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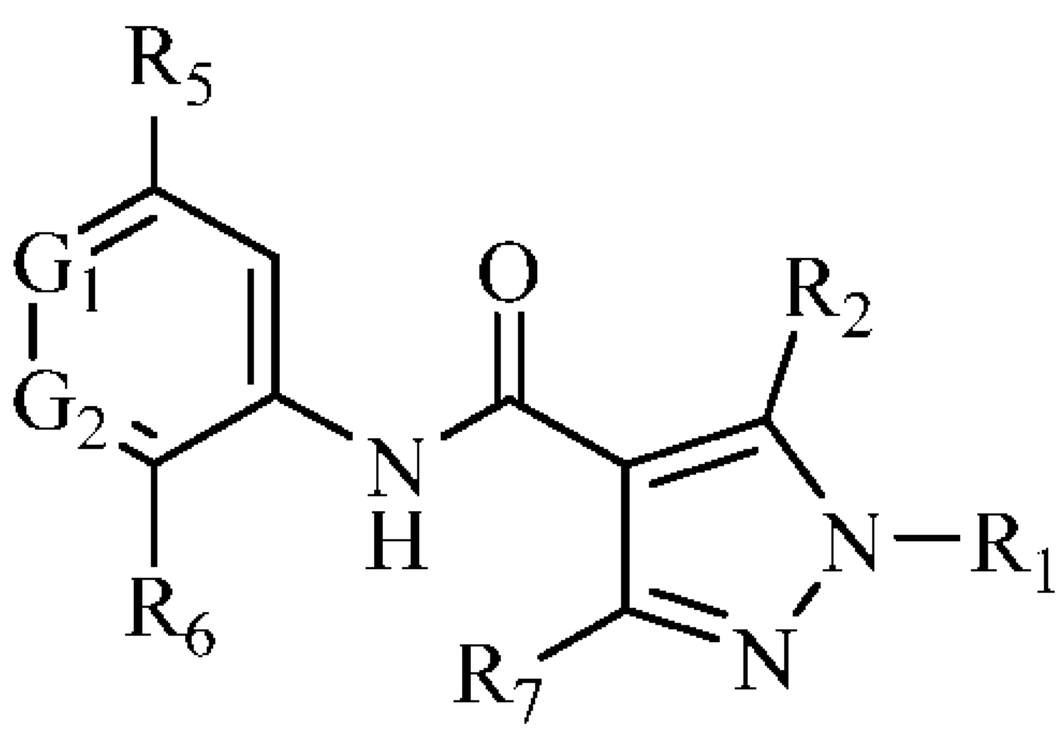
(54) Titre : DERIVES DE PYRAZOLE EN TANT QU'INHIBITEURS DE MALT1
(54) Title: PYRAZOLE DERIVATIVES AS MALT1 INHIBITORS



(I)

(57) Abrégé/Abstract:
Disclosed are compounds, compositions and methods for treating of diseases, syndromes, conditions, and disorders that are affected by the modulation of MALT1. Such compounds are represented by Formula (I) wherein R_1, R_2, R_3, R_4, R_5, R_6, R_5, G_1, and G_2 are defined herein.

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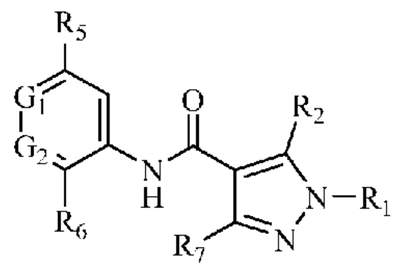

(I)

(57) Abstract: Disclosed are compounds, compositions and methods for treating of diseases, syndromes, conditions, and disorders that are affected by the modulation of MALT1. Such compounds are represented by Formula (I) wherein R_1, R_2, R_3, R_4, R_5, R_6, R_5, G_1, and G_2 are defined herein.

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JUMBO APPLICATIONS/PATENTS

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PYRAZOLE DERIVATIVES AS MALT1 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims priority to United States Provisional Patent Application No. 62/437,384, filed December 21, 2016, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds that are MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) inhibitors. These compounds may be useful for the treatment of a disease, syndrome, condition, or disorder, particularly a MALT1-related disease, syndrome, condition, or disorder, including but not limited to, cancer and immunological diseases. The invention also relates to pharmaceutical compositions comprising one or more of such compounds, to processes to prepare such compounds and compositions, and to the use of such compounds or pharmaceutical compositions for the treatment of cancer and autoimmunological diseases, syndromes, disorders, or conditions associated with MALT1 inhibitors.

BACKGROUND OF THE INVENTION

MALT1 (mucosa-associated lymphoid tissue lymphoma translocation 1) is a key mediator of the classical NF_KB signaling pathway. MALT1 is the only human paracaspase and transduces signals from the B cell receptor (BCR) and T cell receptor (TCR). MALT1 is the active subunit of the CBM complex which is formed upon receptor activation. The CBM complex consists of multiple subunits of three proteins: CARD11 (caspase recruitment domain family member 11), BCL10 (B-cell CLL/Lymphoma 10) and MALT1. MALT1 affects NF_KB signaling by two mechanisms: firstly, MALT1 functions as a scaffolding protein and recruits NF_KB signaling proteins such as TRAF6, TAB-TAK1 or NEMO-IKKα/β; and secondly, MALT1, as a cysteine protease, cleaves and thereby deactivates negative regulators of NF_KB signaling, such as RelB, A20 or CYLD. The

ultimate endpoint of MALT1 activity is the nuclear translocation of the NF_KB transcription factor complex and activation of NF_KB signaling (Jaworski et al., Cell Mol Life Science 2016. 73, 459-473).

Constitutive activation of NF_KB signaling is the hallmark of ABC-DLBCL (Diffuse Large B cell Lymphoma of the Activated B Cell-like subtype), the more aggressive form of DLBCL. DLBCL is the most common form of non-Hodgkin's lymphoma (NHL), accounting for approximately 25% of lymphoma cases while ABC-DLBCL comprises approximately 40% of DLBCL. NF_KB pathway activation is driven by mutations of signaling components, such as CD79A/B, CARD11, MYD88 or A20, in ABC-DLBCL patients (Staudt, Cold Spring Harb Perspect Biol 2010, 2; Lim et al, Immunol Rev 2012, 246, 359-378).

The use of BTK inhibitors, for example Ibrutinib, provides clinical proof-of-concept that inhibiting NF_KB signaling in ABC-DLBCL is efficacious. MALT1 is downstream of BTK in the NF_KB signaling pathway and a MALT1 inhibitor could target ABC-DLBCL patients not responding to Ibrutinib, mainly patients with CARD11 mutations, as well as treat patients that acquired resistance to Ibrutinib.

Small molecule tool compound inhibitors of MALT1 protease have demonstrated efficacy in preclinical models of ABC-DLBCL (Fontan et al., Cancer Cell 2012, 22, 812-824; Nagel et al., Cancer Cell 2012, 22, 825-837). Interestingly, covalent catalytic site and allosteric inhibitors of MALT1 protease function have been described, suggesting that inhibitors of this protease may be useful as pharmaceutical agents (Demeyer et al., Trends Mol Med 2016, 22, 135-150).

The chromosomal translocation creating the API2-MALT1 fusion oncoprotein is the most common mutation identified in MALT (mucosa-associated lymphoid tissue) lymphoma. API2-MALT1 is a potent activator of the NF_KB pathway (Rosebeck et al., World J Biol Chem 2016, 7, 128-137). API2-MALT1 mimics ligand-bound TNF receptor, promotes TRAF2-dependent ubiquitination of RIP1 which acts as a scaffold for activating canonical NF_KB signaling. Furthermore, API2-MALT1 has been shown to cleave and generate a stable, constitutively active fragment of NF_KB-inducing kinase (NIK) thereby

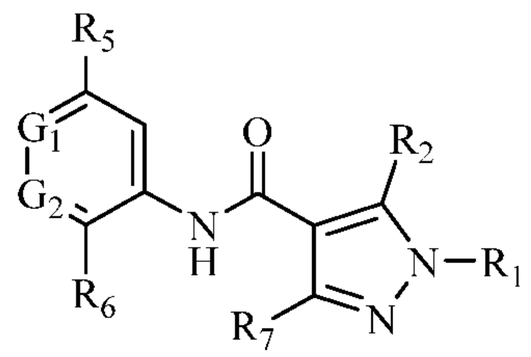
activating the non-canonical NF_KB pathway (Rosebeck et al., Science, 2011, 331, 468-472).

In addition to lymphomas, MALT1 has been shown to play a critical role in innate and adaptive immunity (Jaworski M, etal., Cell Mol Life Sci. 2016). MALT1 protease inhibitor can attenuate disease onset and progression of mouse experimental allergic encephalomyelitis, a mouse model of multiple sclerosis (Mc Guire et al., J. Neuroinflammation 2014, 11, 124). Mice expressing catalytically inactive MALT1 mutant showed loss of marginal zone B cells and B1 B cells and general immune deficiency characterized as decreased T and B cell activation and proliferation. However, those mice also developed spontaneous multi-organ autoimmune inflammation at the age of 9 to 10 weeks. It is still poorly understood why MALT1 protease dead knock-in mice show a break of tolerance while conventional MALT1 KO mice do not. One hypothesis suggests the unbalanced immune homeostasis in MALT1 protease dead knock-in mice may be caused by incomplete deficiency in T and B cell but severe deficiency of immunoregulatory cells (Jaworski et al., EMBO J. 2014; Gewies et al., Cell Reports 2014; Bornancin et al., J. Immunology 2015; Yu et al., PLOS One 2015). Similarly, MALT deficiency in humans has been associated with combined immunodeficiency disorder (McKinnon et al., J. Allergy Clin. Immunol. 2014, 133, 1458-1462; Jabara et al., J. Allergy Clin. Immunol. 2013, 132, 151-158; Punwani et al., J. Clin. Immunol. 2015, 35, 135-146). Given the difference between genetic mutation and pharmacological inhibition, a phenotype of MALT1 protease dead knock-in mice might not resemble that of patients treated with MALT1 protease inhibitors. A reduction of immunosuppressive T cells by MALT1 protease inhibition may be beneficial to cancer patients by potentially increasing antitumor immunity.

Thus, MALT1 inhibitors of the present invention may provide a therapeutic benefit to patients suffering from cancer and/or immunological diseases.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, cyclopropyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, 1-ethoxyethyl, hydroxy, methoxy, ethoxy, fluoro, chloro, bromo, methylthio, cyano, amino, methylamino, dimethylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylcarbonyl, methylaminocarbonyl, oxo, 1-(t-butoxycarbonyl)azetidin-2-yl, N-(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of C_{1-4}alkyl, 1-methoxy-ethyl, difluoromethyl, fluoro, chloro, bromo, cyano, and trifluoromethyl;

G_1 is N or $C(R_4)$;

G_2 is N or $C(R_3)$; such that only one of G_1 and G_2 are N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, C_{1-4}alkyl, fluoro, chloro, bromo, methylcarbonyl, methylthio, methylsulfinyl, and methanesulfonyl; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

R_4 is selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyrrolyl, thiazolyl, tetrazolyl, oxadiazolyl, imidazolyl, 2-amino-pyrimidin-4-yl, 2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl, 1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from oxo, C_{1-4}alkyl, carboxy, methoxycarbonyl, aminocarbonyl, hydroxymethyl, aminomethyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, or cyano;

vi) 1-methyl-piperidin-4-yloxy;

vii) 4-methyl-piperazin-1-ylcarbonyl;

viii) (4-aminobutyl)aminocarbonyl;

ix) (4-amino)butoxy;

x) 4-(4-aminobutyl)-piperazin-1-ylcarbonyl;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

xiv) 3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl;

xv) 2-oxopyrrolidin-1-yl;

xvi) (*E*)- (4-aminobut-1-en-1-yl-aminocarbonyl;

xvii) difluoromethoxy;

and

xviii) morpholin-4-ylcarbonyl;

R_5 is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, methoxy, methylsulfonyl, cyano, C_{1-4}alkyl, ethynyl, morpholin-4-yl, trifluoromethyl, hydroxyethyl, methylcarbonyl, methylsulfinyl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, azetidin-2-yl, methylthio, and 1,1-difluoroethyl;

or R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl, 4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-5-yl, 1,3-dioxolo[4,5]pyridine-5-yl, 1-oxo-1,3-dihydroisobenzofuran-5-yl, 2,2-dimethylbenzo[d][1,3]dioxol-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 1-oxoisoindolin-5-yl, or 2-methyl-1-oxoisoindolin-5-yl, 1*H*-indazol-5-yl;

R_6 is hydrogen, C_{1-4}alkyl, fluoro, 2-methoxy-ethoxy, chloro, cyano, or trifluoromethyl;

R_7 is hydrogen or fluoro;

provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is $C(R_4)$ wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

The present invention also provides a pharmaceutical composition comprising, consisting of and/or consisting essentially of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent and a compound of Formula (I), or a pharmaceutically acceptable salt form thereof.

Also provided are processes for making a pharmaceutical composition comprising, consisting of, and/or consisting essentially of admixing a compound of Formula (I), and a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and/or a pharmaceutically acceptable diluent.

The present invention further provides methods for treating or ameliorating a disease, syndrome, condition, or disorder in a subject, including a mammal and/or human in which the disease, syndrome, or condition is affected by the inhibition of MALT1, including but not limited to, cancer and/or immunological diseases, using a compound of Formula (I).

The present invention also is directed to the use of any of the compounds described herein in the preparation of a medicament wherein the medicament is prepared for treating a disease, syndrome, condition, or disorder that is affected by the inhibition of MALT1, such as cancer and/or immunological diseases.

The present invention is also directed to the preparation of substituted pyrazole derivatives that act as an inhibitor of MALT1.

Exemplifying the invention are methods of treating a disease, syndrome, condition, or disorder mediated by MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chonic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chonic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor), comprising, consisting of, and/or consisting essentially of, administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described in the present invention.

In another embodiment, the present invention is directed to a compound of Formula (I) for use in the treatment of a disease, syndrome, condition, or disorder affected by the inhibition of MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chonic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chonic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic

large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

In another embodiment, the present invention is directed to a composition comprising a compound of Formula (I) for the treatment of a disease, syndrome, condition, or disorder affected by inhibition of MALT1, selected from the group consisting of lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chonic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chonic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

In another embodiment, the present invention is directed to a composition comprising a compound of Formula (I) for the treatment of a disease, syndrome, condition,

or disorder affected by inhibition of MALT1, selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma.

An embodiment of the present invention is directed to a composition comprising a compound of Formula (I) for the treatment of immunological diseases that are affected by the inhibition of MALT1, including but not limited to, autoimmune and inflammatory disorders, e.g. arthritis, inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatits, Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, gout, organ or transplact rejection, chronic allograft rejection, acute or chronic graft-versus-host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet's diseases, uveitis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, Sjoergen's syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including oedema, embolism, fibrosis, sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

In another embodiment, the present invention is directed to a composition comprising a compound of Formula (I) for the treatment of a disease, syndrome, condition, or disorder affected by inhibition of MALT1, selected from the group consisting of rheumatoid arthritis (RA), psoritic arthritis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chronic obstructive pulmonary disease (COPD).

Another embodiment of the present invention is directed to a pharmaceutical composition comprising a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

With reference to substituents, the term "independently" refers to the situation where when more than one substituent is possible, the substituents may be the same or different from each other.

The term "alkyl" whether used alone or as part of a substituent group, refers to straight and branched carbon chains having 1 to 8 carbon atoms. Therefore, designated numbers of carbon atoms (e.g., C_{1-8}) refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger alkyl-containing substituent. In substituent groups with multiple alkyl groups such as, $(C_{1-6}alkyl)_2amino$-, the $C_{1-6}alkyl$ groups of the dialkylamino may be the same or different.

The term "alkoxy" refers to an -O-alkyl group, wherein the term "alkyl" is as defined above.

The terms "alkenyl" and "alkynyl" refer to straight and branched carbon chains having 2 to 8 carbon atoms, wherein an alkenyl chain contains at least one double bond and an alkynyl chain contains at least one triple bond.

The term "cycloalkyl" refers to saturated or partially saturated, monocyclic or polycyclic hydrocarbon rings of 3 to 14 carbon atoms. Examples of such rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and adamantyl.

The term "heterocyclyl" refers to a nonaromatic monocyclic or bicyclic ring system having 3 to 10 ring members that include at least 1 carbon atom and from 1 to 4 heteroatoms independently selected from N, O, and S. Included within the term heterocyclyl is a nonaromatic cyclic ring of 5 to 7 members in which 1 to 2 members are N, or a nonaromatic cyclic ring of 5 to 7 members in which 0, 1 or 2 members are N and up to 2 members are O or S and at least one member must be either N, O, or S; wherein, optionally, the ring contains 0 to 1 unsaturated bonds, and, optionally, when the ring is of 6 or 7 members, it contains up to 2 unsaturated bonds. The carbon atom ring members that form a heterocycle ring may be fully saturated or partially saturated. The term "heterocyclyl" also includes two 5 membered monocyclic heterocycloalkyl groups bridged to form a bicyclic ring. Such groups are not considered to be fully aromatic and are not

referred to as heteroaryl groups. When a heterocycle is bicyclic, both rings of the heterocycle are non-aromatic and at least one of the rings contains a heteroatom ring member. Examples of heterocycle groups include, and are not limited to, pyrrolinyl (including 2H-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, and piperazinyl. Unless otherwise noted, the heterocycle is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

The term "aryl" refers to an unsaturated, aromatic monocyclic or bicyclic ring of 6 to 10 carbon members. Examples of aryl rings include phenyl and naphthalenyl.

The term "heteroaryl" refers to an aromatic monocyclic or bicyclic aromatic ring system having 5 to 10 ring members and which contains carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O, and S. Included within the term heteroaryl are aromatic rings of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen, and sulfur. In the case of 5 membered rings, the heteroaryl ring preferably contains one member of nitrogen, oxygen or sulfur and, in addition, up to 3 additional nitrogens. In the case of 6 membered rings, the heteroaryl ring preferably contains from 1 to 3 nitrogen atoms. For the case wherein the 6 membered ring has 3 nitrogens, at most 2 nitrogen atoms are adjacent. Examples of heteroaryl groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl and quinazolinyl. Unless otherwise noted, the heteroaryl is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine atoms.

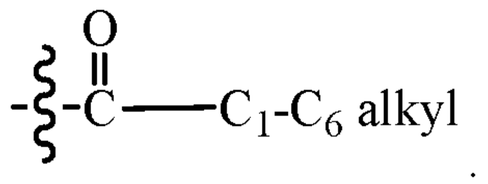
The term "carboxy" refers to the group –C(=O)OH.

The term "formyl" refers to the group –C(=O)H.

The term "oxo" or "oxido" refers to the group (=O).

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl, alkylamino) the name is to be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_1-C_6) refer independently to the number of carbon atoms in an alkyl moiety, an aryl moiety, or in the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl and alkoxy substituents, the designated number of carbon atoms includes all of the independent members included within a given range specified. For example C_{1-6} alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g., C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{2-6}, C_{3-6}, C_{4-6}, C_{5-6}, C_{2-5}, etc.).

In general, under standard nomenclature rules used thoughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a "C_1-C_6 alkylcarbonyl" substituent refers to a group of the formula:



The label "R" at a stereocenter designates that the stereocenter is purely of the *R*-configuration as defined in the art; likewise, the label "S" means that the stereocenter is purely of the *S*-configuration. As used herein, the labels " *R" or " *S" at a stereocenter are used to designate that the stereocenter is of pure but unknown absolute configuration. As used herein, the label "RS" refers to a stereocenter that exists as a mixture of the *R*- and *S*-configurations.

A compound containing one stereocenter drawn without a stereo bond designation is a mixture of two enantiomers. A compound containing two stereocenters both drawn without stereo bond designations is a mixture of four diastereomers. A compound with two stereocenters both labeled "RS" and drawn with stereo bond designations is a mixture of two enantiomers with relative stereochemistry as drawn. A compound with two

stereocenters both labeled " *RS" and drawn with stereo bond designations is a mixture of two enantiomers with a single, but unknown, relative stereochemistry.

Unlabeled stereocenters drawn without stereo bond designations are mixtures of the *R*- and *S*-configurations. For unlabeled stereocenters drawn with stereo bond designations, the relative and absolute stereochemistry is as depicted.

Unless otherwise noted, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The term "subject" refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "therapeutically effective amount" refers to an amount of an active compound or pharmaceutical agent, including a compound of the present invention, which elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, including reduction or inhibition of an enzyme or a protein activity, or ameliorating symptioms, alleviating conditions, slowing or delaying disease progression, or preventing a disease.

In one embodiment, the term "therapeutically effective amount" refers to the amount of a compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent, and/ or ameliorate a condition, or a disorder or a disease (i) mediated by MALT1; or (ii) associated with MALT1 activity; or (iii) characterized by activity (normal or abnormal) of MALT1; or (2) reduce or inhibit the activity of MALT1; or (3) reduce or inhibit the expression of MALT1; or (4) modify the protein levels of MALT1.

The term "composition" refers to a product that includes the specified ingredients in therapeutically effective amounts, as well as any product that results, directly, or indirectly, from combinations of the specified ingredients in the specified amounts.

The term “MALT1-mediated” refers to any disease, syndrome, condition, or disorder that might occur in the absence of MALT1 but can occur in the presence of MALT1. Suitable examples of a disease, syndrome, condition, or disorder mediated by MALT1 include, but are not limited to, lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin’s lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin’s lymphoma, Burkitt’s lymphoma, multiple myeloma, chonic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chonic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head and neck cancer, testicular cancer, Ewing’s sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

As used herein, the term "MALT1 inhibitor" refers to an agent that inhibits or reduces at least one condition, symptom, disorder, and/or disease of MALT1.

As used herein, unless otherwise noted, the term “affect” or “affected” (when referring to a disease, syndrome, condition or disorder that is affected by the inhibition of MALT1) includes a reduction in the frequency and / or severity of one or more symptoms or manifestations of said disease, syndrome, condition or disorder; and / or includes the prevention of the development of one or more symptoms or manifestations of said disease, syndrome, condition or disorder or the development of the disease, condition, syndrome or disorder.

As used herein, the term "treat", "treating", or "treatment" of any disease, condition, syndrome or disorder refers, in one embodiment, to ameliorating the disease, condition, syndrome or disorder (i.e. slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment, "treat", "treating", or "treatment" refers to alleviating or ameliorating at lease one physical parameter including those which may not be discernible by the patient. In a further embodiment, "treat", "treating", or "treatment" refers to modulating the disease, condition, syndrome or disorder either physically (*e.g.* stabilization of a discernible symptom), physiologically, (*e.g.* stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating", or "treatment" refers to preventing or delaying the onset or development or progression of the disease, condition, syndrome or disorder.

The compounds of the instant invention are useful in methods for treating or ameliorating a disease, a syndrome, a condition or a disorder that is affected by the inhibition of MALT1. Such methods comprise, consist of and/or consist essentially of administering to a subject, including an animal, a mammal, and a human in need of such treatment, amelioration and / or prevention, a therapeutically effective amount of a compound of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt thereof.

One embodiment of the present invention is directed to a method of treating a MALT1- dependent or MALT1-mediated disease or condition in a subject in need thereof, including an animal, a mammal, and a human in need of such treatment, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I).

In another embodiment, the MALT1-dependent or MALT1-mediated disease or condition is selected from cancers of hematopoietic origin or solid tumors such as chonic myelogenous leukemia, myeloid leukemia, non-Hodgkin lymphoma, and other B cell lymphomas.

