 3.02 (2H, t, J = 7.3 Hz), 3.20 (3H, s), 3.36 - 3.43 (4H, m), 3.54 (2H, t, J = 7.3 Hz), 4.56 (2H, d, J = 5.8 Hz), 5.14 (2H, s), 6.51 (1H, s), 7.21 (1H, d, J = 7.0 Hz), 7.51 (1H, s), 7.67 (2H, d, J = 7.0 Hz), 7.77 (1H, s), 8.10 (1H, d, J = 2.1 Hz), 8.17 (1H, s), 8.52 (1H, d, J = 8.7 Hz), 8.67 (1H, s), 8.98 (2H, s), 13.14 (1H, s)	486.2

Example Number	Chemical shift	$[M+H]^+$
25	2.56 (3H, s), 3.19 (3H, s), 4.53 (2H, s), 4.60 (2H, d, J = 5.4 Hz), 5.30 (4H, d, J = 4.2 Hz), 6.25 (1H, t, J = 2.1 Hz), 7.17-7.26 (4H, m), 7.37 (1H, d, J = 7.4 Hz), 7.44 (1H, dd, J = 0.7, 1.8 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.70 (1H, d, J = 7.4 Hz), 7.80 (1H, dd, J = 0.7, 2.3 Hz), 8.28 (1H, s), 8.38 (1H, d, J = 8.6 Hz), 8.50 (1H, t, J = 5.7 Hz), 9.00 (2H, s br), 13.13 (1H, s br)	496.3
28	3.23 (3H, s), 4.01 (3H, s), 4.51 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.28-5.33 (4H, m), 6.25 (1H, t, J = 2.1 Hz), 7.17-7.22 (3H, m), 7.26 (2H, d, J = 8.2 Hz), 7.44 (1H, d, J = 1.8 Hz), 7.56 (1H, dd, J = 6.9, 4.7 Hz), 7.71 (1H, s), 7.81 (1H, d, J = 2.2 Hz), 8.06 (1H, s), 8.33 (1H, s), 8.47 (1H, t, J = 5.9 Hz), 9.00 (2H, br s), 13.33 (1H, s)	512.1
32	1.01 (3H, t, J = 7.0 Hz), 3.43 (2H, q, J = 7.0 Hz), 4.54 - 4.65 (4H, m), 5.25 - 5.35 (4H, m), 6.24 - 6.28 (1H, m), 7.18 - 7.24 (3H, m), 7.23 - 7.32 (2H, m), 7.45 (1H, d, J = 1.2 Hz), 7.60 - 7.74 (2H, m), 7.82 (2H, d, J = 1.6 Hz), 8.30 (1H, s), 8.54 (1H, d, J = 8.6 Hz), 8.64 (1H, s), 9.05 (2H, s), 13.11 (1H, s)	496.3
35	1.98 (3H, s), 3.22 (3H, s), 4.56 (2H, s), 4.60 (2H, d, J = 5.8 Hz), 5.27 (2H, s), 5.34 (2H, s), 7.05-7.17 (3H, m), 7.20 (1H, d, J = 7.0 Hz), 7.23 (1H, s), 7.53 (1H, s), 7.64-7.73 (2H, m), 7.80 (1H, s), 8.33 (1H, s), 8.55 (1H, d, J = 8.7 Hz), 8.65 (1H, t, J = 5.9 Hz), 9.09 (2H, br, s), 13.25 (1H, s)	514.1
36	1.99 (3H, s), 3.21 (3H, s), 4.55 (2H, s), 4.59 (2H, d, J = 5.9 Hz), 5.25 (2H, s), 5.35 (2H, s), 7.00-7.06 (2H, m), 7.20 (1H, d, J = 7.0 Hz), 7.24-7.31 (2H, m), 7.58 (1H, s), 7.64-7.71 (2H, m), 7.80 (1H, s), 8.29 (1H, s), 8.56 (1H, d, J = 8.6 Hz), 8.66 (1H, t, J = 5.9 Hz), 9.12 (2H, br s), 13.21 (1H, s)	514.3
37	0.71-0.75 (2H, m), 0.77-0.83 (2H, m), 2.56-2.61 (1H, m), 4.57 (2H, d, J = 5.5 Hz), 5.25 (2H, s), 5.35 (2H, s), 6.28 (1H, t, J = 2.0 Hz), 7.02 (1H, s), 7.04 (1H, d, J = 4.8 Hz), 7.21 (1H, t, J = 7.9 Hz), 7.23 (1H, d, J = 7.0 Hz), 7.47 (1H, d, J = 1.7 Hz), 7.67 (1H, d, J = 6.8 Hz), 7.69 (1, dd, J = 8.8, 1.2 Hz), 7.80 (1H, s), 7.84 (1H, d, J = 2.2 Hz), 8.16 (1H, s), 8.53 (1H, d, J = 8.6 Hz), 8.62 (1H, t, J = 5.9 Hz), 9.02 (2H, br.s), 13.07 (1H, br.s)	496.2