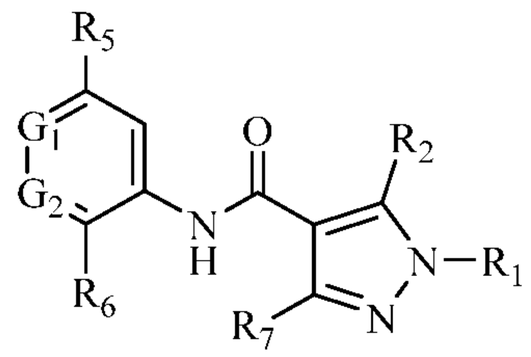
In particular, the compounds of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof are useful for treating or

ameliorating diseases, syndromes, conditions, or disorders such as diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma.

More particularly, the compounds of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof, are useful for treating or ameliorating diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof as herein defined.

Further, the compounds of Formula (I), or an enantiomer, diastereomer, solvate or pharmaceutically acceptable salt form thereof, are useful for treating or ameliorating an immunological disease, syndrome, disorder, or condition selected from the group consisting of rheumatoid arthritis (RA), psoritic arthritis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chronic obstructive pulmonary disease (COPD).

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

AA) R_1 is

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; or

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, methoxy, fluoro, chloro, bromo, cyano, amino, methylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylaminocarbonyl, oxo, N-(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

BB) R_1 is

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; or

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, difluoromethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, aminocarbonyl, methylaminocarbonyl, oxo, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

CC) R_1 is

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; or

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, 3-hydroxyazetidinyl, or oxo;

DD) R_1 is

i) naphthalen-1-yl, 4-amino-naphthalen-1-yl, 4-fluoronaphthalen-1-yl, or 5-fluoronaphthalen-1-yl;

or

ii) a heteroaryl selected from the group consisting of isoquinolin-1-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-7-yl, cinnolin-4-yl, imidazo[1,2-a]pyrazin-8-yl, phthalazin-1-yl, naphthyridin-5-yl, thieno[3,2-c]pyridin-4-yl, furo[3,2-c]pyridin-4-yl, furo[2,3-c]pyridin-7-yl, quinoxalin-5-yl, 1*H*-indazolylfuro[3,2-b]pyridin-7-yl, pyrazolo[1,5-a]pyrazin-4-yl, quinolin-4-yl, quinolin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-5-yl, benzo[d]thiazol-7-yl, 1-hydroxyisoquinolin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, thieno[2,3-c]pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl, thieno[3,2-b]pyridin-7-yl, 2-oxo-1,2-dihydroquinolin-4-yl, 1-amino-8-fluoroisoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 1-cyanoisoquinolin-5-yl, pyrrolo[2,1-f][1,2,4]triazin-4-yl, 7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl, thieno[2,3-d]pyrimidin-4-yl, thieno[2,3-c]pyridin-7-yl, 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-

yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-(hydroxyethyl)quinolin-4-yl, 1-(methoxymethyl)isoquinolin-4-yl, 1-fluoroisoquinolin-4-yl, 1-(difluoromethyl)isoquinolin-4-yl, 8-fluoroquinolin-4-yl, 8-fluoroquinolin-5-yl, 1-(tetrahydrofuran-2(*R*)-yl)isoquinolin-4-yl, 2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 2-(aminocarbonyl)quinolin-4-yl, 1H-indazol-7-yl, 1-(1,4-dioxan-2-yl)isoquinolin-4-yl, 2-methylimidazo[1,2-a]pyridin-5-yl, 1-chloroisoquinolin-4-yl, 2-cyanoquinolin-4-yl, 8-fluoro-1-(methylamino)isoquinolin-4-yl, benzo[d]isoxazol-3-yl, 2-aminobenzo[d]thiazol-7-yl, 2-fluoroquinolin-5-yl, 1,7-naphthyridin-4-yl, imidazo[1,2-a]pyrazin-5-yl, (N-(methyl)formamido)methyl)isoquinolin-4-yl, [1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methylbenzo[d]oxazol-7-yl, 1,5-naphthyridin-4-yl, 5-oxopyrrolidin-2-ylisoquinolin-4-yl, 1-methyl-1H-indazol-3-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(1,1-difluoroethyl)isoquinolin-4-yl, 1-(1(*S)-hydroxyethyl)isoquinolin-4-yl, 1-(methylamino)isoquinolin-4-yl, 4-fluoroisoquinolin-1-yl, 1H-pyrazolo[4,3-b]pyridin-7-yl, 5-fluoroquinolin-8-yl, 6-fluoroimidazo[1,2-a]pyridin-5-yl, 2-methylfuro[3,2-b]pyridin-7-yl, 8-(difluoromethyl)quinolin-5-yl, 1-(4-

oxotetrahydrofuran-2*R*-yl)isoquinolin-4-yl, 1-(dimethylamino)isoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methoxyquinolin-4-yl, imidazo[1,2-a]pyrimidin-5-yl, 2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, quinolin-5-yl, 1-(1-ethoxyethyl)isoquinolin-4-yl, 2-(azetidin-2-yl)quinolin-4-yl, 2-methylbenzo[d]thiazol-7-yl, 2-acetylquinolin-4-yl, 1-(methylthio)isoquinolin-4-yl, 2-aminoquinolin-5-yl, 1-methoxyisoquinolin-5-yl, imidazo[1,2-b]pyridazin-6-yl, 1-(pyrrolidin-2-yl)isoquinolin-4-yl, 4-(difluoromethyl)quinolin-5-yl, 1-acetylisoquinolin-5-yl, 2-aminoquinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-4-yl, 1-ethoxyisoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl, 1-aminoisoquinolin-5-yl, 1-methyl-1H-indazol-4-yl, 2-aminoquinolin-4-yl, 2-oxo-1,2-dihydroquinolin-5-yl, 1-(azetidin-3-yl)isoquinolin-4-yl, 2-methylthieno[3,2-b]pyridin-7-yl, benzo[d][1,2,3]thiadiazol-4-yl, 1-(1(*S*)-hydroxyethyl)isoquinolin-5-yl, imidazo[1,2-a]pyridin-8-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl, 2-(tetrahydrofuran-2-yl)quinolin-5-yl, , 1-(1(*R*)-hydroxyethyl)isoquinolin-5-yl, 1,6-naphthyridin-4-yl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 2-aminocarbonyl-quinolin-5-yl, 2-chloroquinolin-5-yl, 2-chloroquinolin-4-yl, 2-cyanoquinolin-5-yl, 1-aminoisoquinolin-5-yl, 2-methoxyquinolin-5-yl, 2-methylbenzo[d]oxazol-4-yl, 2-(difluoromethyl)quinolin-5-yl, 2-(azetidin-2-yl)quinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-5-yl, 1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-

yl)isoquinolin-5-yl, and 1-(1-t-butoxycarbonylazetidin-2-yl)isoquinolin-5-yl;

EE) R_1 is

i) napthalen-1-yl or 4-fluoronaphthalen-1-yl, 4-amino-naphthalen-1-yl or 5-fluoronaphthalen-1-yl;

or

ii) a heteroaryl selected from the group consisting of thieno[3,2-c]pyridin-4-yl, isoquinolin-4-yl, 8-fluoroquinolin-4-yl, furo[3,2-c]pyridin-4-yl, quinolin-5-yl, furo[2,3-c]pyridin-7-yl, benzofuran-4-yl 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, pyrrolo[1,2-a]pyrazin-1-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, benzo[d]thiazol-4-yl, 1-aminoisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, imidazo[1,2-a]pyridin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-

yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-5-yl, and 1-(hydroxyethyl)quinolin-4-yl;

FF) R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, bromo, chloro, and trifluoromethyl;

GG) R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl;

HH) R_2 is trifluoromethyl;

II) R_3 is independently selected from the group consisting of trifluoromethyl, cyano, methylcarbonyl, methylthio, methylsulfinyl, methanesulfonyl, and chloro; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

JJ) R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

KK) G_2 is N or C(R_3), wherein R_3 is chloro;

LL) G_2 is N;

MM) R_4 is selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) carboxy;

vi) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, imidazolyl, and pyrimidin-4-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of C_{1-4}alkyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, and cyano;

vii) 1-methyl-piperidin-4-yloxy;

viii) 4-methyl-piperazin-1-ylcarbonyl;

ix) (4-aminobutyl)aminocarbonyl;

x) (4-amino)butoxy;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl; and

xiv) morpholin-4-ylcarbonyl;

NN) R_4 is selected from the group consisting of

i) hydrogen;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, and imidazolyl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of methyl, carboxy, methoxycarbonyl,

hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, and amino, methoxymethyl;

vi) (4-amino)butoxy;

vii) methoxycarbonyl;

viii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl; and

ix) 1,1-dioxo-isothiazolidin-2-yl;

OO) R_4 is selected from the group consisting of

i) methoxy;

ii) a heteroaryl independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, 1,3,4-oxadiazol-2-yl, 2-methyl-2H-tetrazol-5-yl, 5-amino-1-methyl-1H-pyrazol-3-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-cyano-2H-1,2,3-triazol-2-yl, 5-amino-1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-4-yl, 2H-tetrazol-5-yl, 4-(aminomethyl)-1H-pyrazol-1-yl, 4-(methoxymethyl)-2H-1,2,3-triazol-2-yl, 2-methyl-2H-tetrazol-5-yl, and 4-methyl-1H-1,2,3-triazol-1-yl; and

iii) methoxycarbonyl;

PP) R_4 is independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 1*H*-imidazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl,

4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, and 1,3,4-oxadiazol-2-yl;

QQ) R_5 is hydrogen, chloro, fluoro, bromo, cyano, methyl, ethyl, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl;

RR) R_5 is hydrogen, chloro, bromo, cyano, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl;

SS) R_5 is hydrogen, chloro, bromo, or cyano;

TT) R_5 is hydrogen, chloro, or cyano;

UU) R_6 is hydrogen or methyl;

VV) R_7 is hydrogen;

and any combination of embodiments AA) though VV) above, provided it is understood that combinations in which different embodiments of the same substituent would be combined are excluded; such that only one of G_1 and G_2 are N in any instance; and provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

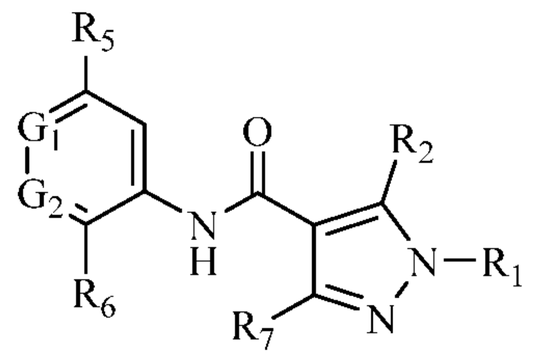
a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is $C(R_4)$ wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, 4-amino-naphthalen-1-yl, or 4-fluoronaphthalen-1-yl, 5-fluoronaphthalen-1-yl;

and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, methoxy, fluoro, chloro, bromo, cyano, amino,

methylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylaminocarbonyl, oxo, N-(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, bromo, chloro, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, methylcarbonyl, methylthio, methylsulfinyl, methanesulfonyl, and chloro; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

R_4 is independently selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) carboxy;

vi) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, imidazolyl, and pyrimidin-4-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of C_{1-4}alkyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, and cyano;

vii) 1-methyl-piperidin-4-yloxy;

viii) 4-methyl-piperazin-1-ylcarbonyl;

ix) (4-aminobutyl)aminocarbonyl;

x) (4-amino)butoxy;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

and

xiv) morpholin-4-ylcarbonyl;

R_5 is hydrogen, chloro, fluoro, bromo, cyano, methyl, ethyl, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

and provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

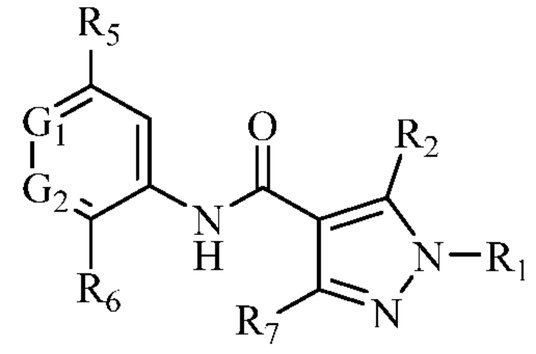
a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is $C(R_4)$ wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent;

or

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, difluoromethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, aminocarbonyl, methylaminocarbonyl, oxo, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is independently selected from the group consisting of

i) hydrogen;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, and imidazolyl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of methyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, and amino, methoxymethyl;

vi) (4-amino)butoxy;

vii) methoxycarbonyl;

viii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl; and

ix) 1,1-dioxo-isothiazolidin-2-yl;

R_5 is hydrogen, chloro, bromo, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

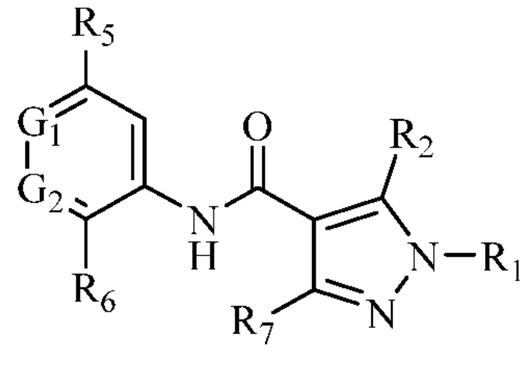
a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is $C(R_4)$ wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, oxo, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is selected from the group consisting of

i) methoxy;

ii) a heteroaryl selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, 1,3,4-oxadiazol-2-yl, 2-methyl-2H-tetrazol-5-yl, 5-amino-1-methyl-1H-pyrazol-3-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-cyano-2H-1,2,3-triazol-2-yl, 5-amino-1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-4-yl, 2H-tetrazol-5-yl, 4-(aminomethyl)-1H-pyrazol-1-yl, 4-(methoxymethyl)-2H-1,2,3-triazol-2-yl, 2-methyl-2H-tetrazol-5-yl, and 4-methyl-1H-1,2,3-triazol-1-yl;

and

iii) methoxycarbonyl;

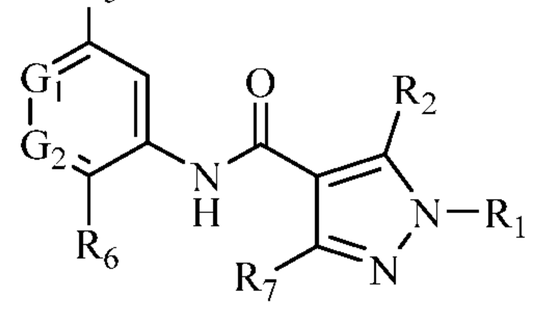
R_5 is hydrogen, chloro, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

R_1 is independently selected from the group consisting of

i) naphthalen-1-yl, 4-amino-naphthalen-1-yl, 4-fluoronaphthalen-1-yl, or 5-fluoronaphthalen-1-yl;

and

ii) a heteroaryl selected from the group consisting of isoquinolin-1-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-7-yl, cinnolin-4-yl, imidazo[1,2-a]pyrazin-8-yl, phthalazin-1-yl, naphthyridin-5-yl, thieno[3,2-c]pyridin-4-yl, furo[3,2-c]pyridin-4-yl, furo[2,3-c]pyridin-7-yl, quinoxalin-5-yl, 1*H*-indazolylfuro[3,2-b]pyridin-7-yl, pyrazolo[1,5-a]pyrazin-4-yl, quinolin-4-yl, quinolin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-5-yl, benzo[d]thiazol-7-yl, 1-hydroxyisoquinolin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, thieno[2,3-c]pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl, thieno[3,2-b]pyridin-7-yl, 2-oxo-1,2-dihydroquinolin-4-yl, 1-amino-8-fluoroisoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 1-cyanoisoquinolin-5-yl, pyrrolo[2,1-f][1,2,4]triazin-4-yl, 7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl, thieno[2,3-d]pyrimidin-4-yl, thieno[2,3-c]pyridin-7-yl, 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-oxo-quinolin-4-yl, 8-

aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-(hydroxyethyl)quinolin-4-yl, 1-(methoxymethyl)isoquinolin-4-yl, 1-fluoroisoquinolin-4-yl, 1-(difluoromethyl)isoquinolin-4-yl, 8-fluoroquinolin-4-yl, 8-fluoroquinolin-5-yl, 1-(tetrahydrofuran-2(*R*)-yl)isoquinolin-4-yl, 2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 2-(aminocarbonyl)quinolin-4-yl, 1H-indazol-7-yl, 1-(1,4-dioxan-2-yl)isoquinolin-4-yl, 2-methylimidazo[1,2-a]pyridin-5-yl, 1-chloroisoquinolin-4-yl, 2-cyanoquinolin-4-yl, 8-fluoro-1-(methylamino)isoquinolin-4-yl, benzo[d]isoxazol-3-yl, 2-aminobenzo[d]thiazol-7-yl, 2-fluoroquinolin-5-yl, 1,7-naphthyridin-4-yl, imidazo[1,2-a]pyrazin-5-yl, (N-(methyl)formamido)methyl)isoquinolin-4-yl, [1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methylbenzo[d]oxazol-7-yl, 1,5-naphthyridin-4-yl, 5-oxopyrrolidin-2-ylisoquinolin-4-yl, 1-methyl-1H-indazol-3-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(1,1-difluoroethyl)isoquinolin-4-yl, 1-(1(^{x}*S*)-hydroxyethyl)isoquinolin-4-yl, 1-(methylamino)isoquinolin-4-yl, 4-fluoroisoquinolin-1-yl, 1H-pyrazolo[4,3-b]pyridin-7-yl, 5-fluoroquinolin-8-yl, 6-fluoroimidazo[1,2-a]pyridin-5-yl, 2-methylfuro[3,2-b]pyridin-7-yl, 8-(difluoromethyl)quinolin-5-yl, 1-(4-oxotetrahydrofuran-2*R*-yl)isoquinolin-4-yl, 1-(dimethylamino)isoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methoxyquinolin-4-yl, imidazo[1,2-

a]pyrimidin-5-yl, 2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, quinolin-5-yl, 1-(1-ethoxyethyl)isoquinolin-4-yl, 2-(azetidin-2-yl)quinolin-4-yl, 2-methylbenzo[d]thiazol-7-yl, 2-acetylquinolin-4-yl, 1-(methylthio)isoquinolin-4-yl, 2-aminoquinolin-5-yl, 1-methoxyisoquinolin-5-yl, imidazo[1,2-b]pyridazin-6-yl, 1-(pyrrolidin-2-yl)isoquinolin-4-yl, 4-(difluoromethyl)quinolin-5-yl, 1-acetylisoquinolin-5-yl, 2-aminoquinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-4-yl, 1-ethoxyisoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl, 1-aminoisoquinolin-5-yl, 1-methyl-1H-indazol-4-yl, 2-aminoquinolin-4-yl, 2-oxo-1,2-dihydroquinolin-5-yl, 1-(azetidin-3-yl)isoquinolin-4-yl, 2-methylthieno[3,2-b]pyridin-7-yl, benzo[d][1,2,3]thiadiazol-4-yl, 1-(1(*S*)-hydroxyethyl)isoquinolin-5-yl, imidazo[1,2-a]pyridin-8-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl, 2-(tetrahydrofuran-2-yl)quinolin-5-yl, , 1-(1(*R*)-hydroxyethyl)isoquinolin-5-yl, 1,6-naphthyridin-4-yl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 2-aminocarbonyl-quinolin-5-yl, 2-chloroquinolin-5-yl, 2-chloroquinolin-4-yl, 2-cyanoquinolin-5-yl, 1-aminoisoquinolin-5-yl, 2-methoxyquinolin-5-yl, 2-methylbenzo[d]oxazol-4-yl, 2-(difluoromethyl)quinolin-5-yl, 2-(azetidin-2-yl)quinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-5-yl, 1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-5-yl, and 1-(1-t-butoxycarbonylazetidin-2-yl)isoquinolin-5-yl;

R_2 is trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 1*H*-imidazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, and 1,3,4-oxadiazol-2-yl;

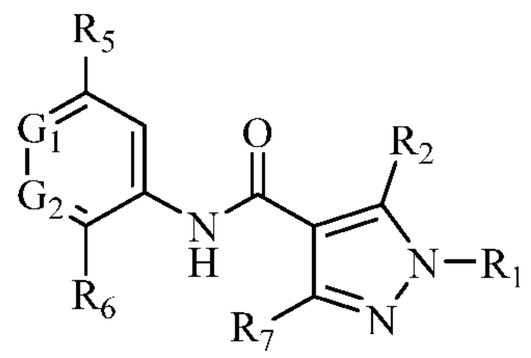
R_5 is hydrogen, chloro, bromo, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

Embodiments of the present invention include a compound of Formula (I)



Formula (I)

wherein

R_1 is independently selected from the group consisting of

i) napthalen-1-yl, 4-amino-naphthalen-1-yl, 4-fluoronaphthalen-1-yl, or 5-fluoronaphthalen-1-yl;

and

ii) a heteroaryl selected from the group consisting of thieno[3,2-c]pyridin-4-yl, isoquinolin-4-yl, 8-fluoroquinolin-4-yl, furo[3,2-c]pyridin-4-yl, quinolin-5-yl, furo[2,3-c]pyridin-7-yl, benzofuran-4-yl 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, pyrrolo[1,2-a]pyrazin-1-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, benzo[d]thiazol-4-yl, 1-aminoisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, imidazo[1,2-a]pyridin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-

yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-5-yl and 1-(hydroxyethyl)quinolin-4-yl;

R_2 is trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 1*H*-imidazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, and 1,3,4-oxadiazol-2-yl;

R_5 is hydrogen, chloro, or cyano;

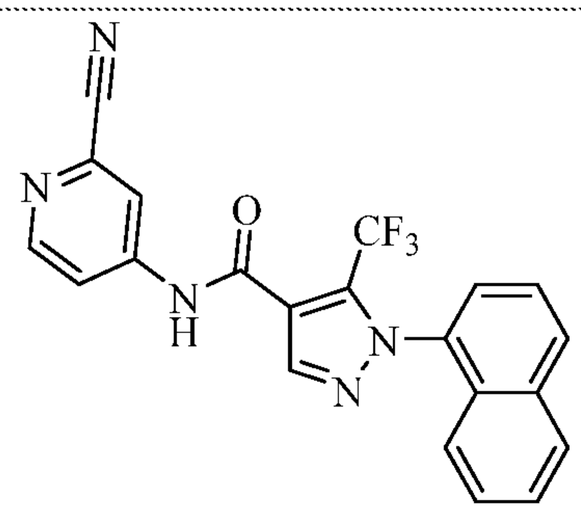
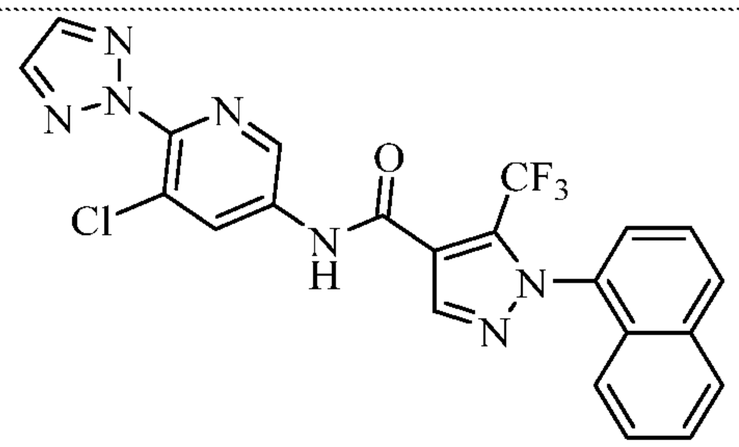
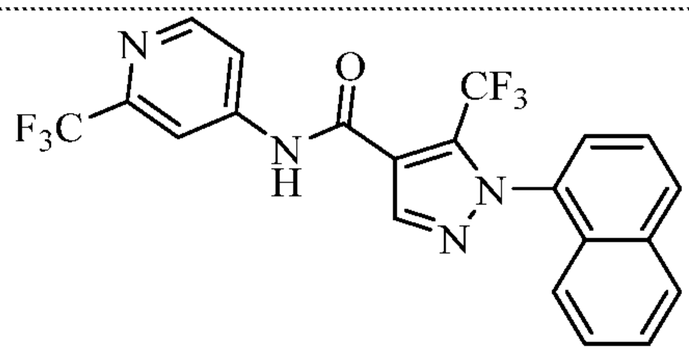
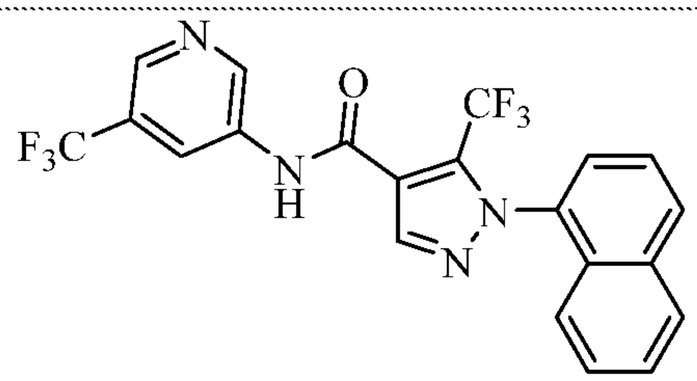
R_6 is hydrogen or methyl;