Example Number	Chemical shift	$[M+H]^+$
38	0.71 - 0.78 (2H, m), 0.78 - 0.87 (2H, m), 2.55 - 2.63 (1H, m), 4.58 (2H, d, J = 5.8 Hz), 5.22 (4H, s), 7.19 - 7.27 (5H, m), 7.48 (1H, d, J = 4.3 Hz), 7.63 - 7.75 (2H, m), 7.81 (1H, s), 7.97 (1H, dd, J = 0.8, 4.6 Hz), 8.19 (1H, s), 8.53 (1H, d, J = 8.7 Hz), 8.63 (1H, t, J = 6.0 Hz), 9.04 (2H, s), 13.09 (1H, s)	496.2
39	3.22 (3H, s), 4.56 (2H, s), 4.59 (2H, d, J = 5.8 Hz), 5.22 (2H, s), 5.31 (2H, s), 7.17-7.29 (5H, m), 7.46 (1H, dd, J = 4.3, 0.9 Hz), 7.63-7.74 (2H, m), 7.80 (1H, s), 7.95 (1H, dd, J = 4.6, 0.9 Hz), 8.31 (1H, s), 8.55 (1H, d, J = 8.7 Hz), 8.64 (1H, t, J = 5.9 Hz), 9.11 (2H, br s), 13.29 (1H, s)	500.3
40	2.57 (3H, s), 3.20 (3H, s), 4.54 (2H, s), 4.61 (2H, d, J = 5.6 Hz), 5.22 (2H, s), 5.31 (2H, s), 7.18 - 7.30 (4H, m), 7.38 (1H, d, J = 7.3 Hz), 7.47 (1H, d, J = 4.3 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.71 (1H, d, J = 7.4 Hz), 7.96 (1H, d, J = 4.6 Hz), 8.30 (1H, s), 8.39 (1H, d, J = 8.6 Hz), 8.45 - 8.55 (1H, m), 8.99 (2H, s), 13.13 (1H, s)	514.3
43	3.23 (3H, s), 4.01 (3H, s), 4.52 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.22 (2H, s), 5.31 (2H, s), 7.16 (3H, m), 7.27 (2H, d, J = 8.2 Hz), 7.46 (1H, d, J = 4.3 Hz), 7.54-7.59 (1H, m), 7.72 (1H,s), 7.96 (1H, d, J = 4.6 Hz), 8.06 (1H, s), 8.34 (1H, s), 8.48 (1H, t = 5.9 Hz), 9.00 (2H, br s), 13.32 (1H, s)	530.1
47	4.59 (2H, d, J = 5.9 Hz), 5.24 (2H, s), 5.45 (2H, s), 7.16 - 7.29 (3H, m), 7.28 - 7.37 (2H, m), 7.49 (1H, d, J = 4.3 Hz), 7.60 - 7.76 (2H, m), 7.81 (1H, s), 7.98 (1H, d, J = 4.6 Hz), 8.48 - 8.58 (2H, m), 8.84 - 9.16 (3H, m), 12.99 (1H, s).	524.2
48	1.98 (3H, s), 3.22 (3H, s), 4.55 (2H, s), 4.61 (2H, d, J = 5.7 Hz), 5.21 (2H, s), 5.30 (2H, s), 7.14-7.29 (6H, m), 7.53 (1H, s), 7.65 (1H, d, J = 6.9 Hz), 7.90 (1H, d, J = 7.3 Hz), 8.30 (1H, s), 8.46 (1H, d, J = 11.2 Hz), 8.60 (1H, s), 8.99 (2H, s br), 13.14 (1H, s br)	514.0
49	1.98 (3H, s), 3.23 (3H, s), 4.01 (3H, s), 4.51 (2H, d, J = 5.8 Hz), 4.56 (2H, s), 5.22 (2H, s), 5.30 (2H, s), 7.16-7.22 (3H, m), 7.22-7.28 (3H, m), 7.52-7.61 (2H, m), 7.71 (1H, s), 8.06 (1H, s), 8.33 (1H, s), 8.48 (1H, t, J = 5.9 Hz), 9.01 (2H, s br), 13.34 (1H, s)	526.1