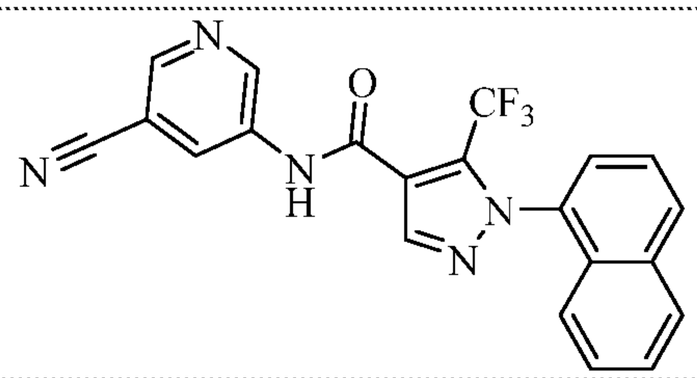
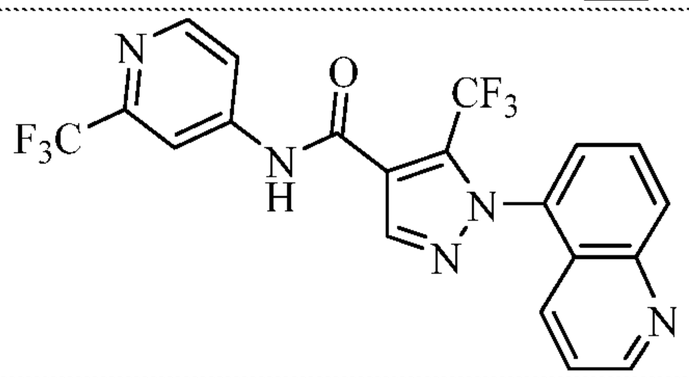
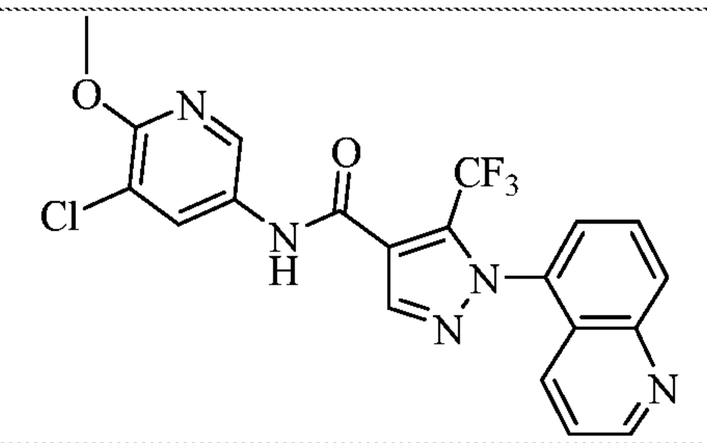
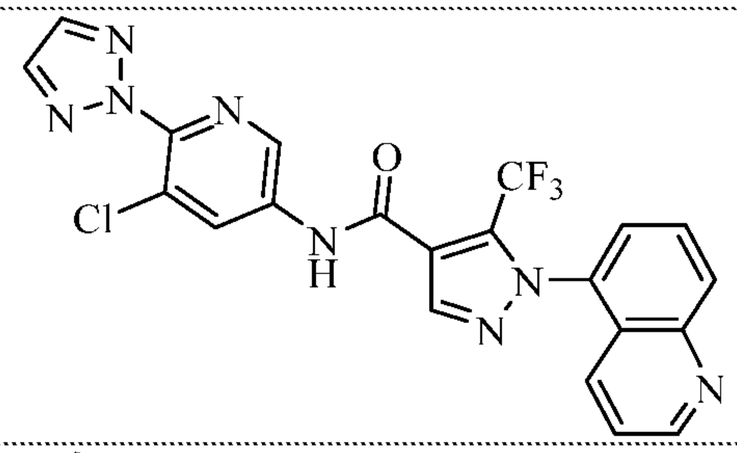
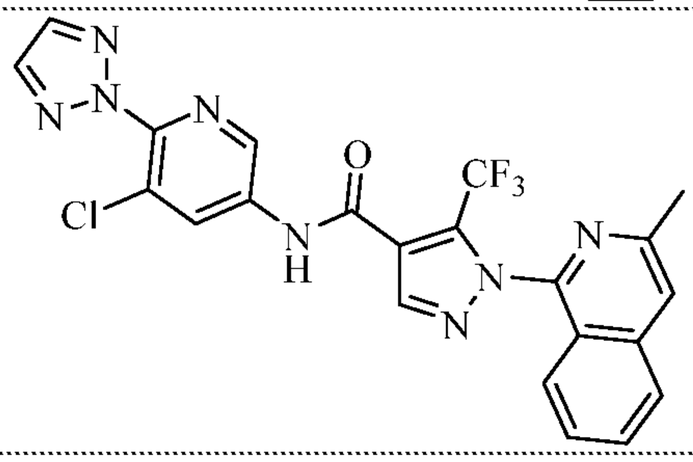
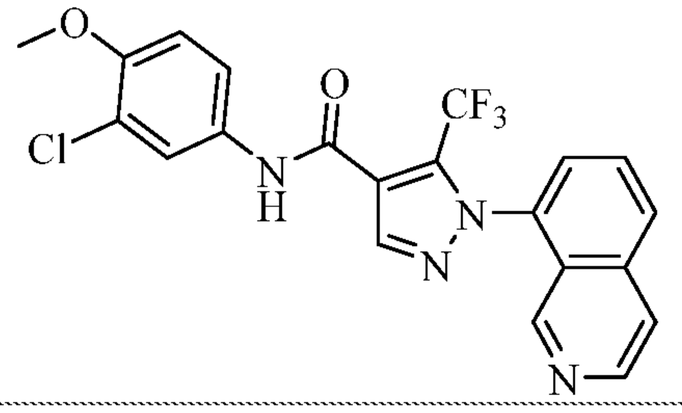
R_7 is hydrogen;

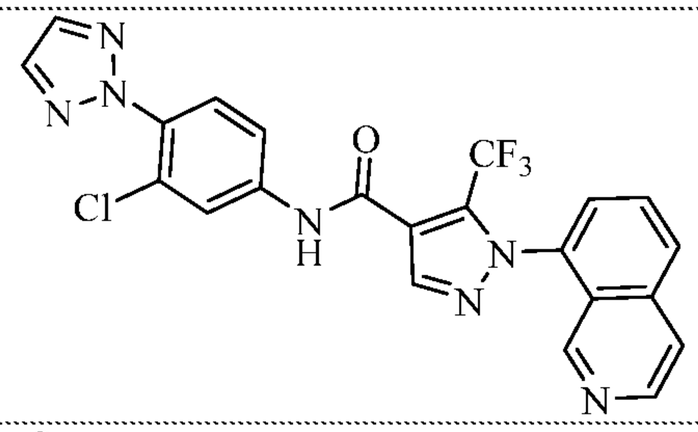
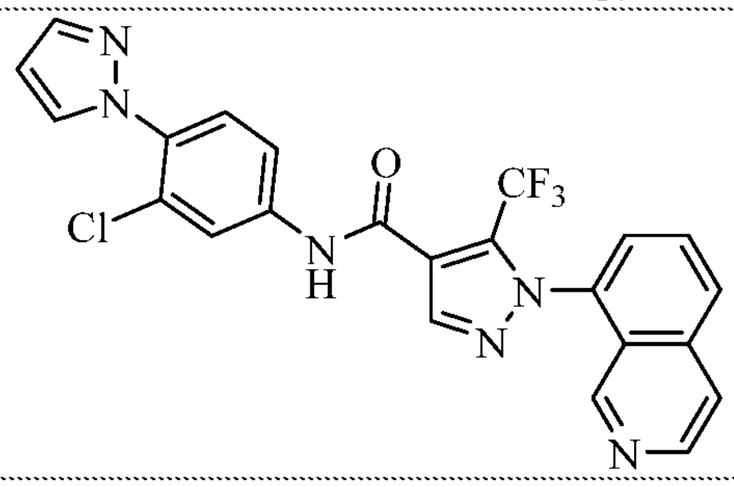
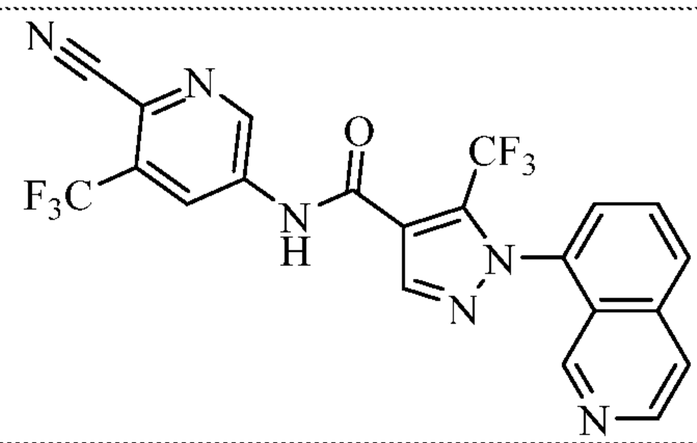
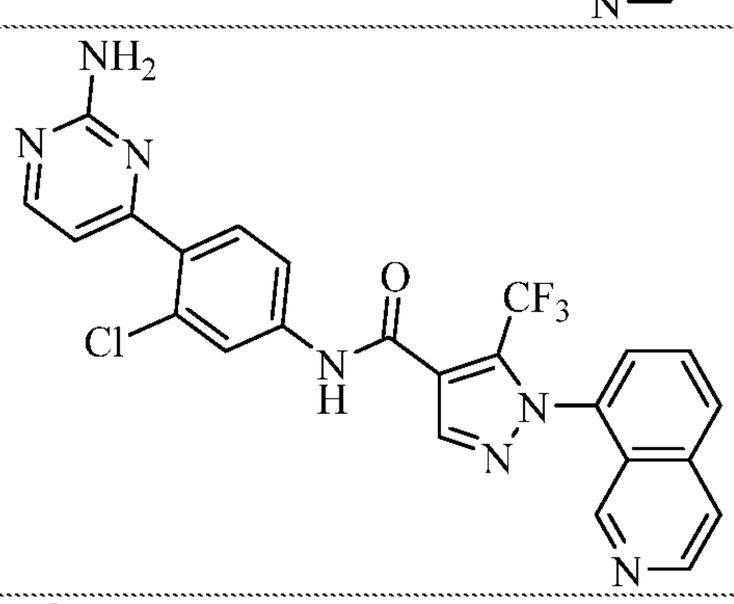
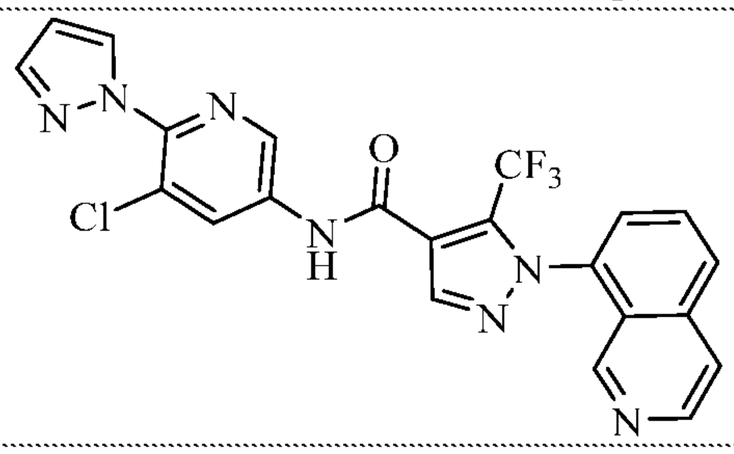
or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

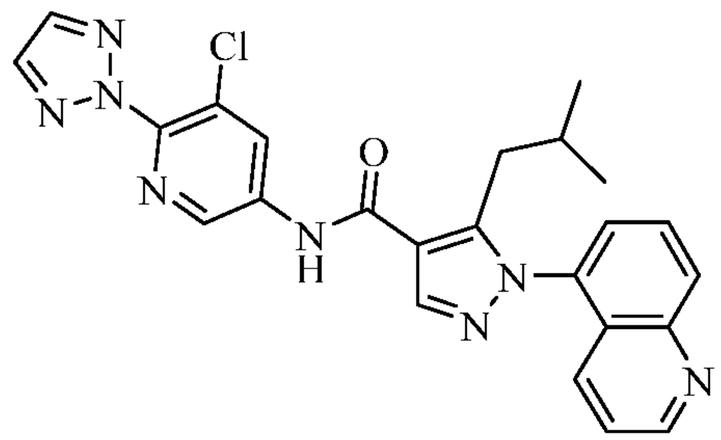
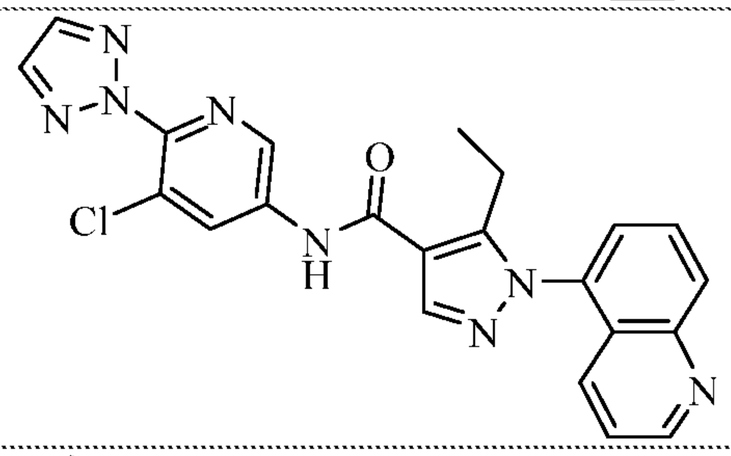
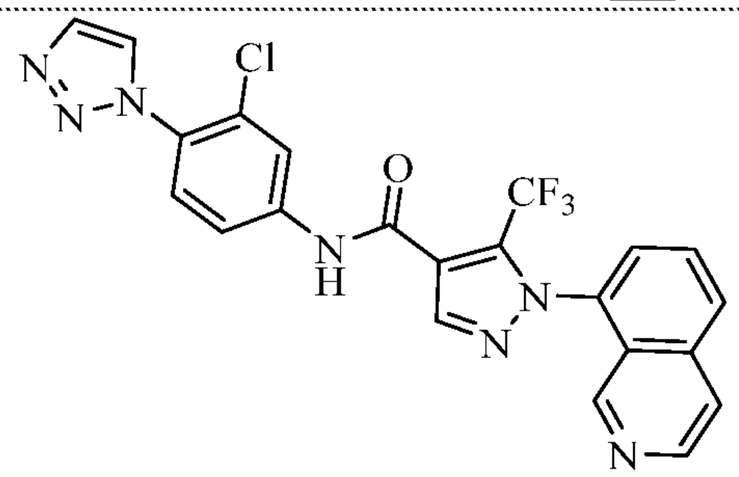
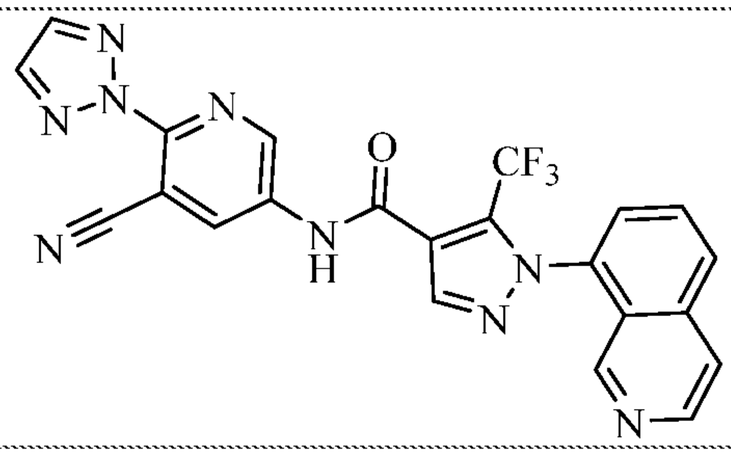
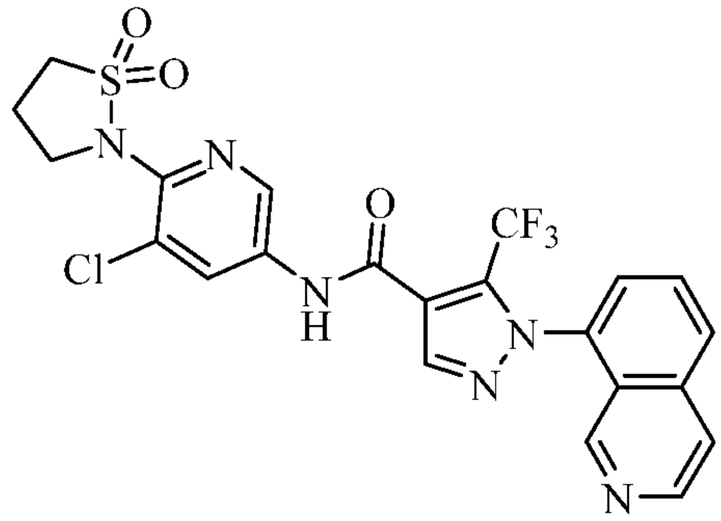
Additional embodiments of the present invention include compounds of Formula (I) as herein defined, or an enantiomer, diastereomer, solvate, or a pharmaceutically acceptable salt form thereof, as exemplified in the listing in Table 1, below.

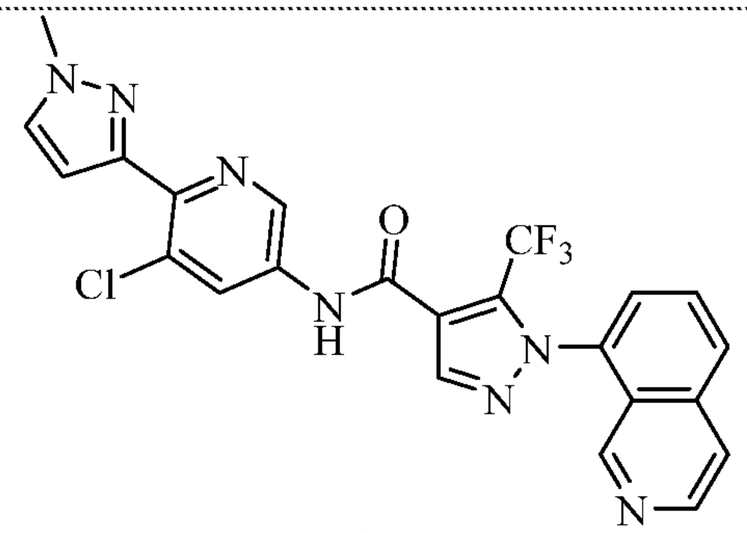
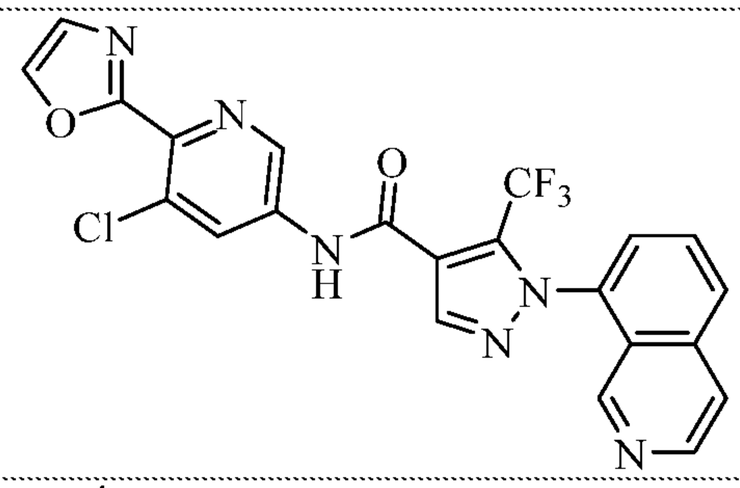
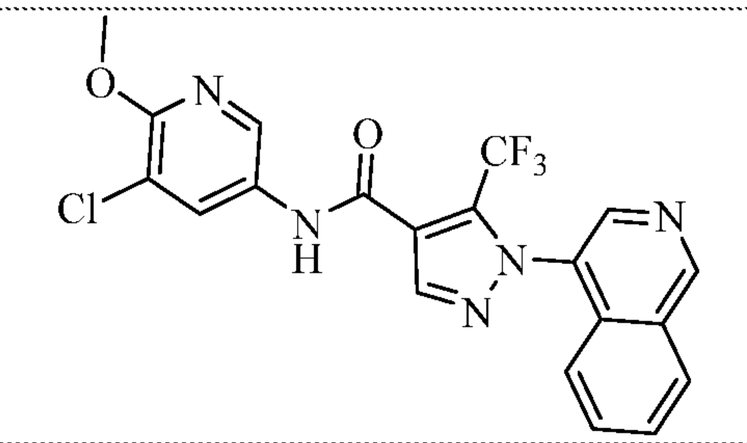
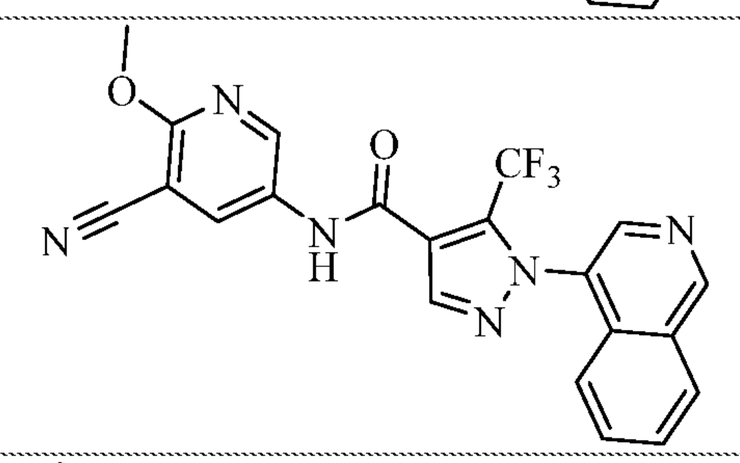
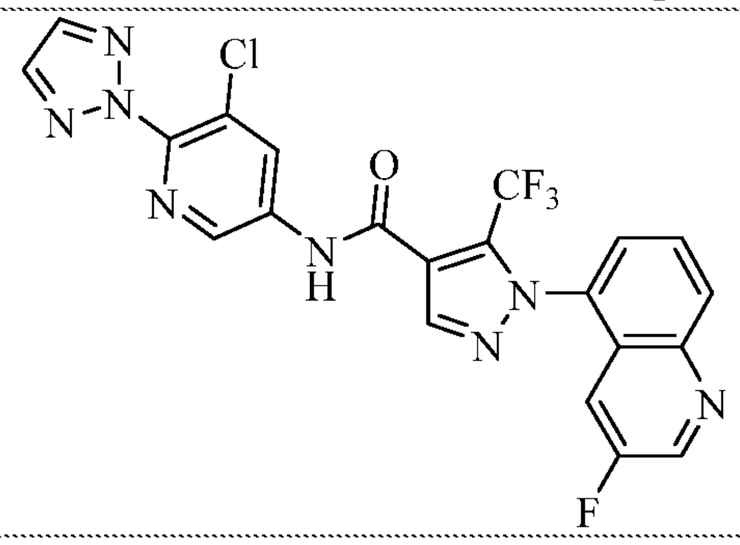
Table 1.