Example Number	Chemical shift	$[M+H]^+$
50	1.98 (3H, d, J = 0.7 Hz), 3.22 (3H, s), 4.54 (2H, s), 4.62 (2H, d, J = 4.9 Hz), 5.21 (2H, s), 5.29 (2H, s), 7.17-7.27 (6H, m), 7.52 (1H, t, J = 0.9 Hz), 7.67-7.78 (2H, m), 8.26 (1H, s), 8.36 (1H, d, J = 8.6 Hz), 8.60 (1H, t, J = 5.9 Hz), 9.12 (2H, s br), 13.15 (1H, s br)	514.1
51	1.98 (3H, s), 3.21 (3H, s), 3.90 (3H, s), 4.54 (2H, s), 4.61 (2H, d, J = 5.8 Hz), 5.22 (2H, s), 5.30 (2H, s), 7.18 (2H, d, J = 8.2 Hz), 7.21-7.27 (4H, m), 7.55 (1H, s), 7.66 (1H, d, J = 8.6 Hz), 7.69-7.75 (1H, m), 8.31 (1H, s), 8.36 (1H, d, J = 8.7 Hz), 8.62 (1H, t, J = 5.9 Hz), 9.20 (2H, s br), 13.37 (1H, s)	526.3
52	1.99 (3H, s), 3.22 (3H, s), 4.05 (3H, s), 4.54 – 4.61 (4H, m), 5.22 (2H, s), 5.31 (2H, s), 7.08 (1H, d, J = 7.1 Hz), 7.16 – 7.28 (6H, m), 7.31 (1H, s), 7.54 (1H, s), 7.59 – 7.65 (1H, m), 8.31 (1H, s), 8.53 – 8.64 (1H, m), 8.82 (2H, s), 12.77 (1H, s)	526.2
53	1.98 (3H, s), 2.56 (3H, s), 3.19 (3H, s), 4.53 (2H, s), 4.60 (2H, d, J = 5.3 Hz), 5.21 (2H, s), 5.29 (2H, s), 7.16-7.25 (5H, m), 7.37 (1H, d, J = 7.3 Hz), 7.53 (1H, d, J = 0.9 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.70 (1H, d, J = 7.4 Hz), 8.29 (1H, s), 8.39 (1H, d, J = 8.7 Hz), 8.51 (1H, t, J = 5.7 Hz), 9.02 (2H, s br), 13.19 (1H, s br)	510.3
54	1.98 (3H, s), 2.49 (3H, s), 3.21 (3H, s), 4.50-4.61 (4H, m), 5.22 (2H, s), 5.30 (2H, s), 7.13-7.22 (3H, m), 7.22-7.30 (3H, m), 7.54 (1H, s), 7.61 (1H, dd, J = 6.9, 4.9 Hz), 7.72 (1H, s), 8.34 (1H, s), 8.44 (1H, s), 8.53 (1H, t, J = 5.7 Hz), 9.05 (2H, br s), 13.32 (1H, s)	510.3
55	1.91-1.93 (4H, m), 3.35-3.45 (4H, m), 4.49 (2H, d, J = 5.7 Hz), 5.25 (2H, s), 6.43 (1H, d, J = 8.7 Hz), 7.48 (1H, dd, J = 2.4, 8.8 Hz), 7.68 (1H, s), 7.82 (1H, d, J = 2.0 Hz), 8.13 (1H, d, J = 2.2 Hz), 8.26 (1H, d, J = 1.9 Hz), 8.34 (1H, s), 8.82 (1H, t, J = 5.8Hz), 11.97 (1H, s)	504.1
57	2.01 (4H, t, J = 7.1 Hz), 3.47 (4H, t, J = 6.5 Hz), 4.35 (2H, d, J = 5.8 Hz), 4.49 (2H, d, J = 5.7 Hz), 5.20 (2H, s), 6.51 (1H, d, J = 6.6 Hz), 6.92 (1H, s), 7.66(1H, d, J = 2.7 Hz), 7.83 (1H, d, J = 1.5 Hz), 8.09 (1H, s), 8.22 (1H, d, J = 1.9 Hz), 8.28 (1H, d, J = 1.9 Hz), 8.41 (1H, t, J = 5.9 Hz), 11.92 (1H, s)	450.9
64	1.89-1.93 (4H, m), 3.44-3.47 (4H, m), 4.49 (2H, d, J = 5.8 Hz), 5.26 (2H, s), 7.66 (1H, d, J = 2.7 Hz), 7.82 (1H, d, J = 1.5 Hz), 8.27 (1H, d, J = 1.9 Hz), 8.36 (1H, s), 8.41 (2H, s), 8.77 (1H, t, J= 5.6 Hz), 11.93 (1H, s)	505.0