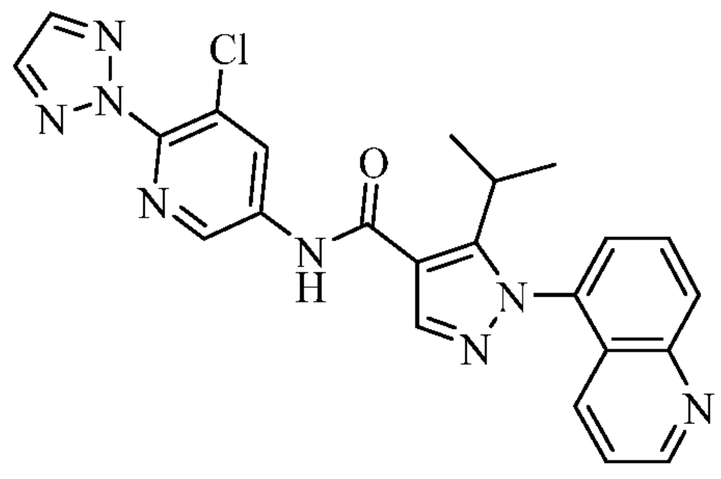
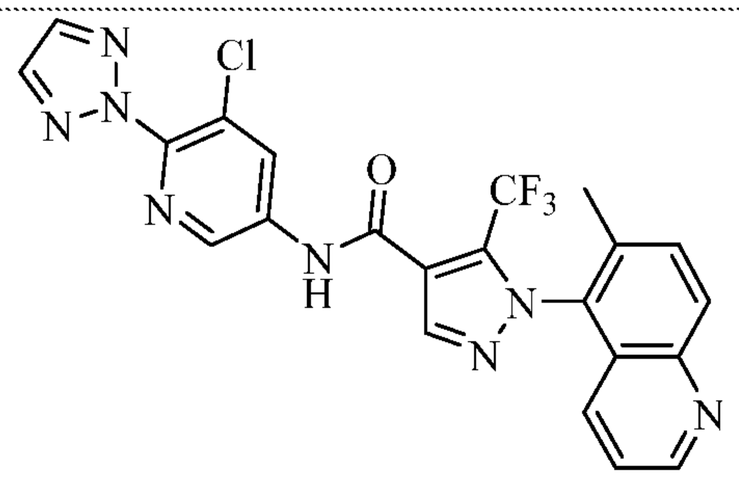
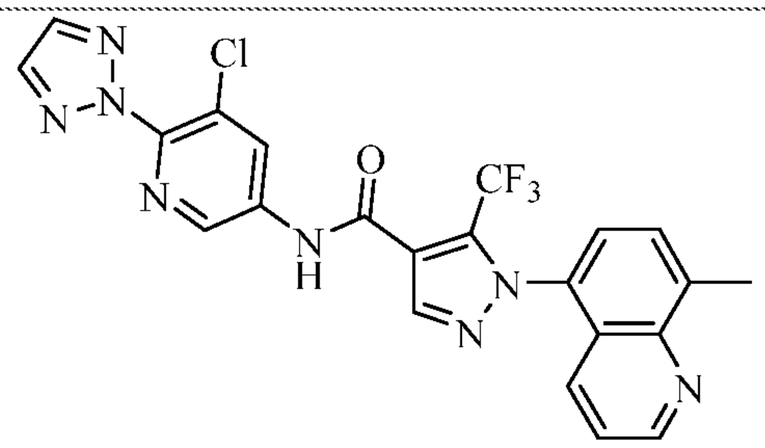
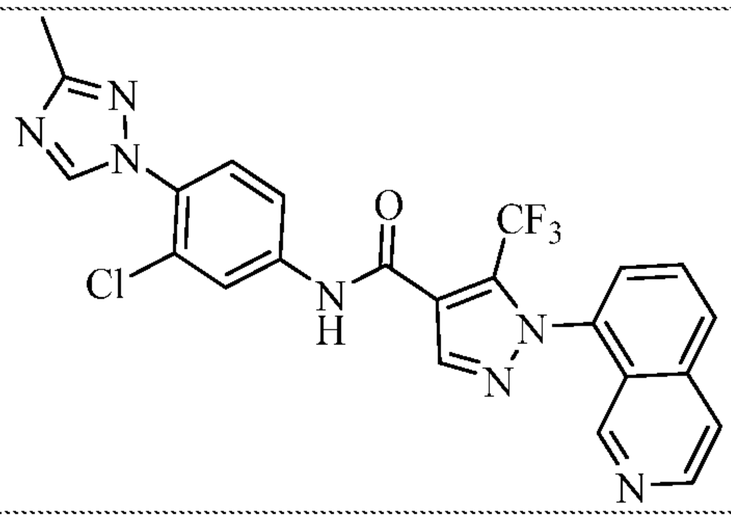
Structure	Cpd No.	Cpd Name
	**1**	*N*-(2-cyanopyridin-4-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**2**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**3**	1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide
	**4**	1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(5-(trifluoromethyl)pyridin-3-yl)-*1H*-pyrazole-4-carboxamide

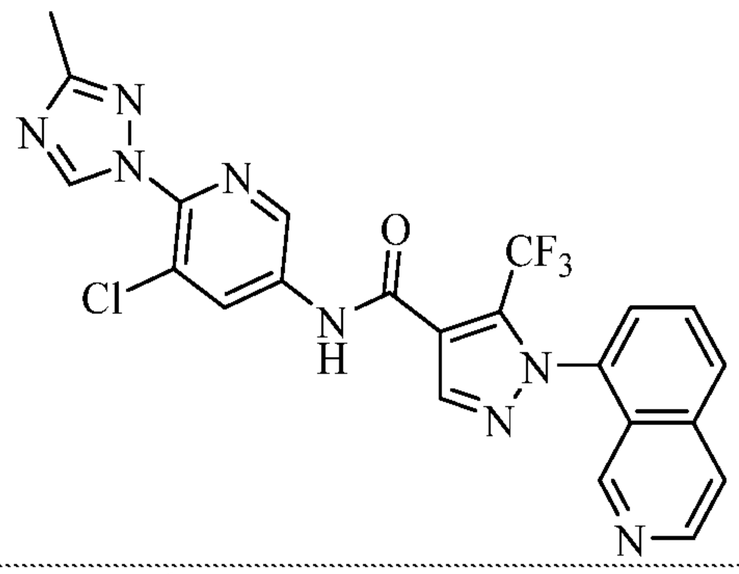
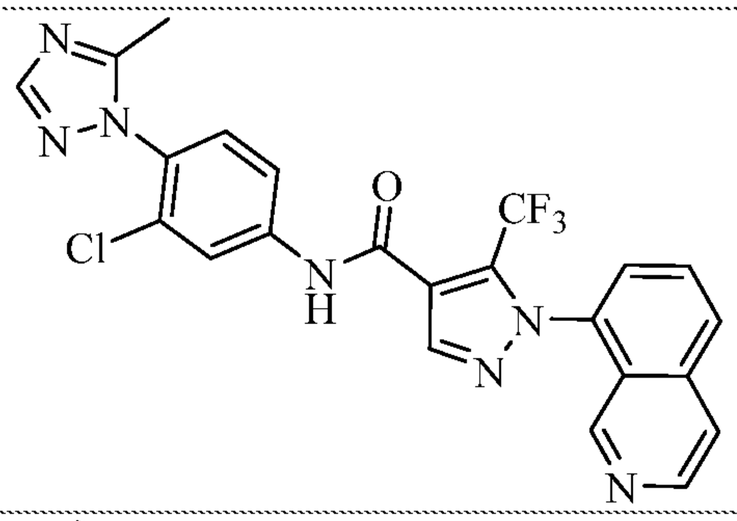
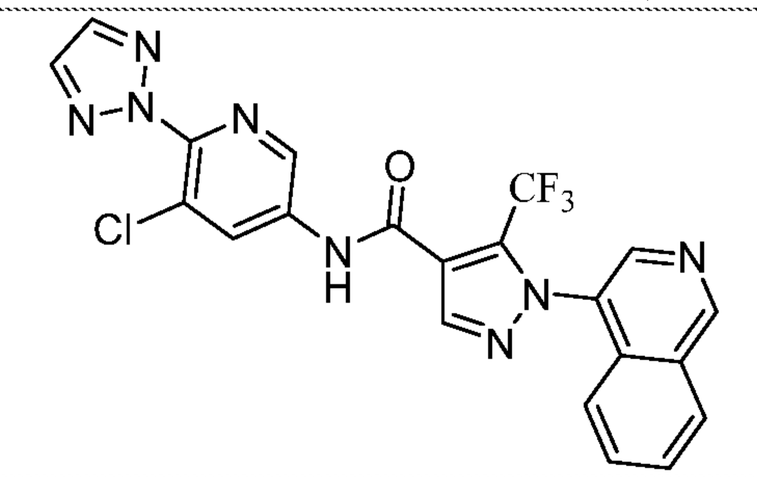
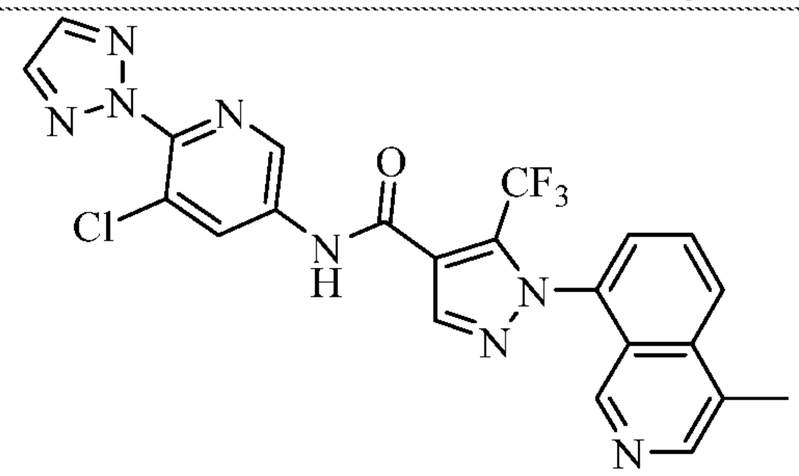
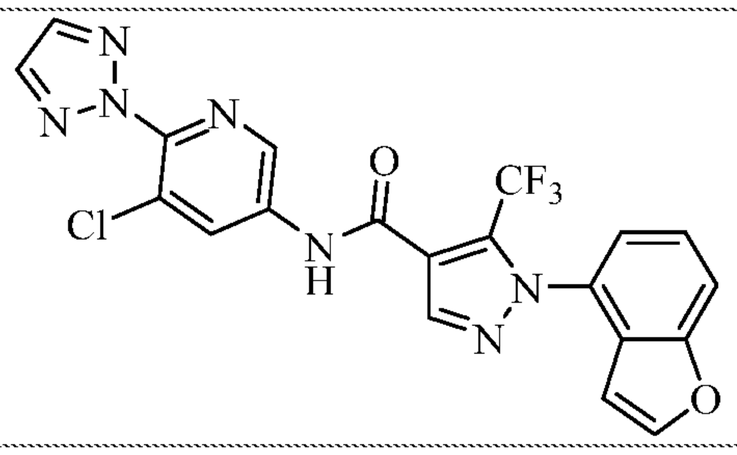
Structure	Cpd No.	Cpd Name
	**5**	*N*-(5-cyanopyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**6**	1-(quinolin-5-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide
	**7**	*N*-(5-chloro-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**8**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**9**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**10**	*N*-(3-chloro-4-methoxyphenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

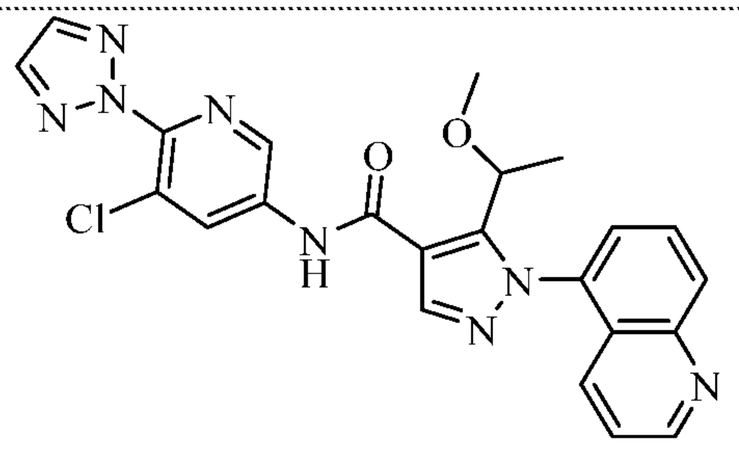
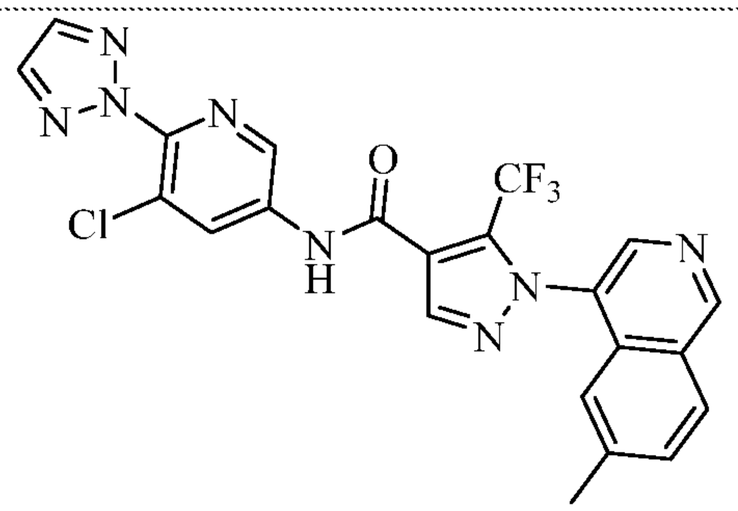
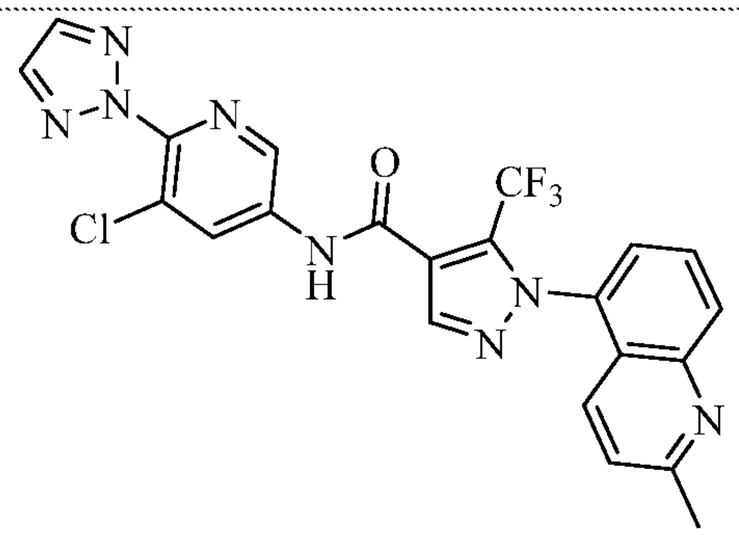
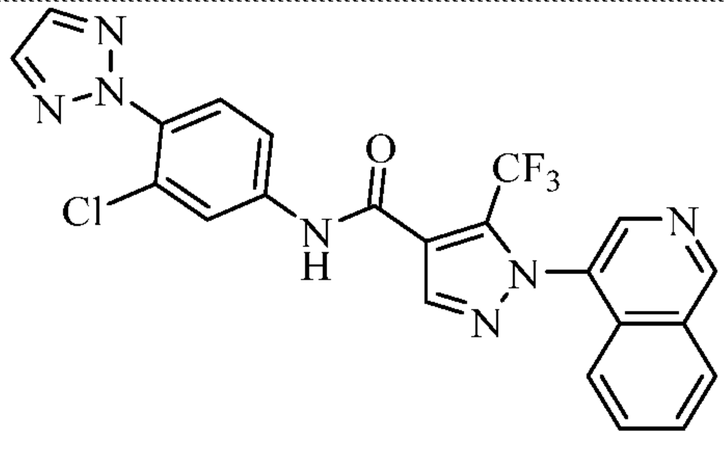
Structure	Cpd No.	Cpd Name
	**11**	*N*-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**12**	*N*-(3-chloro-4-(*1H*-pyrazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**13**	*N*-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**14**	*N*-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**15**	*N*-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

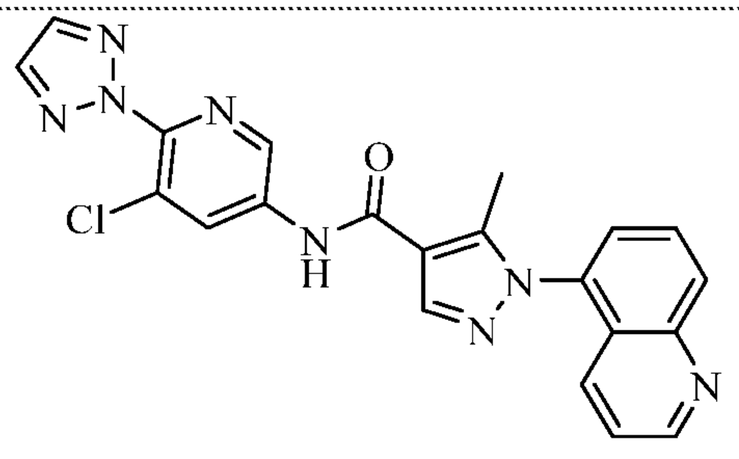
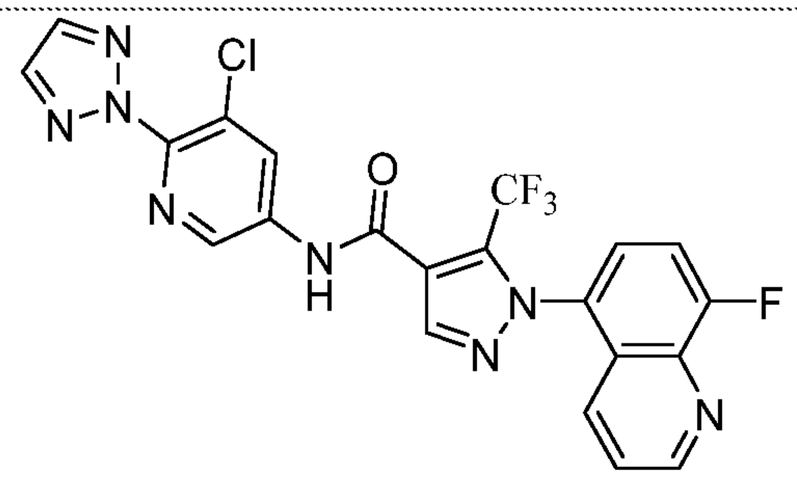
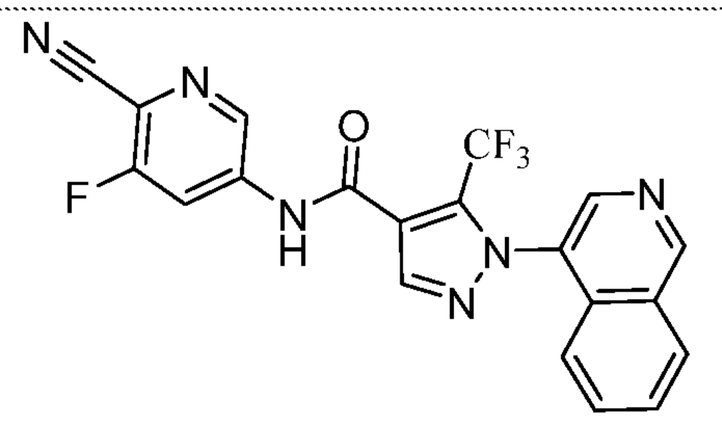
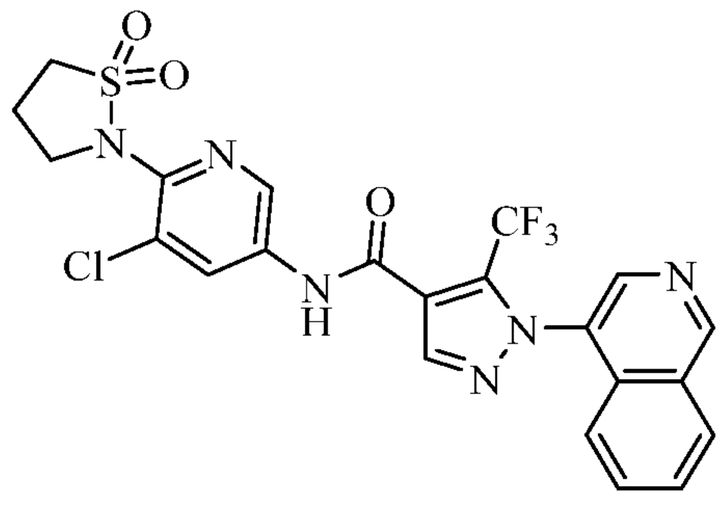
Structure	Cpd No.	Cpd Name
	**16**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isobutyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**17**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-ethyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**18**	*N*-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**19**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**20**	*N*-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

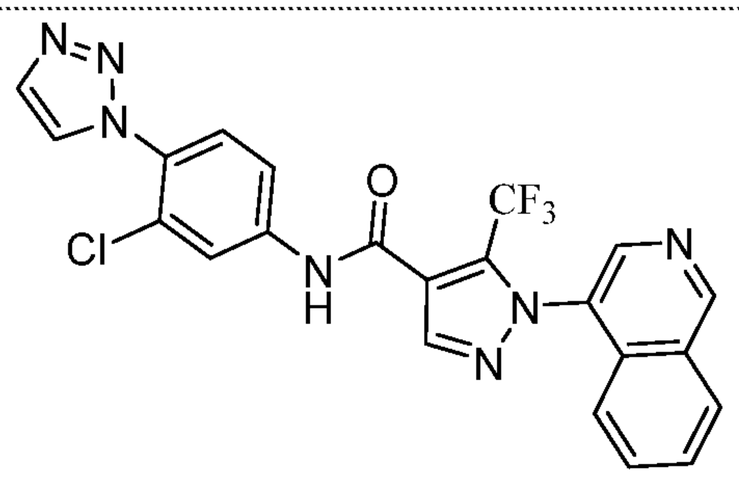
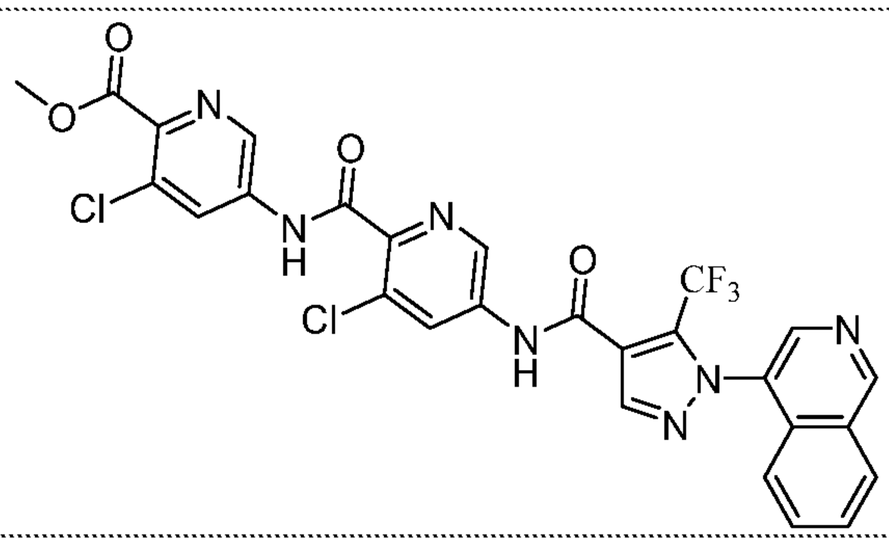
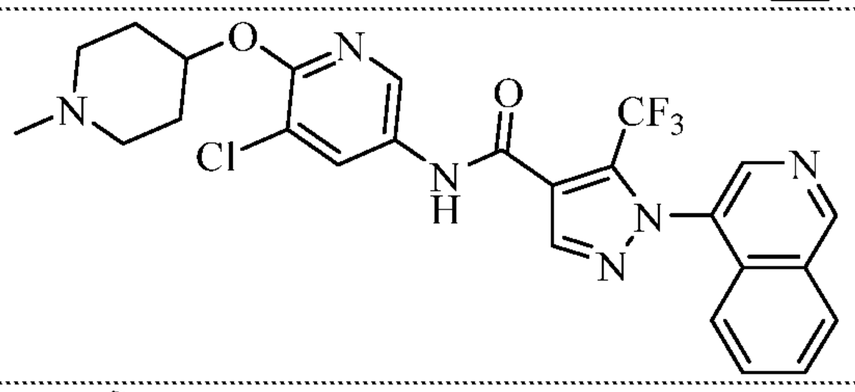
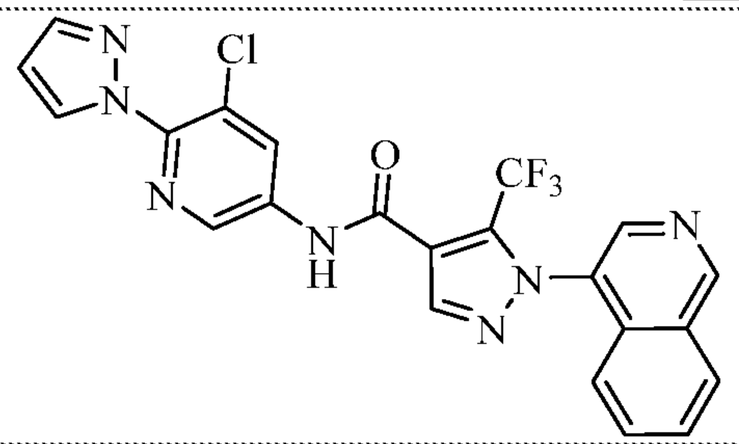
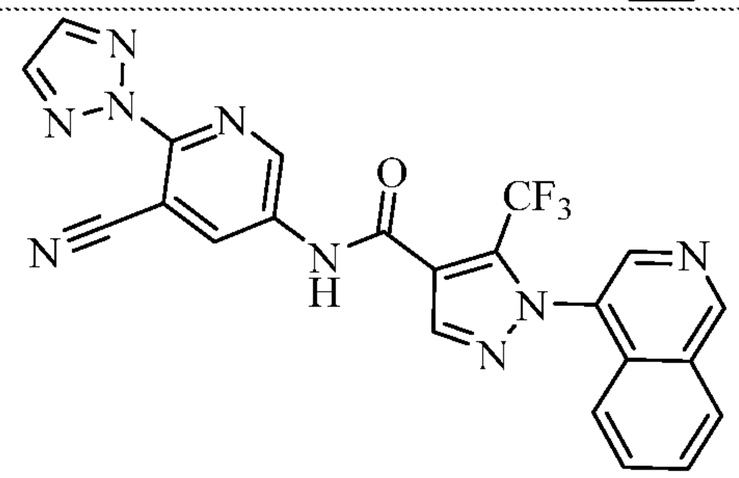
Structure	Cpd No.	Cpd Name
	**21**	*N*-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**22**	*N*-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**23**	*N*-(5-chloro-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**24**	*N*-(5-cyano-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**25**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

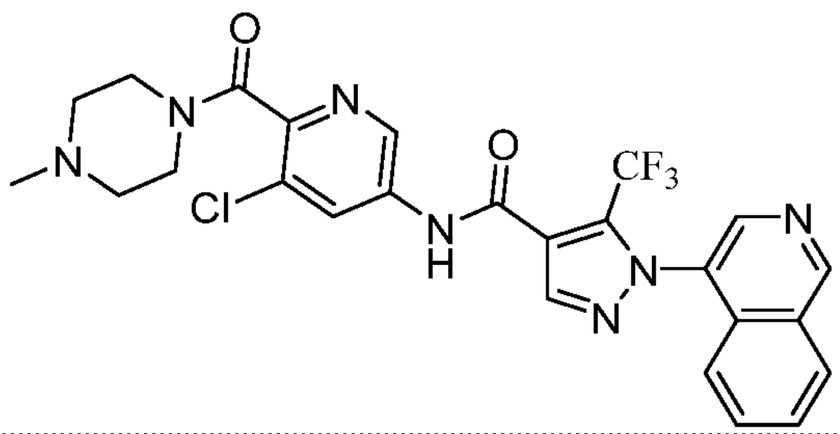
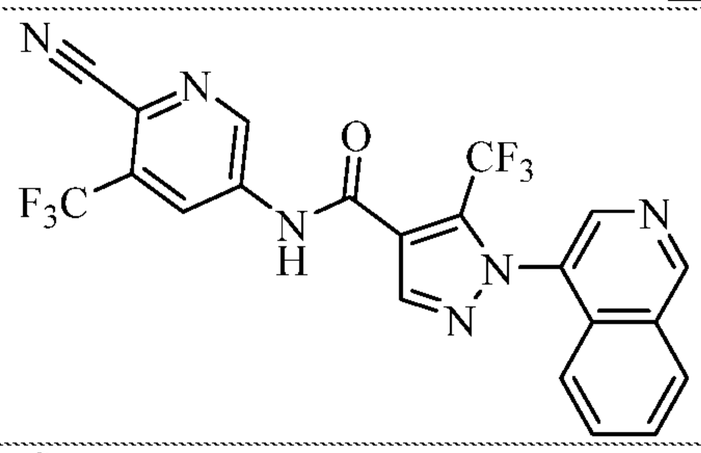
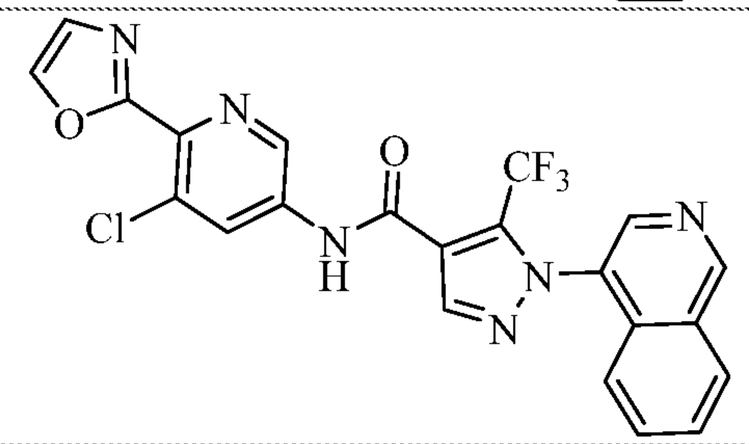
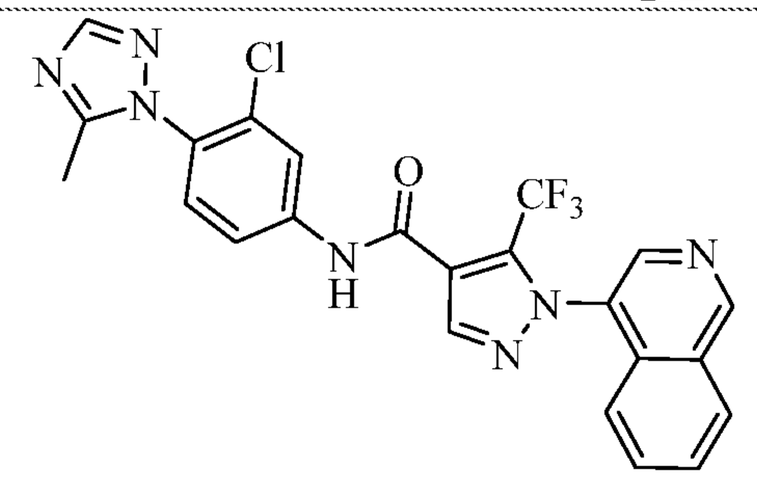
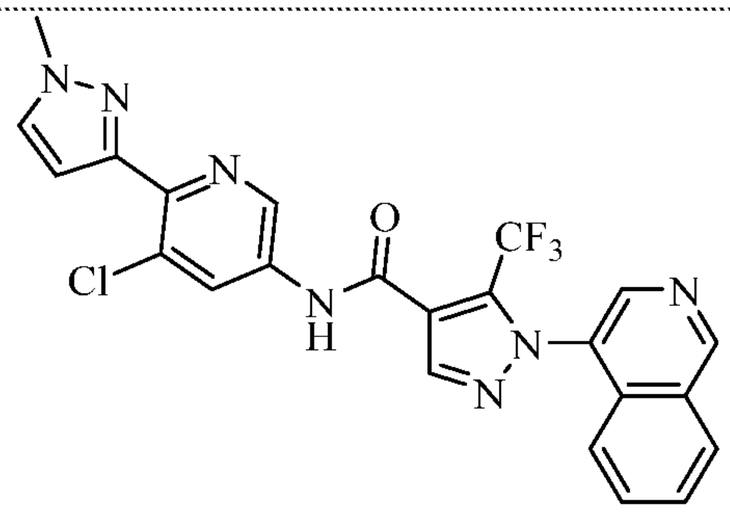
Structure	Cpd No.	Cpd Name
	**26**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isopropyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**27**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**28**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**29**	*N*-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

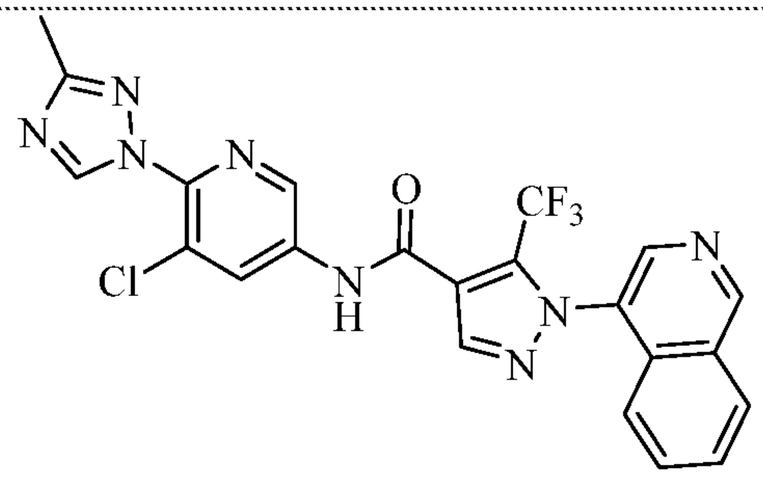
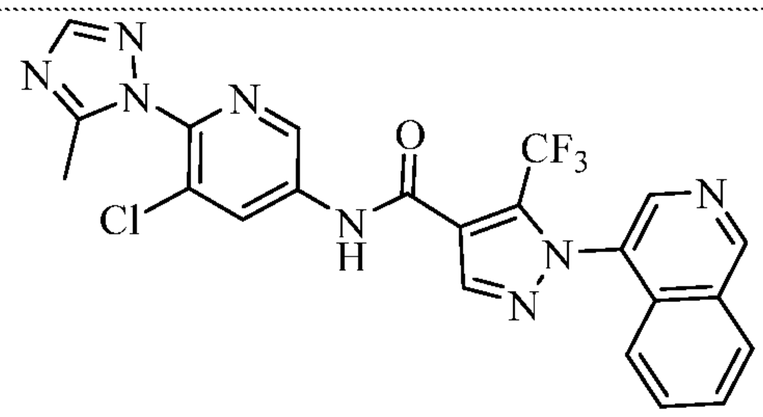
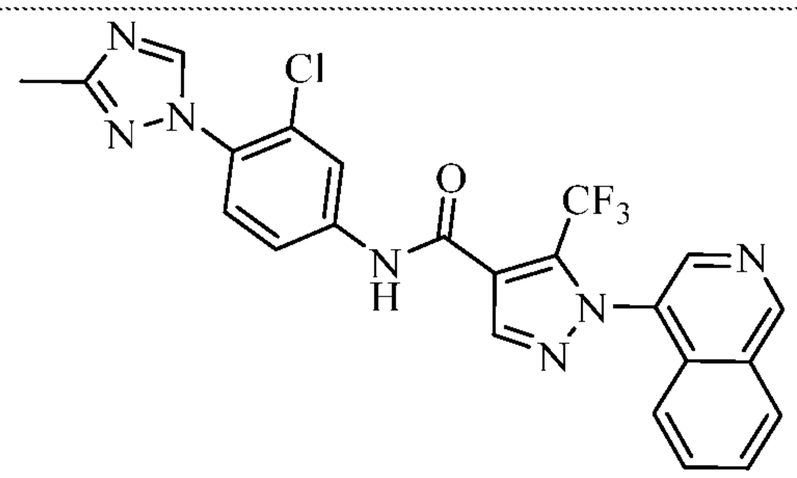
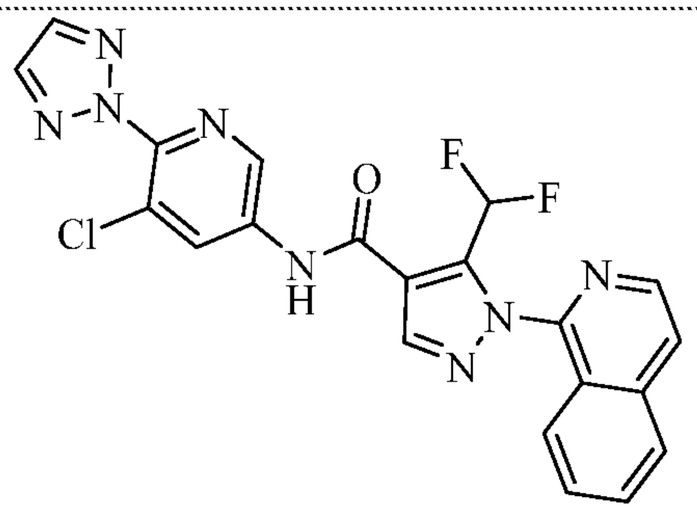
Structure	Cpd No.	Cpd Name
	**30**	*N*-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**31**	*N*-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**32**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**33**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**34**	1-(benzofuran-4-yl)-*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

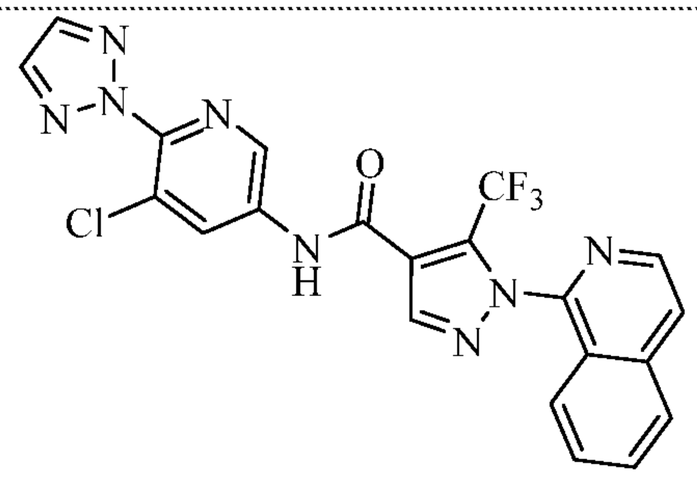
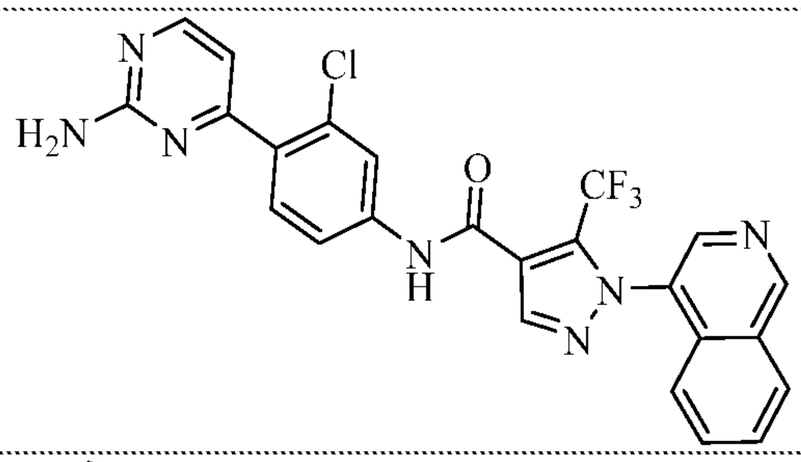
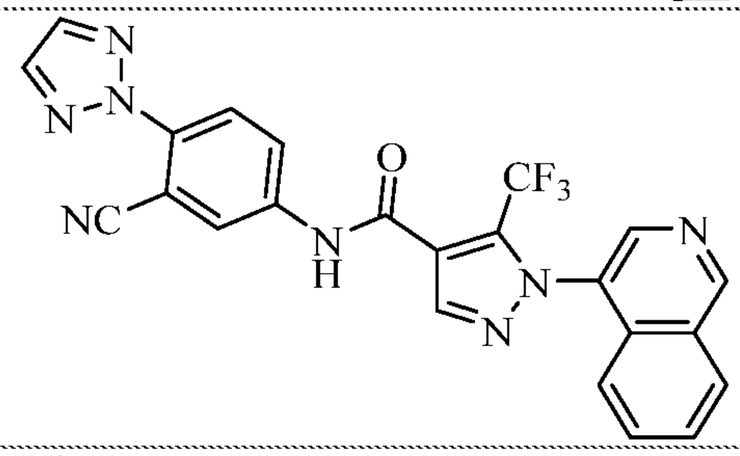
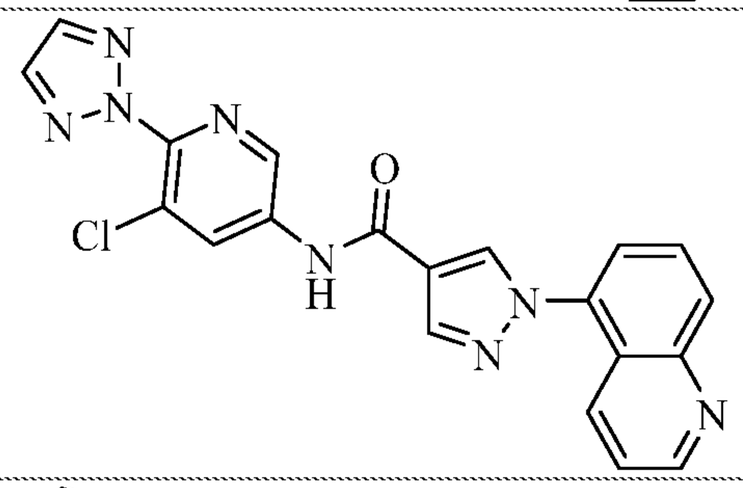
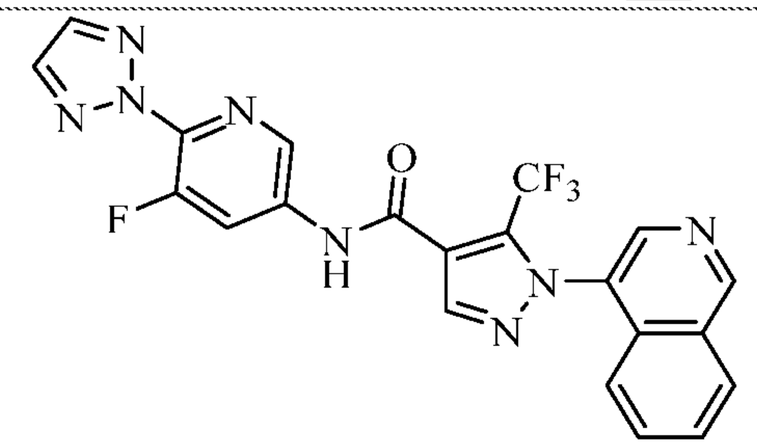
Structure	Cpd No.	Cpd Name
	**35**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(1-methoxyethyl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**36**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**37**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**38**	*N*-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