Example Number	Chemical shift	$[M+H]^+$
66	3.35-3.37 (2H, m), 3.60 (2H, t, J = 7.3 Hz), 3.81 (2H, t, J = 13.4 Hz), 4.49 (2H, d, J = 5.8 Hz), 5.29 (2H, s), 6.55 (1H, d, J = 8.7 Hz), 7.57(1H, dd, J = 2.3, 8.7 Hz), 7.66 (1H, d, J = 2.6 Hz), 7.82 (1H, d, J = 1.5 Hz), 8.18 (1H, d, J = 2.2 Hz), 8.26 (1H, d, J = 1.9 Hz), 8.34 (1H, s), 8.77 (1H, t, J = 5.6Hz), 11.92 (1H, s)	540.0
70	1.13 (6H, t, J = 7.5 Hz), 2.84 (3H, s), 4.35 (1H, d, J = 5.8 Hz), 4.50 (2H, d, J = 5.8 Hz), 5.30 (2H, s), 6.95 (1H, s), 7.08 (1H, s), 7.21 (1H, s), 7.66 (1H, d, J = 2.7 Hz), 7.83 (1H, d, J = 1.5 Hz), 8.10 (1H, d, J = 2.1 Hz), 8.26 (1H, d, J = 1.9 Hz), 8.80 (1H, t, J = 5.6 Hz), 11.94 (1H, s)	505.4
74	1.97 (3H, s), 3.19 (3H, s), 4.49 (2H, d, J = 5.7 Hz), 4.53 (2H, s), 5.20 (2H, s), 5.28 (2H, s), 7.18-7.22 (5H, m), 7.52 (1H, s), 7.68 (1H, s), 7.83 (1H, d, J = 1.7Hz), 8.22 (1H, s), 8.27 (1H, d, J = 1.7 Hz), 8.43 (1H, t, J = 5.6 Hz), 11.96 (1H, s)	504.0
75	1.98 (3H, s), 4.51 (2H, d, J = 5.6 Hz), 5.22 (2H, s), 5.44 (2H, s), 7.18-7.28 (5H, m), 7.54 (1H, s), 7.69 (1H, d, J = 2.2 Hz), 7.85 (1H, d, J = 1.6 Hz), 8.28 (1H, d, J = 1.9 Hz), 8.45 (1H, s), 8.94 (1H, d, J = 5.6 Hz), 11.99 (1H,s)	484.9
79	2.64 (3H, s), 3.21 (3H, s), 4.50 (2H, d, J = 5.7 Hz), 4.56 (2H, s), 5.50 (2H, s), 7.41 (1H, d, J = 8.5 Hz), 7.58 (1H, dd, J = 2.0, 8.7 Hz), 7.65 (1H, d, J = 2.4 Hz), 7.79 (1H, d, J = 1.5 Hz), 7.84 (1H, d J = 1.8 Hz), 7.89 (1H, d J = 8.7 Hz), 8.22 (1H, d, J = 8.4 Hz), 8.27 (1H, d, J = 2.0 Hz), 8.30 (1H, s), 8.43 (1H, t, J = 5.7 Hz), 11.92 (1H, s)	474.8
103	1.98 (3H, s), 3.24 (3H, s), 4.56 (2H, s), 4.63 (2H, d, J = 5.7 Hz), 5.22 (2H, s), 5.30 (2H, s), 7.18 (2H, d, J = 8.2 Hz), 7.23-7.26 (3H, m), 7.53 (1H, s), 7.65 (1H, dd, J = 2.0, 8.7 Hz), 7.70 (1H, s), 8.11 (1H, d. J = 1.7 Hz), 8.16 (1H, d, J = 8.7 Hz), 8.30 (1H, s), 8.59 (1H, t, J = 5.7 Hz), 9.32 (1H,s)	515.0
104	1.91-1.94 (4H, m), 3.35-3.42 (4H, s), 4.61 (2H, d, J = 5.8 Hz), 5.29 (2H, s), 6.45 (1H, d, J = 8.7 Hz), 7.53 (1H, dd, J = 2.4, 8.6 Hz), 7.64-7.68 (2H, m), 8.11 (1H, d, J = 1.8 Hz), 8.16 (2H, dd, J = 2.8, 5.2 Hz), 8.44 (1H, s), 8.95 (1H, t, J = 5.8 Hz), 9.31 (1H, s)	515.0