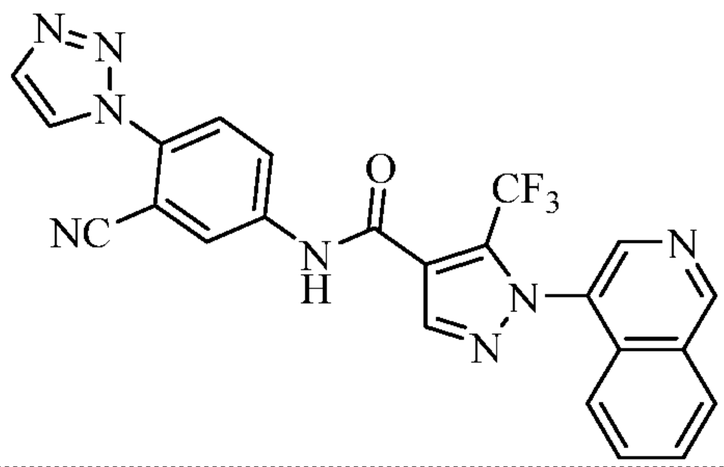
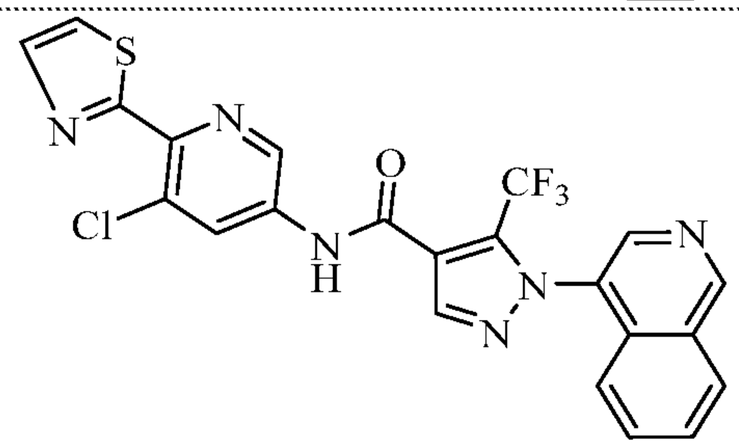
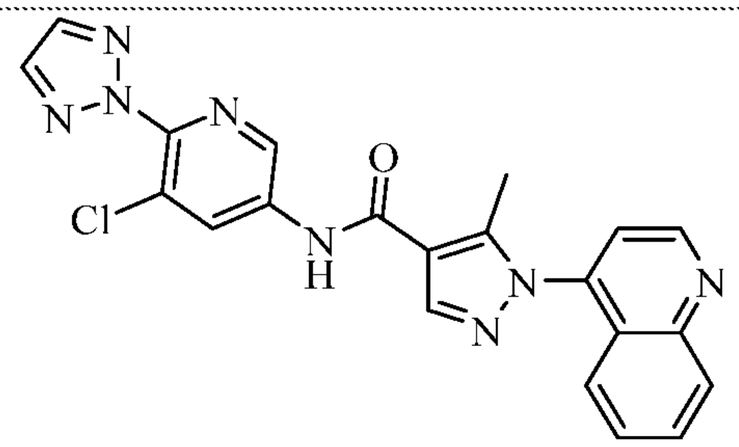
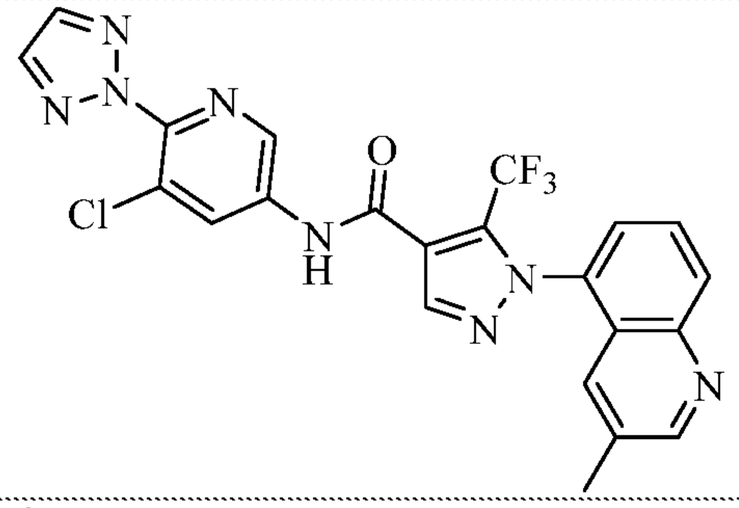
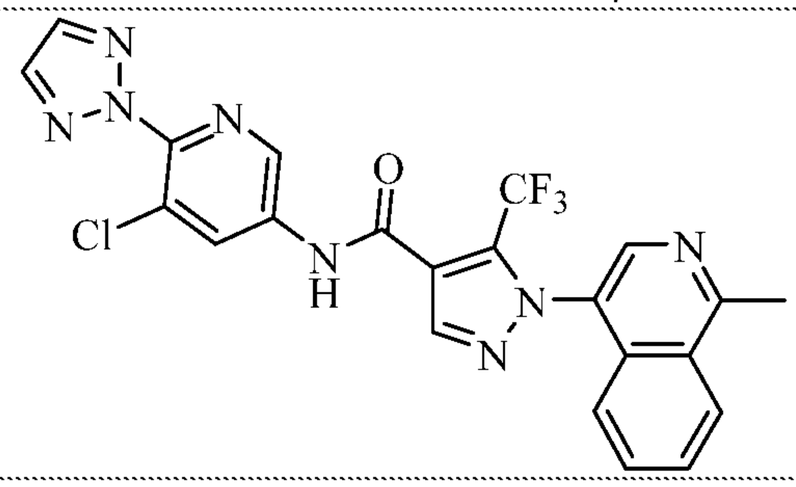
Structure	Cpd No.	Cpd Name
	**39**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**40**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**41**	*N*-(6-cyano-5-fluoropyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**42**	*N*-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

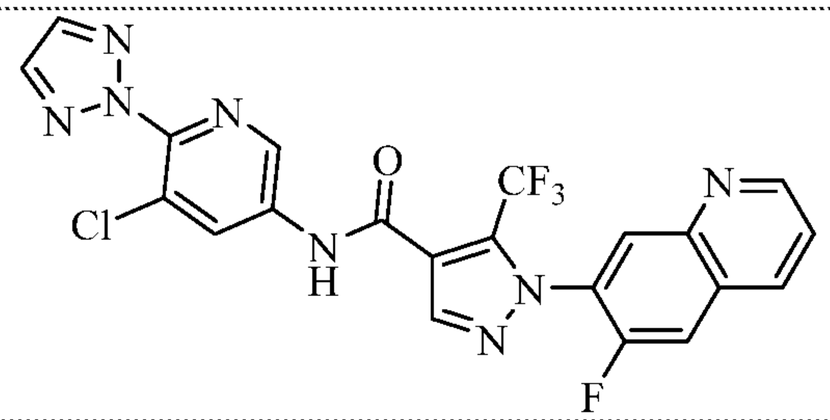
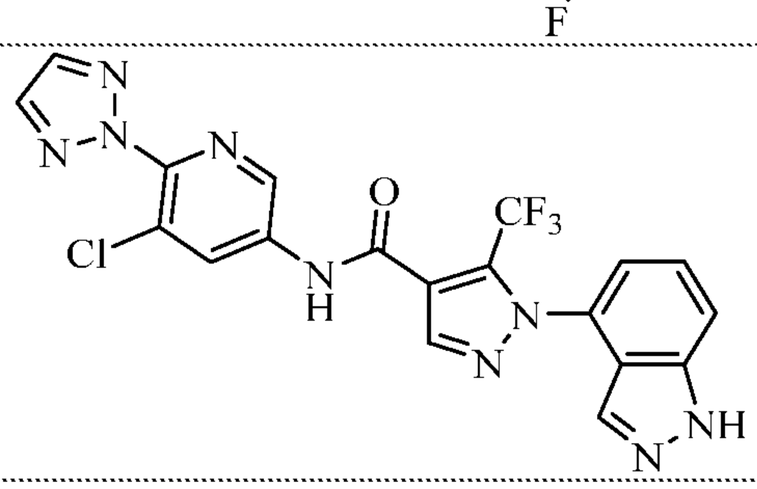
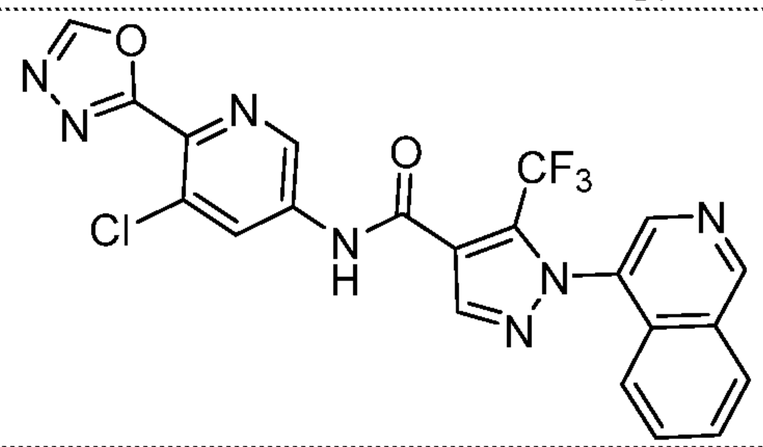
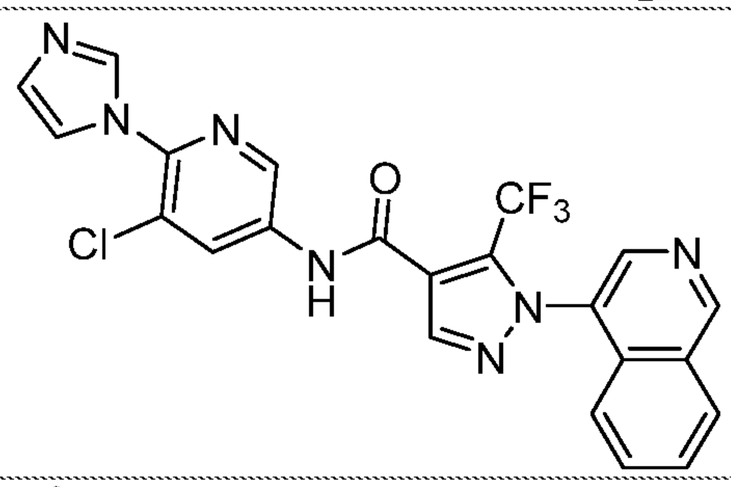
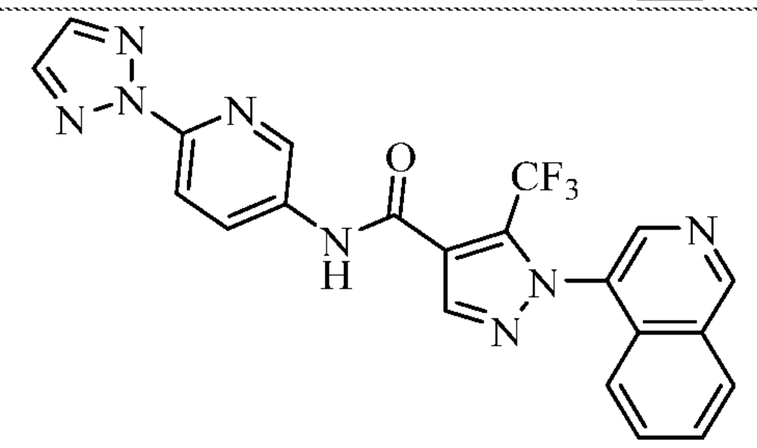
Structure	Cpd No.	Cpd Name
	**43**	*N*-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**44**	methyl 3-chloro-5-(3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamido) picolinate
	**45**	*N*-(5-chloro-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**46**	*N*-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**47**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

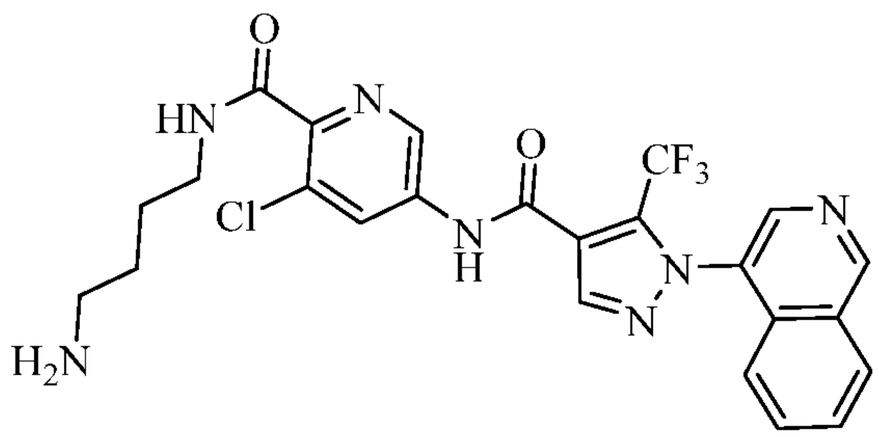
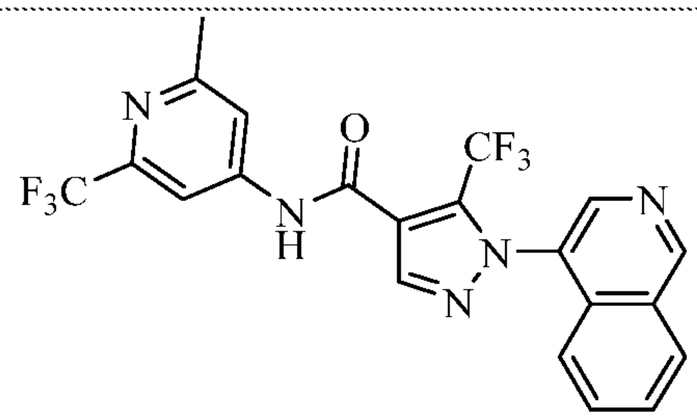
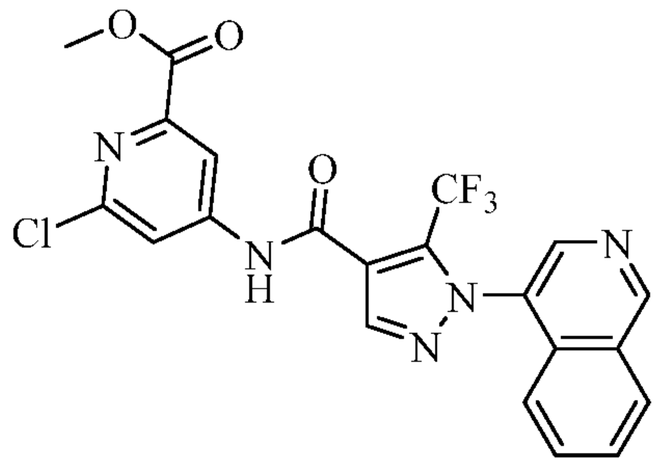
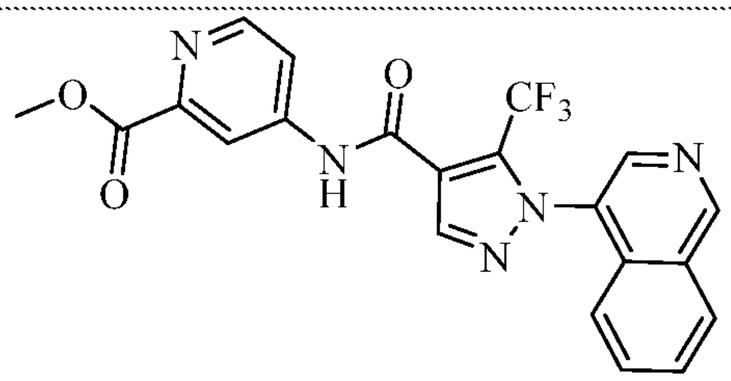
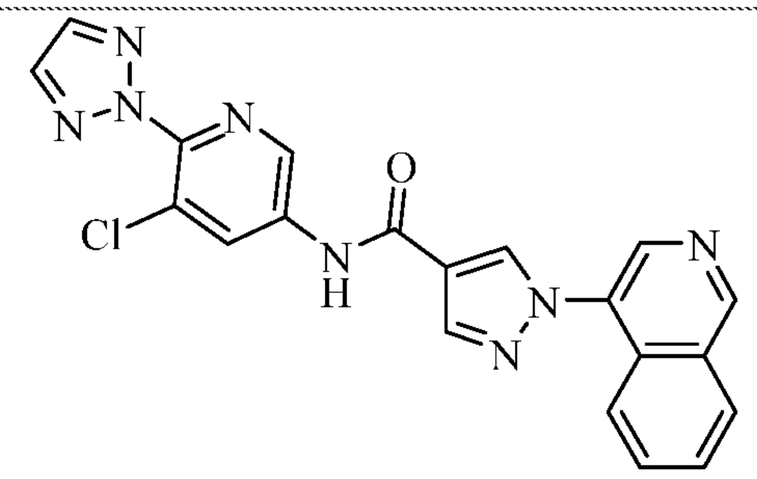
Structure	Cpd No.	Cpd Name
	**48**	*N*-(5-chloro-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**49**	*N*-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**50**	*N*-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**51**	*N*-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**52**	*N*-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

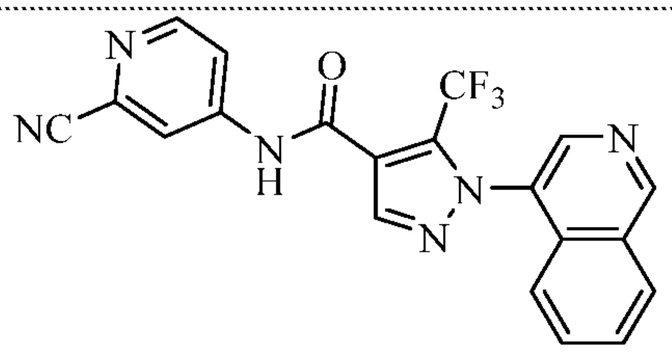
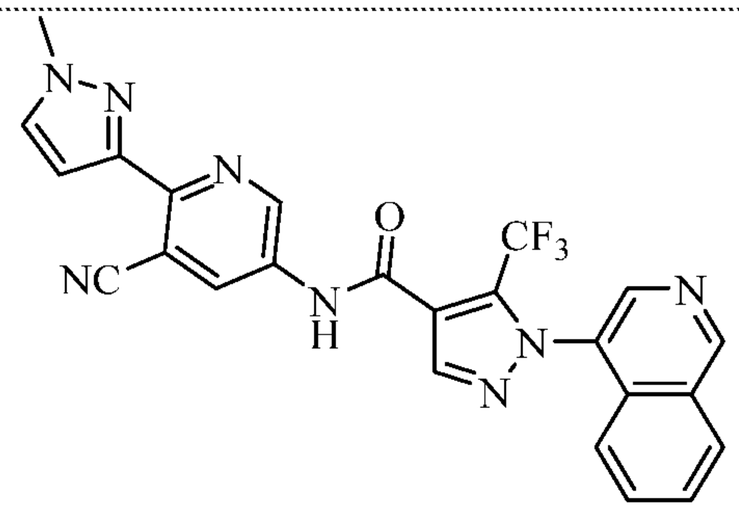
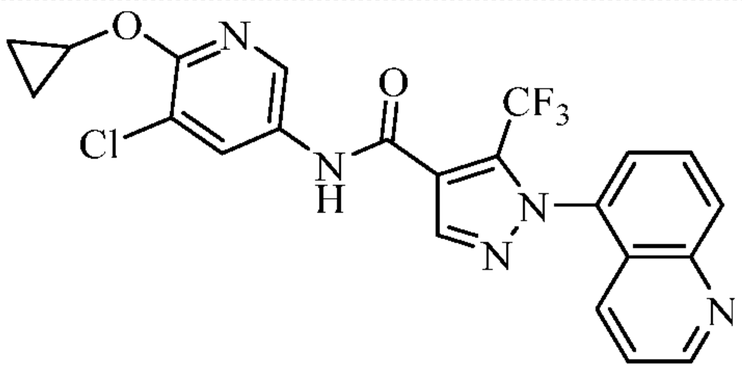
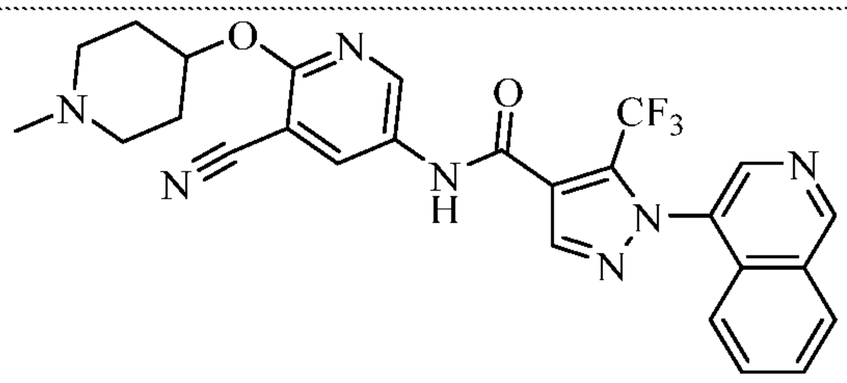
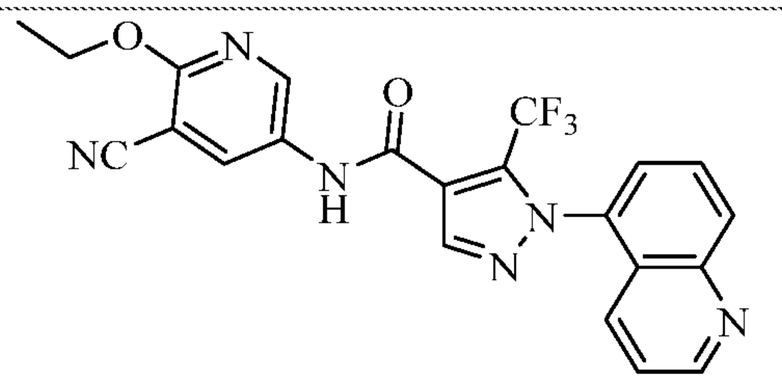
Structure	Cpd No.	Cpd Name
	**53**	*N*-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**54**	*N*-(5-chloro-6-(5-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**55**	*N*-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**56**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(difluoromethyl)-1-(isoquinolin-1-yl)-*1H*-pyrazole-4-carboxamide

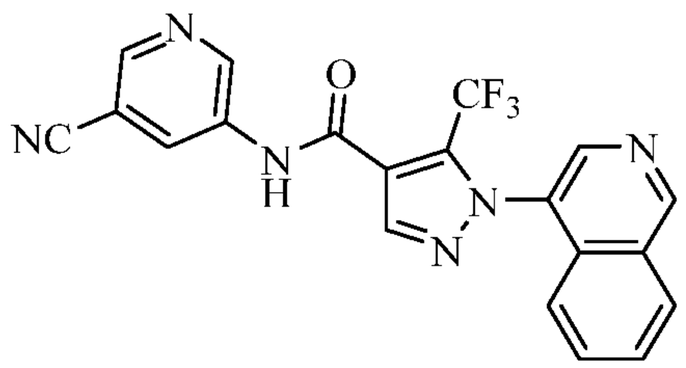
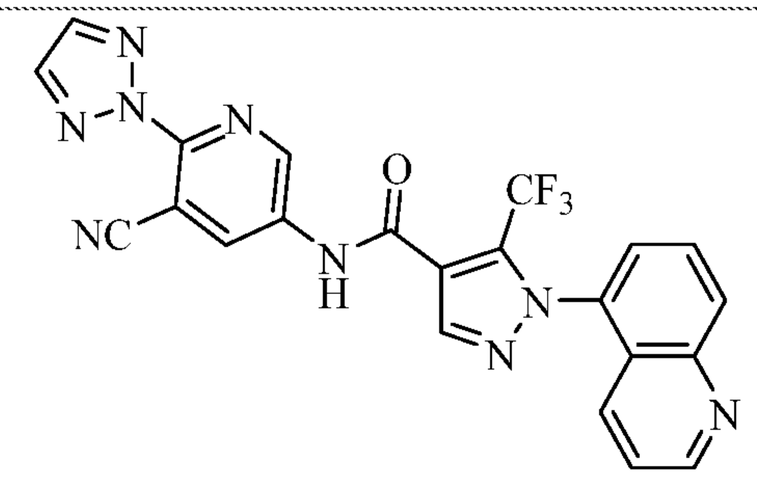
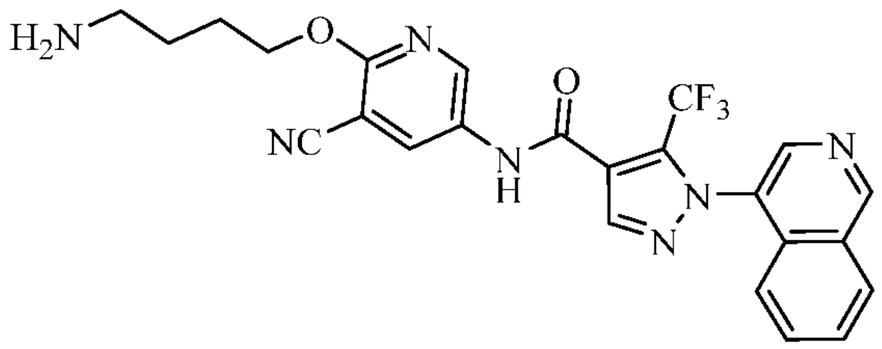
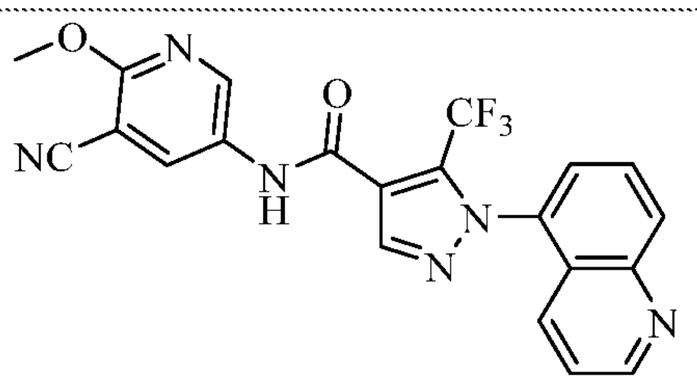
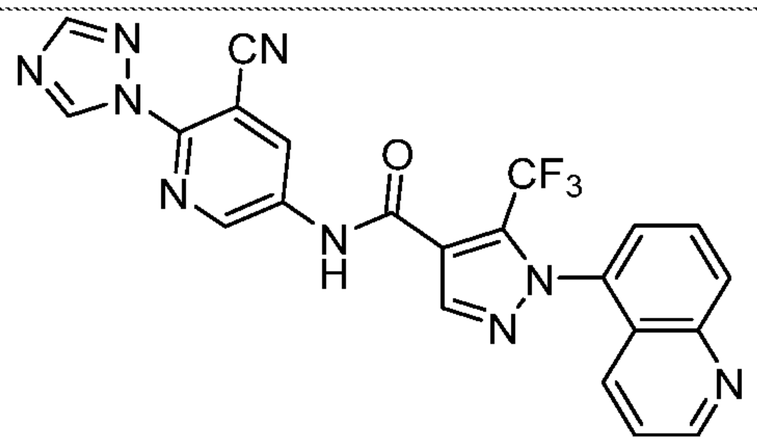
Structure	Cpd No.	Cpd Name
	**57**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**58**	*N*-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**59**	*N*-(3-cyano-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**60**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide
	**61**	*N*-(5-fluoro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