Example Number	Chemical shift	$[M+H]^+$
148	1.88-1.95 (4H, m), 2.30 (3H, s), 3.34 (4H, m, under water peak), 4.50 (2H, d, J = 6.3 Hz), 5.01 (2H, s), 6.43 (1H, d, J = 8.7 Hz), 6.86 (1H, d, J = 6.0 Hz), 6.87-7.00 (2H, br s), 7.38-7.44 (2H, m), 7.50 (1H, s), 7.62 (1H, s), 7.73 (1H, d, J = 5.9 Hz), 8.08 (1H, d, J =2.3 Hz), 8.13 (1H, d, J = 8.6 Hz), 8.52 (1H, t, J = 6.4 Hz)	442.3
164	1.98 (3H, s), 2.25 (3H, s), 4.48 (2H, d, J = 6.3 Hz), 5.16 (2H, s), 5.21 (2H, s), 7.16-7.19 (4H, m), 7.22 (1H, s), 7.51 (1H, s), 7.63 (2H, s), 7.84 (1H, d, J = 1.5 Hz), 8.27 (1H, d, J = 1.9 Hz), 8.51 (1H, s br), 11.88 (1H, s)	473.9
166		443.0
207	1.98 (3H,s), 2.47 (3H,s), 4.60 (2H, d, J = 6.1 Hz), 5.22 (2H, s), 5.41 (2H, s), 7.18-7.24 (6H, m), 7.53 (1H, s), 7.64-7.70 (2H, m), 7.78 (1H, s), 8.53 (1H, d, J = 8.6 Hz), 9.05 (2H, s), 9.17 (1H, t, J = 6.2 Hz), 13.17 (1H, s)	467.0
208	1.98 (3H, s), 3.31 (3H, s), 4.60 (2H, d, J = 6.2 Hz), 4.67 (2H, s), 5.22 (2H, s), 5.45 (2H, s), 7.17-7.27 (6H, m), 7.53 (1H, s), 7.65-7.71 (2H, m), 7.78 (1H, s), 8.52 (1H, d, J = 8.6 Hz), 9.02 (2H, s), 9.23 (1H, t, J = 6.2 Hz), 13.12 (1H,s)	497.0
293	1.11-1.16 (2H, m), 1.25-1.29 (2H, m), 1.99 (3H, s), 2.29-2.36 (1H, m), 4.64 (2H, d, J = 5.9 Hz), 5.25 (2H, s), 5.47 (2H, s), 7.18 (1H, d,J = 7.0 Hz), 7.23-7.25 (3H, m), 7.35 (2H, d, J = 8.2 Hz), 7.56 (1H, s), 7.67-7.71 (2H, m), 7.82 (1H, s), 8.17 (1H, s), 8.58 (1H, d, J = 8.6 Hz), 9.16 (2H, s), 9.64 (1H, s), 13.35 (1H, s)	492.0

Biological Methods

The ability of the compounds to inhibit plasma kallikrein may be determined using the following biological assays:

Determination of the IC_{50} for plasma kallikrein

Plasma kallikrein inhibitory activity *in vitro* was determined using standard published methods (see e.g. Johansen *et al.*, Int. J. Tiss. Reac. 1986, **8**, 185; Shori *et al.*, Biochem. Pharmacol., 1992, **43**, 1209; Stürzebecher *et al.*, Biol. Chem. Hoppe-Seyler, 1992, **373**, 1025). Human plasma kallikrein (Protogen)

was incubated at 25 °C with the fluorogenic substrate H-DPro-Phe-Arg-AFC and various concentrations of the test compound. Residual enzyme activity (initial rate of reaction) was determined by measuring the change in optical absorbance at 410nm and the IC_{50} value for the test compound was determined.

Data acquired from these assays are shown in Table 12

Selected compounds were further screened for inhibitory activity against the related enzyme KLK1. The ability of the compounds of formula (I) to inhibit KLK1 may be determined using the following biological assay:

Determination of the IC_{50} for KLK1

KLK1 inhibitory activity *in vitro* was determined using standard published methods (see e.g. Johansen *et al.*, Int. J. Tiss. Reac. 1986, **8**, 185; Shori *et al.*, Biochem. Pharmacol., 1992, **43**, 1209; Stürzebecher *et al.*, Biol. Chem. Hoppe-Seyler, 1992, **373**, 1025). Human KLK1 (Callbiochem) was incubated at 25°C with the fluorogenic substrate H-DVal-Leu-Arg-AFC and various concentrations of the test compound. Residual enzyme activity (initial rate of reaction) was determined by measuring the change in optical absorbance at 410nm and the IC_{50} value for the test compound was determined.

Data acquired from this assay are shown in Table 12

Table 12

Example Number	IC_{50} (human PKal) nM	IC_{50} (human KLK1) nM
1	7.0	3720
2	6.8	>10000
3	15.5	3560
4	1.0	>10000
8	9.8	2650
9	5.3	2160

Example Number	IC_{50} (human PKal) nM	IC_{50} (human KLK1) nM
12	2.6	>10000
13	1.8	>10000
16	15.8	9110
17	10.4	6800
24	10.6	2060
25	0.56	>10000
28	0.48	>10000
32	1.3	>10000
35	2.0	9730
36	1.8	8480
37	2.5	9000
38	4.7	7170
39	1.8	>10000
40	1.0	7700
43	1.0	>10000
47	1.9	9820
48	11.3	>10000
49	1.0	>10000
50	1.2	>10000
51	19.1	>10000

Example Number	IC_{50} (human PKal) nM	IC_{50} (human KLK1) nM
52	7.0	>10000
53	1.1	5600
54	1.0	>10000
55	12.0	>10000
57	45.4	5500
64	19.0	6290
66	20.7	>10000
70	25.4	>40000
74	8.7	>10000
75	1.0	>10000
79	30.4	665
103	287	>40000
104	221	>40000
148	11.9	4640
164	12.7	>10000
166	35.9	11700
207	10.6	>10000
208	19.0	7730
293	4.3	6540

Determination of enzyme selectivity

Selected compounds were further screened for inhibitory activity against other trypsin-like serine proteases using the appropriate enzyme and chromogenic substrate (Chromogenix AB). The activity against the following human enzymes was tested (substrate in brackets):- thrombin (S-2238), plasmin (S-2390) and trypsin (S-2222). The enzyme was incubated at 25 °C with the chromogenic substrate. Residual enzyme activity (initial rate of reaction) was determined by measuring the change in optical absorbance at 405nm.

Data acquired from these assays are shown in Table 13

Table 13: (Selectivity data)

Example No	IC50 (nM)		
	Thrombin	Trypsin	Plasmin
8	>40000	>40000	>40000
16	>40000	>40000	>40000
55	>4000	>4000	>4000

Pharmacokinetics

Pharmacokinetic studies of the compounds in Table 14 were performed to assess the pharmacokinetics following a single oral dose in male Sprague-Dawley rats. Two rats were given a single po dose of 5 mL/kg of a nominal 2 mg/mL (10 mg/kg) composition of test compound in 10% DMSO / 10% cremophor / 80% sterile water for injection. Following dosing, blood samples were collected over a period of 24 hours. Sample times were 5, 15 and 30 minutes then 1, 2, 4, 6, 8 and 12 hours. Following collection, blood samples were centrifuged and the plasma fraction analysed for concentration of test compound by LCMS. Oral exposure data acquired from these studies are shown below:

Table 14: (Oral exposure data)

Example Number	Dose po (mg/kg)	Cmax (ng/mL)	Tmax (min)
1	5.2	180	180
4	11.0	287	30
8	10.2	540	45

12	10.9	70	45
16	10.0	280	120
24	12.2	56	150
37	9.9	267	180
39	7.8	104	68
55	14.1	672	90
64 *	10.5	437	150
148	22.1	146	60

* Example 64 was formulated in 20% Labrasol (aq)