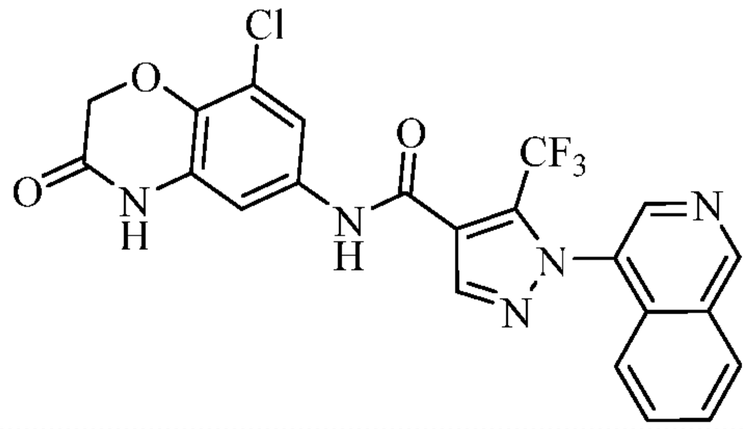
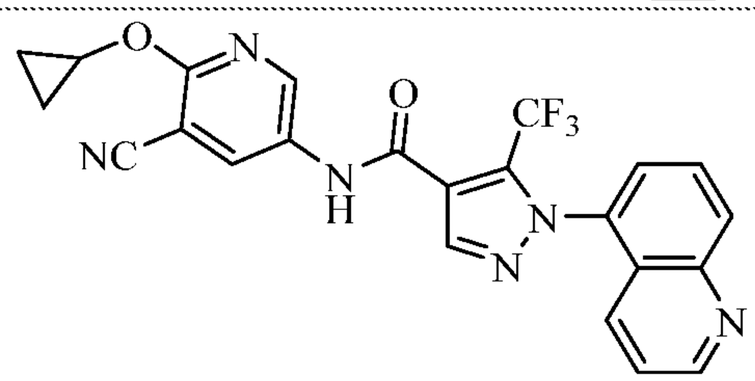
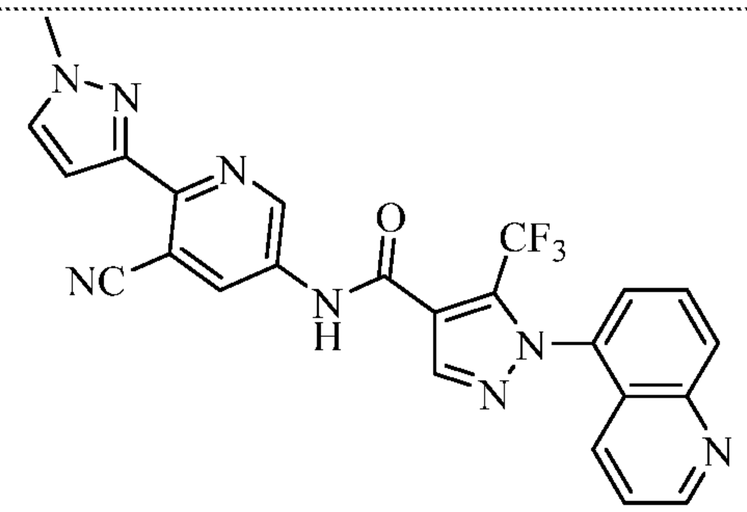
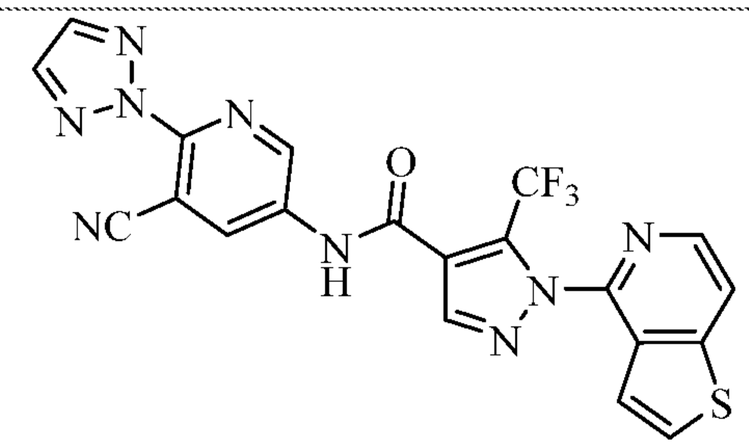
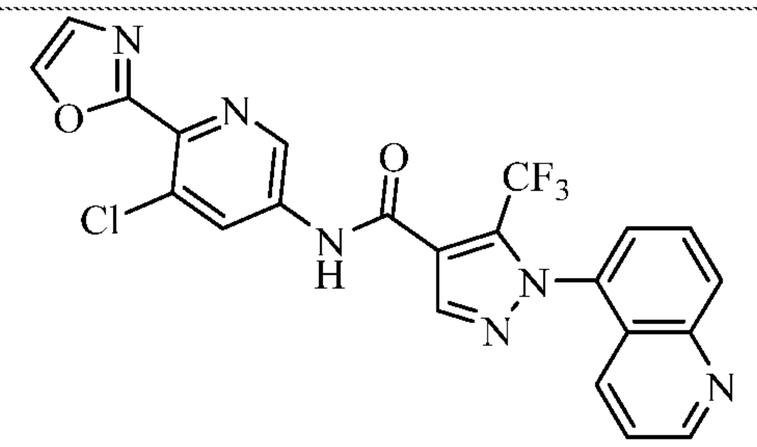
Structure	Cpd No.	Cpd Name
	**62**	*N*-(3-cyano-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**63**	*N*-(5-chloro-6-(thiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**64**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-*1H*-pyrazole-4-carboxamide
	**65**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**66**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

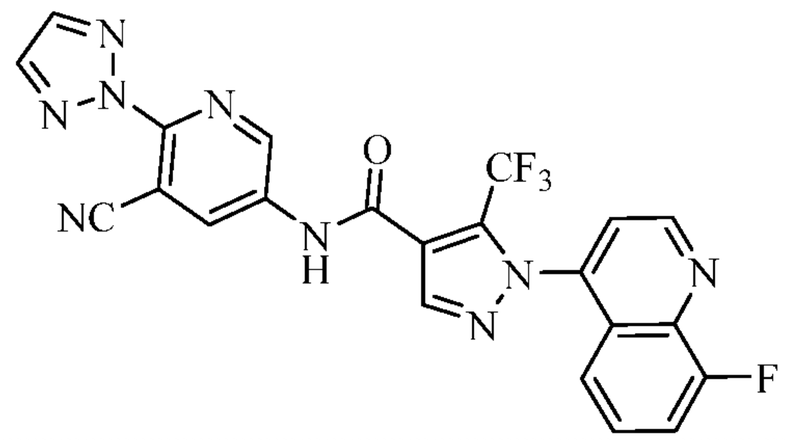
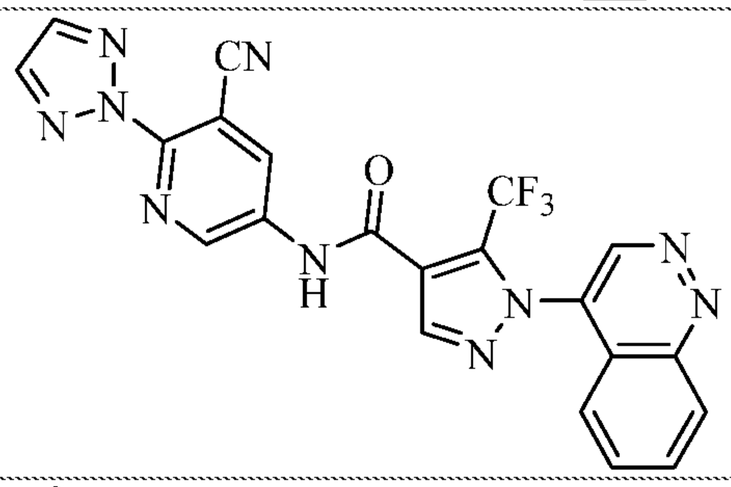
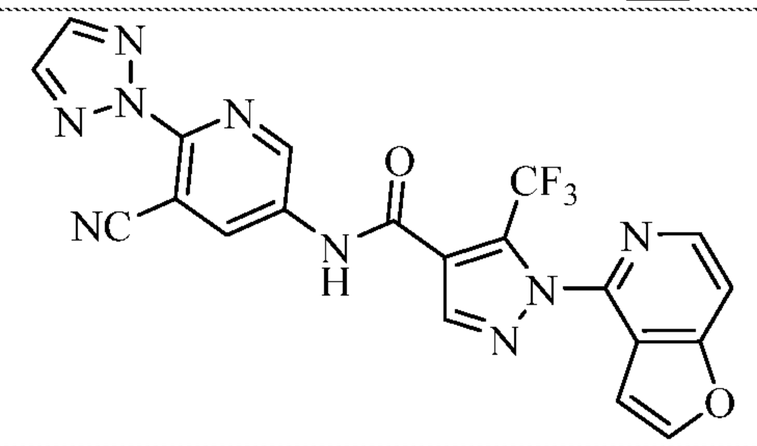
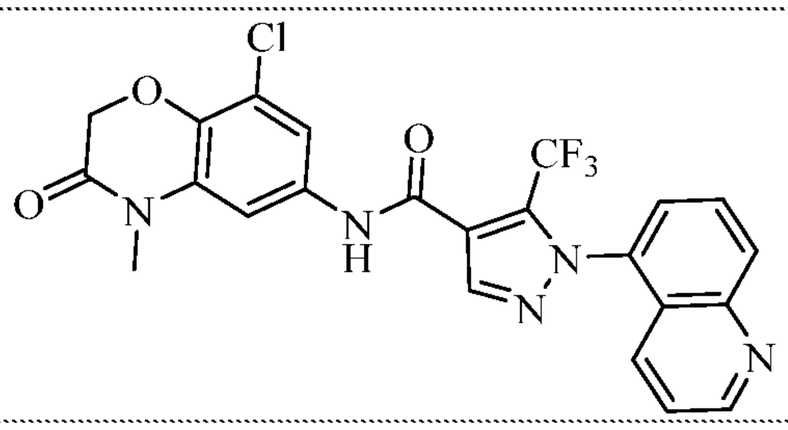
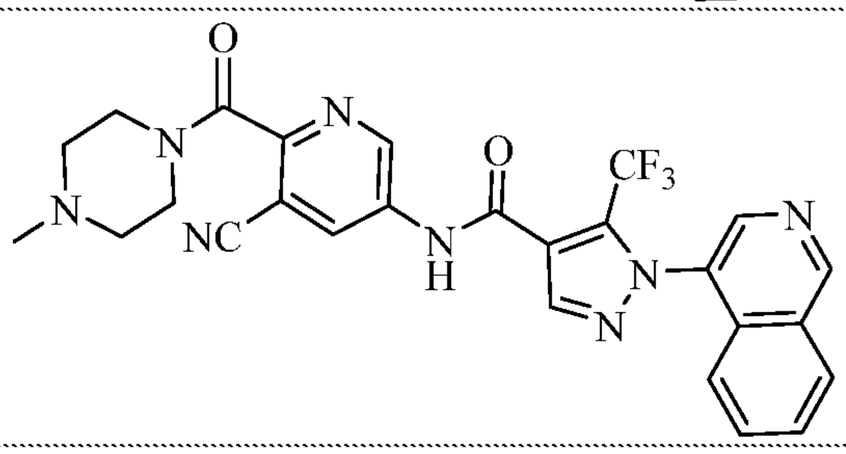
Structure	Cpd No.	Cpd Name
	**67**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**68**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(*1H*-indazol-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**69**	*N*-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**70**	*N*-(5-chloro-6-(*1H*-imidazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**71**	*N*-(6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

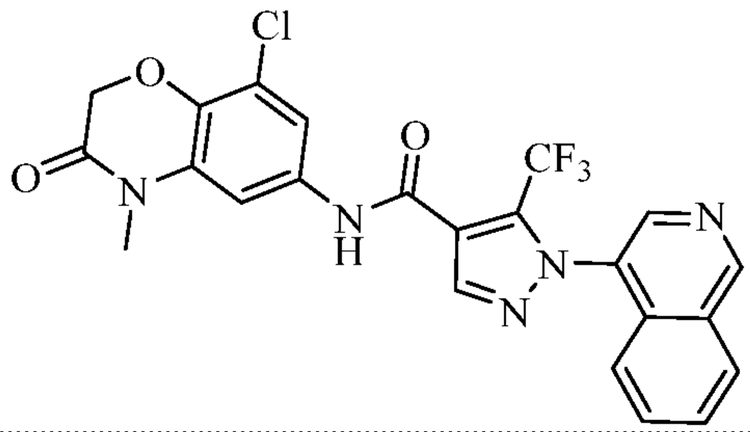
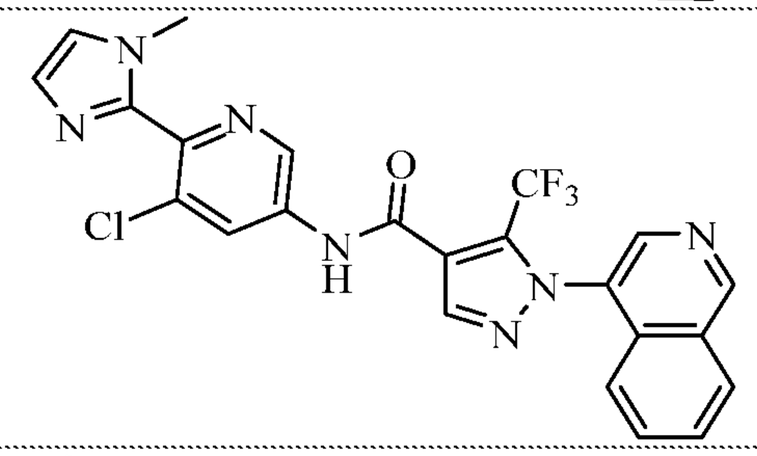
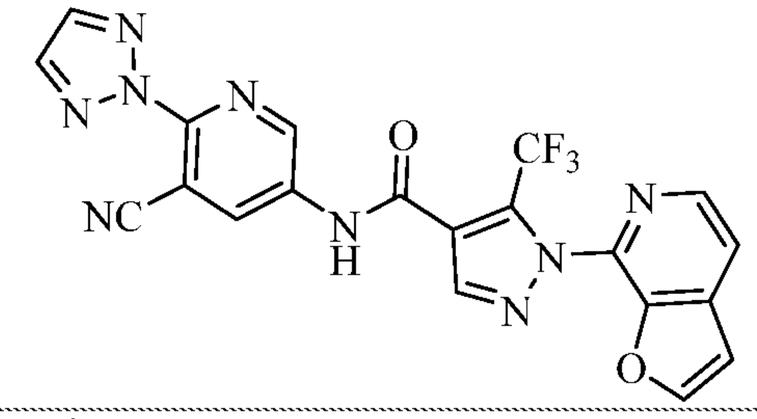
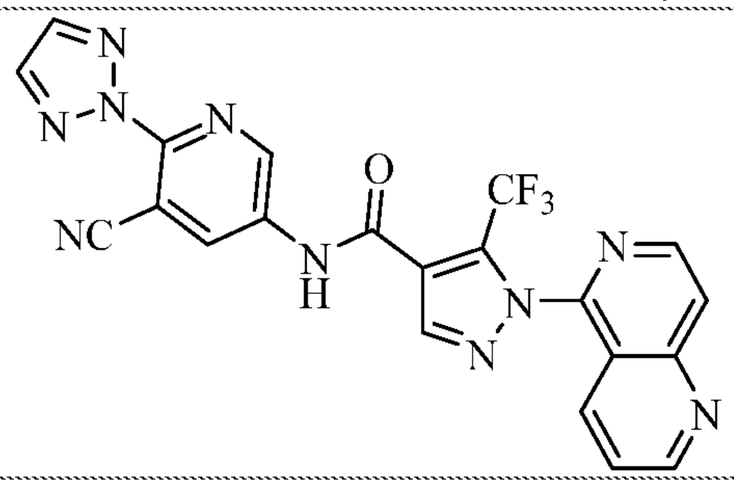
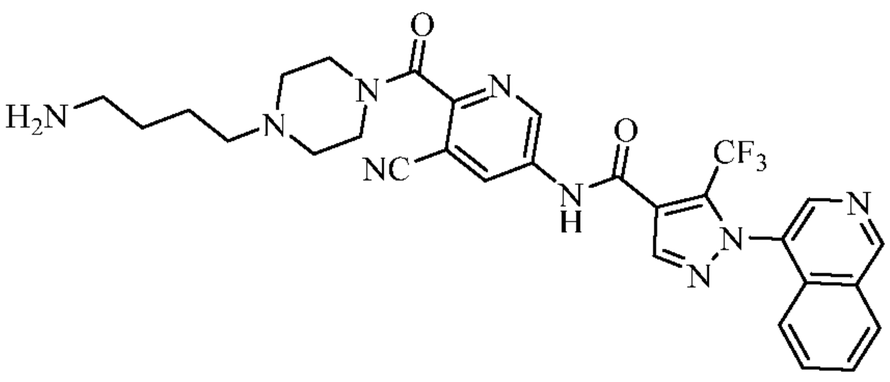
Structure	Cpd No.	Cpd Name
	**72**	*N*-(4-aminobutyl)-3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamide
	**73**	1-(isoquinolin-4-yl)-*N*-(2-methyl-6-(trifluoromethyl)pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**74**	methyl 6-chloro-4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate
	**75**	methyl 4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate
	**76**	*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-*1H*-pyrazole-4-carboxamide

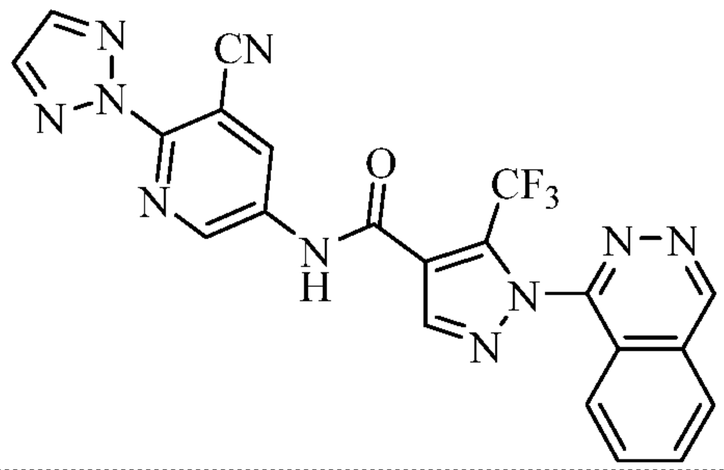
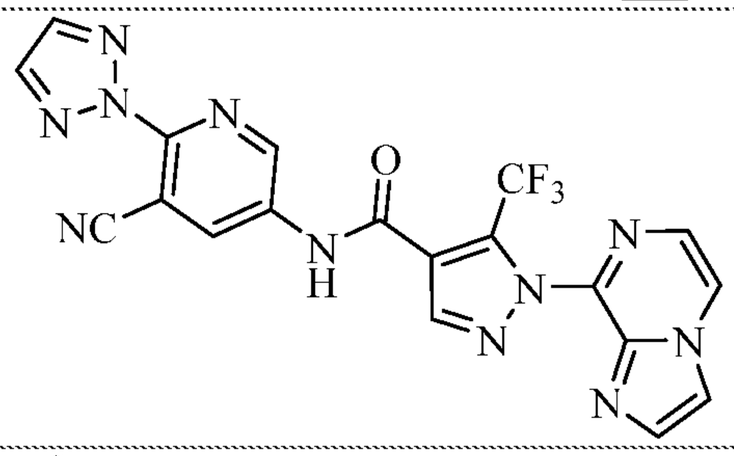
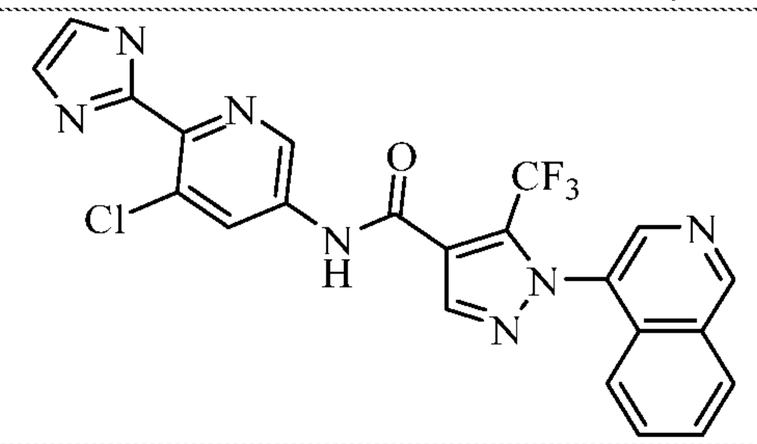
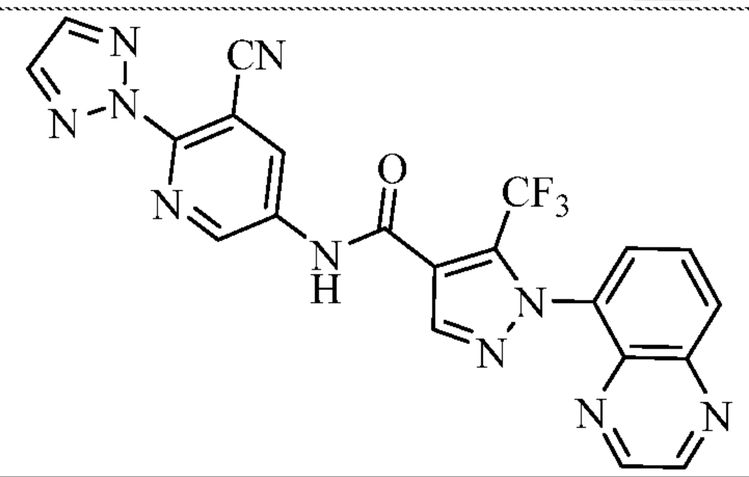
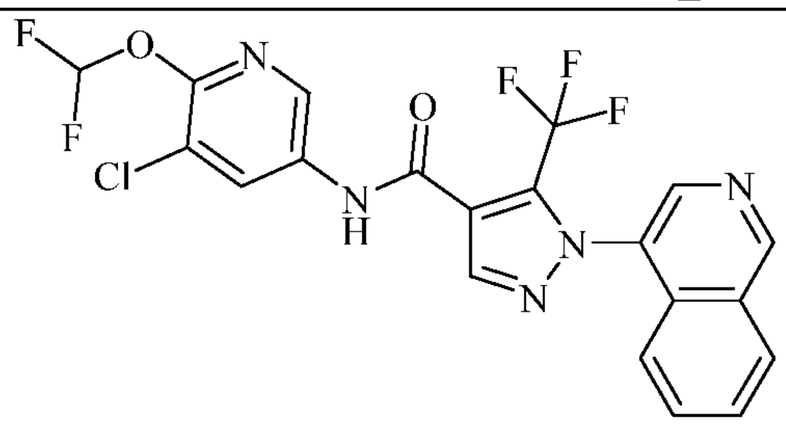
Structure	Cpd No.	Cpd Name
	77	*N*-(2-cyanopyridin-4-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**78**	*N*-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**79**	*N*-(5-chloro-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**80**	*N*-(5-cyano-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**81**	*N*-(5-cyano-6-ethoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