CLAIMS

1. A compound selected from:

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-pyrazole-4-carboxamide dihydrochloride;

N-((1-Aminoisoquinolin-6-yl)methyl)-3-(methoxymethyl)-1-((5-((4-methyl-1H-pyrazol-1-yl)methyl)pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide;

3-Cyano-1-[6-(3,3-difluoro-pyrrolidin-1-yl)-5-methoxy-pyridin-3-ylmethyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-Methoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}pyrazole-4-carboxamide;

1-[2-(3,3-difluoro-pyrrolidin-1-yl)-pyrimidin-5-ylmethyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-3-(methoxymethyl)pyrazole-4-carboxamide;

3-(2-methoxy-ethyl)-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide;

3-ethoxymethyl-1-(4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-{[2-(pyrazol-1-ylmethyl)pyrimidin-5-yl]methyl}-3-(trifluoromethyl)pyrazole-4-carboxamide

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({3-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({2-fluoro-4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

3-cyclopropyl-1-(2-fluoro-4-pyrazol-1-ylmethyl-benzyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

3-cyclopropyl-1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

1-[4-(4-fluoro-pyrazol-1-ylmethyl)-benzyl]-3-methoxymethyl-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(methoxymethyl)pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-3-(trifluoromethyl)pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

2-methyl-1-(6-pyrrolidin-1-yl-pyridin-3-ylmethyl)-1H-imidazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-2-methylimidazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[6-(3,3-difluoropyrrolidin-1-yl)pyridin-3-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-2-cyclopropyl-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}imidazole-4-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}pyrazole-4-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-({4-[(4-fluoropyrazol-1-yl)methyl]phenyl}methyl)-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-(methoxymethyl)-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-(methoxymethyl)-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[6-(pyrrolidin-1-yl)pyridin-3-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-5-methyl-1-{[2-(pyrrolidin-1-yl)pyrimidin-5-yl]methyl}-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methylisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-5-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-7-fluoroisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-amino-8-methoxyisoquinolin-6-yl)methyl]-1-{[2-(3,3-difluoropyrrolidin-1-yl)pyrimidin-5-yl]methyl}-5-methyl-1,2,4-triazole-3-carboxamide;

N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound according to claim 1, which is N-[(1-amino-7-methoxyisoquinolin-6-yl)methyl]-3-(methoxymethyl)-1-{[4-(pyrazol-1-ylmethyl)phenyl]methyl}pyrazole-4-carboxamide, and pharmaceutically acceptable salts and solvates thereof.

3. A compound according to claim 1, which is 3-methoxymethyl-1-(2-pyrrolidin-1-yl-pyrimidin-5-ylmethyl)-1H-pyrazole-4-carboxylic acid (1-amino-isoquinolin-6-ylmethyl)-amide, and pharmaceutically acceptable salts and solvates thereof.

4. A compound according to claim 1, which is N-[(1-aminoisoquinolin-6-yl)methyl]-2-cyclopropyl-1-({4-[(4-methylpyrazol-1-yl)methyl]phenyl}methyl)imidazole-4-carboxamide, and pharmaceutically acceptable salts and solvates thereof.

5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier, diluent or excipient.

6. A compound according to any one of claims 1 to 4 for use in medicine.

7. The use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment or prevention of a disease or condition in which plasma kallikrein activity is implicated selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

8. A compound according to any one of claims 1 to 4 for use in a method of treatment of a disease or condition in which plasma kallikrein activity is implicated selected from impaired visual acuity, diabetic retinopathy, diabetic macular edema, hereditary angioedema, diabetes, pancreatitis, cerebral haemorrhage, nephropathy, cardiomyopathy, neuropathy, inflammatory bowel disease, arthritis, inflammation, septic shock, hypotension, cancer, adult respiratory distress syndrome, disseminated intravascular coagulation, cardiopulmonary bypass surgery and bleeding from post operative surgery.

9. The use of claim 7, or a compound for use according to claim 8, wherein the disease or condition in which plasma kallikrein activity is implicated is retinal vascular permeability associated with diabetic retinopathy and diabetic macular edema.

10. The use of claim 7, or a compound for use according to claim 8, wherein the disease or condition in which plasma kallikrein activity is implicated is hereditary angioedema.

11. The use of claim 7, or a compound for use according to claim 8, wherein the disease or condition in which plasma kallikrein activity is diabetic macular edema.