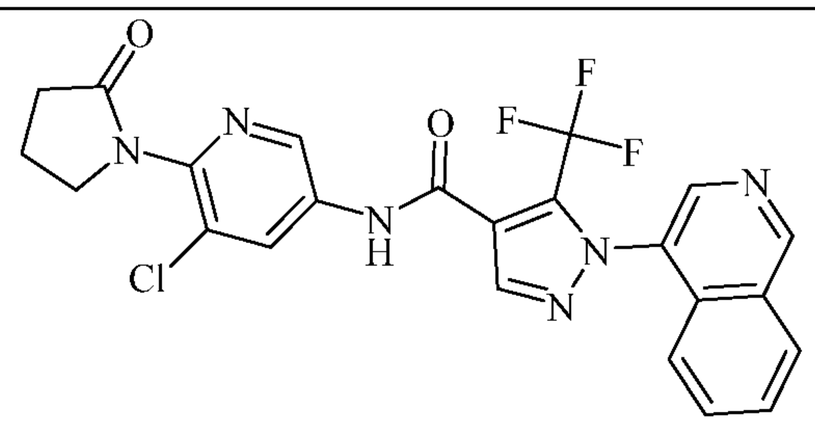
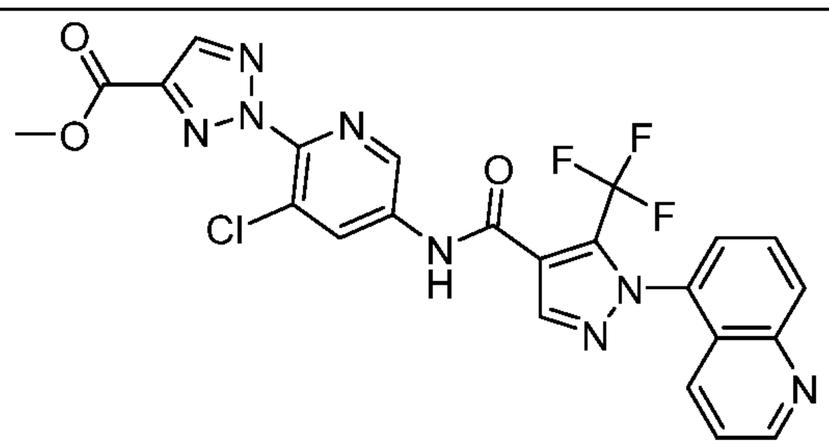
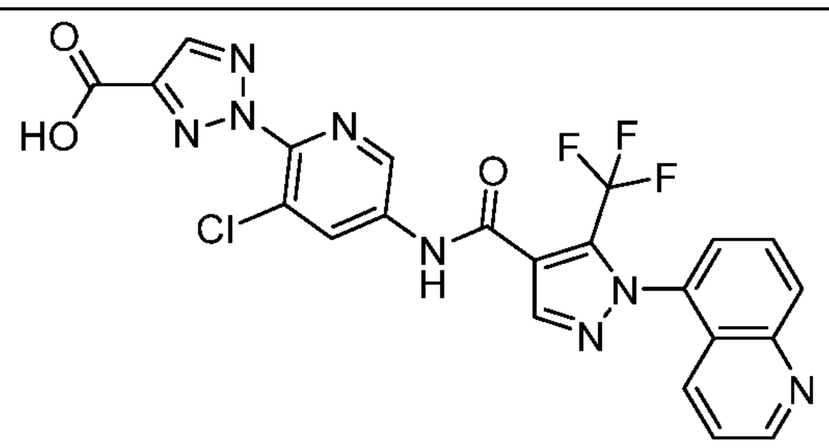
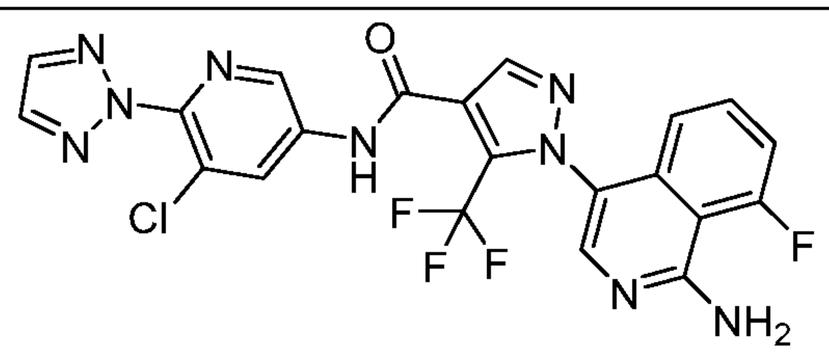
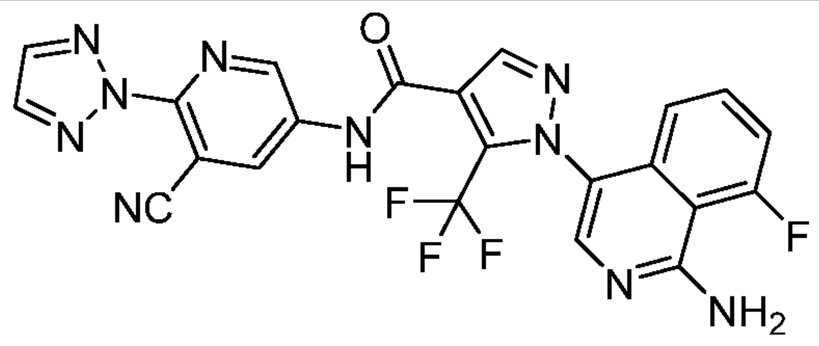
Structure	Cpd No.	Cpd Name
	**82**	*N*-(5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**83**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**84**	*N*-(6-(4-aminobutoxy)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**85**	*N*-(5-cyano-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**86**	*N*-(5-cyano-6-(*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

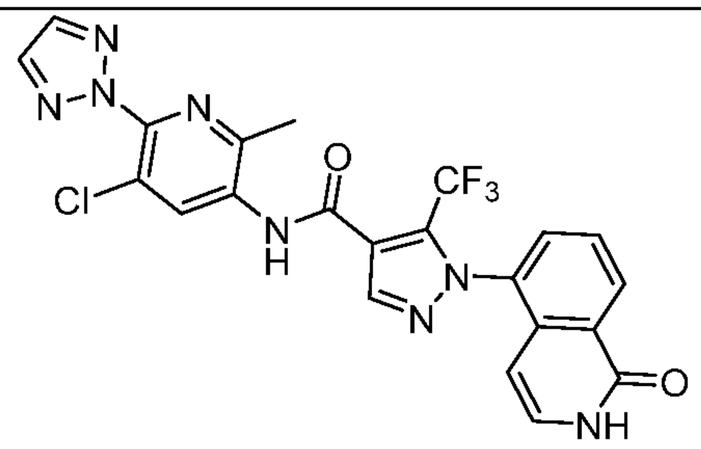
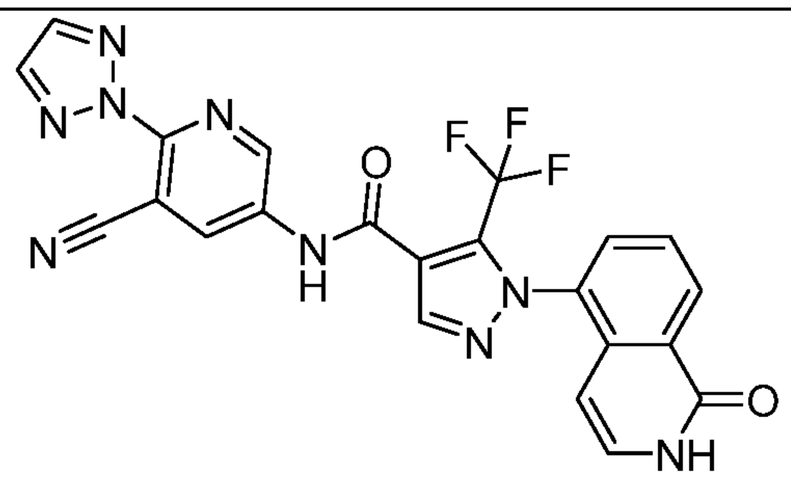
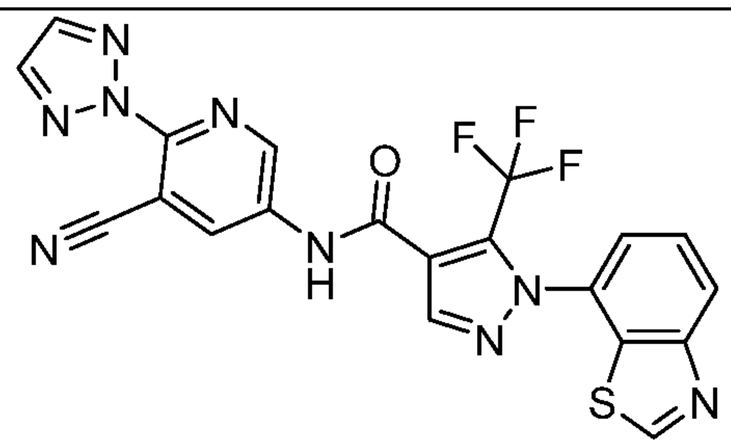
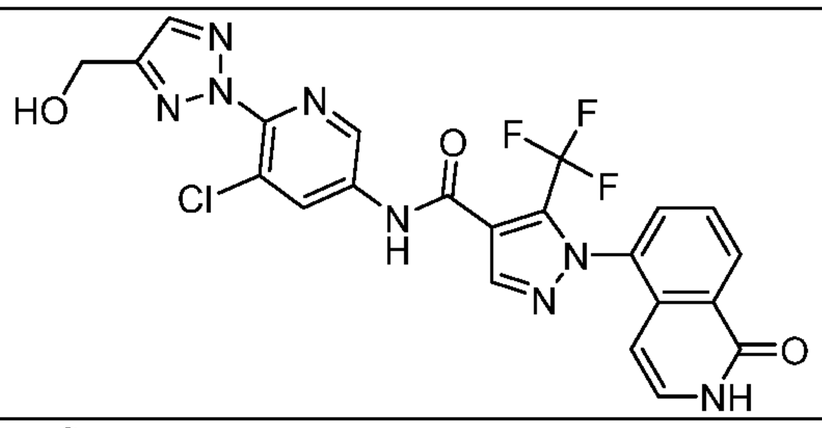
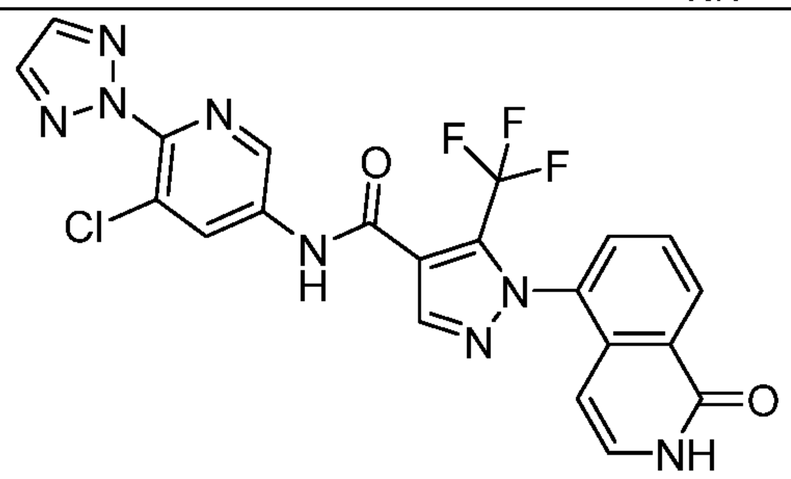
Structure	Cpd No.	Cpd Name
	**87**	*N*-(8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**88**	*N*-(5-cyano-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**89**	*N*-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**90**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**91**	*N*-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

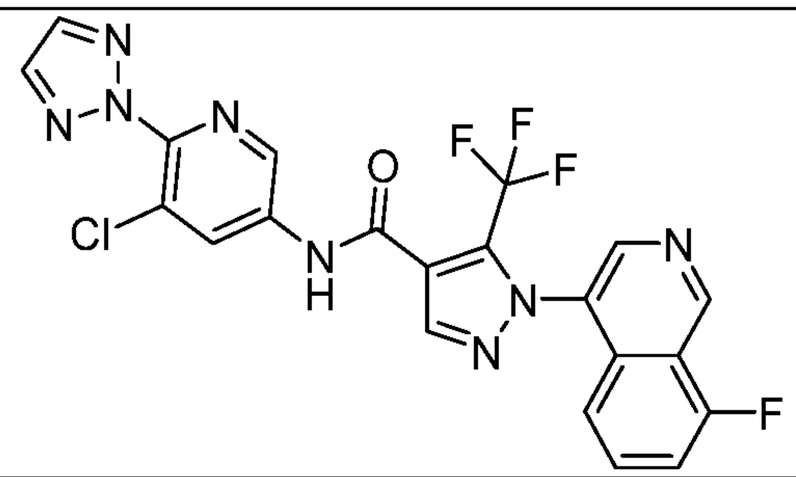
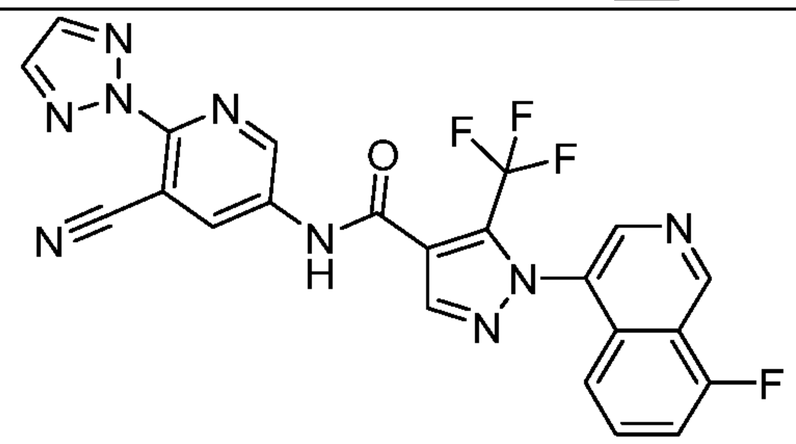
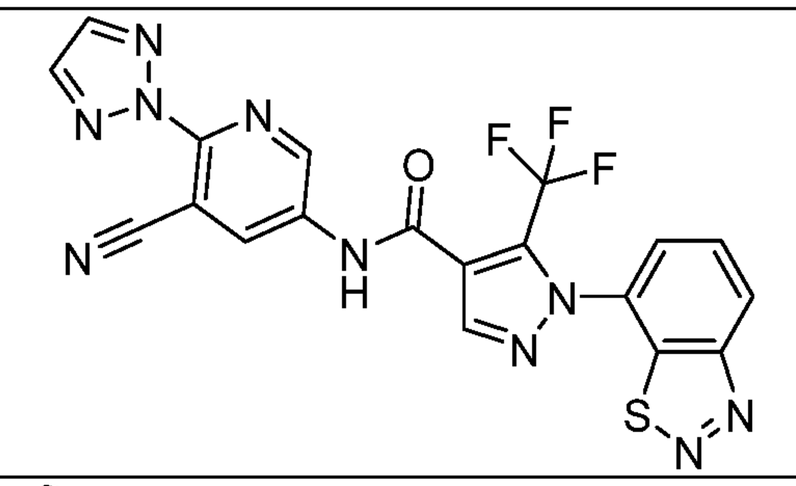
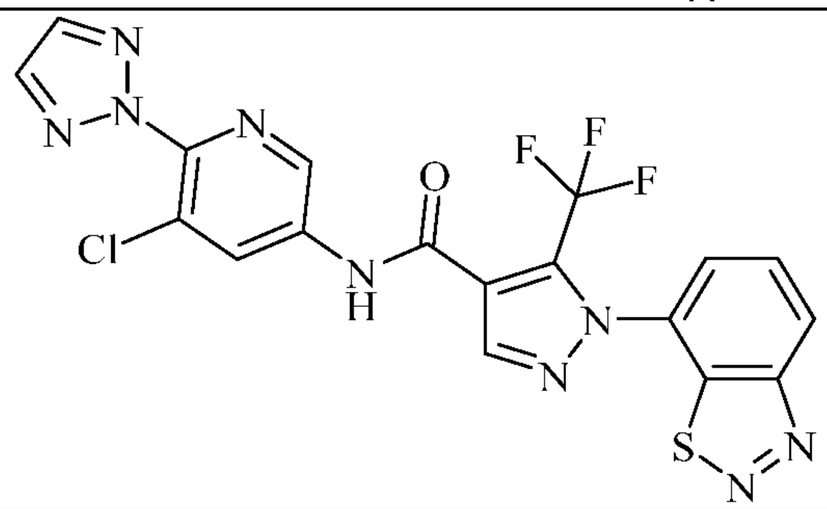
Structure	Cpd No.	Cpd Name
	**92**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**93**	1-(cinnolin-4-yl)-*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**94**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**95**	*N*-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**96**	*N*-(5-cyano-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

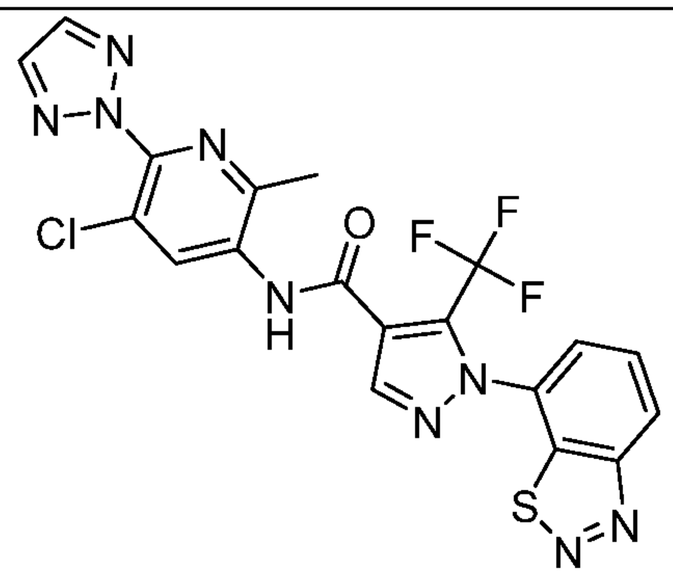
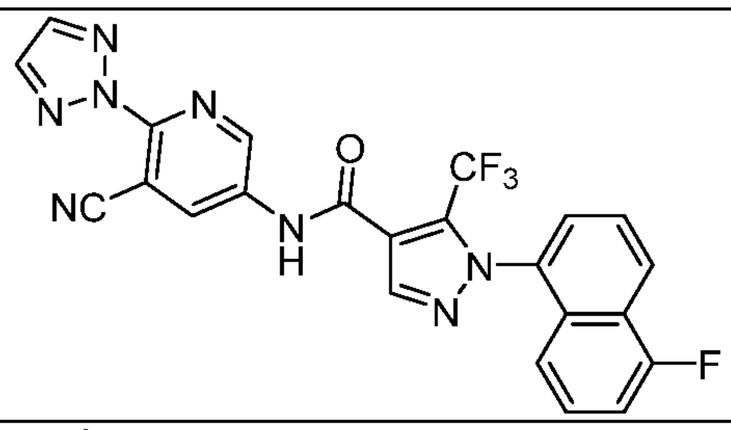
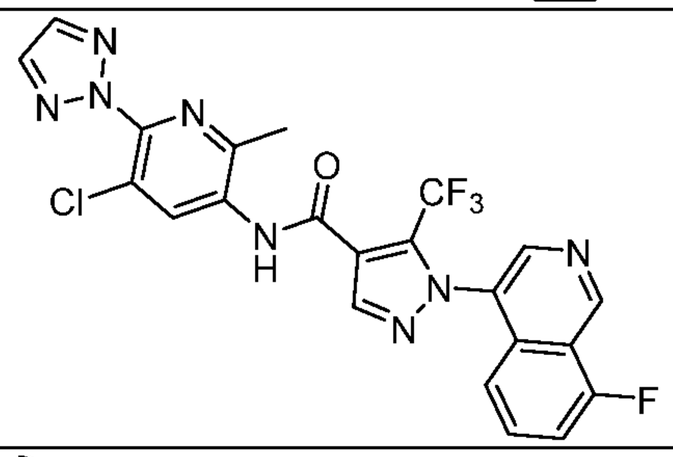
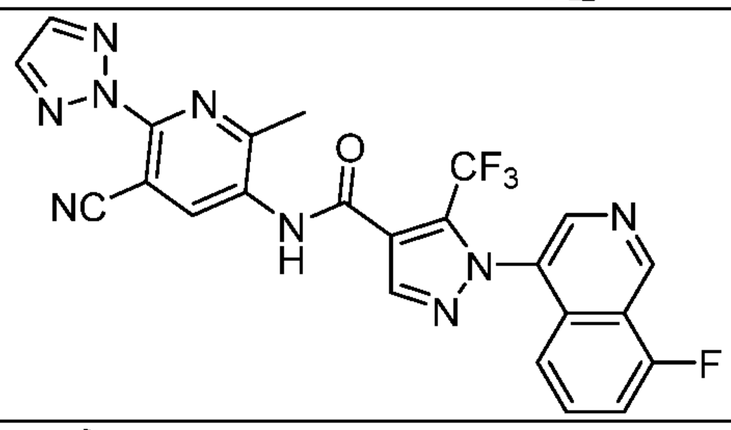
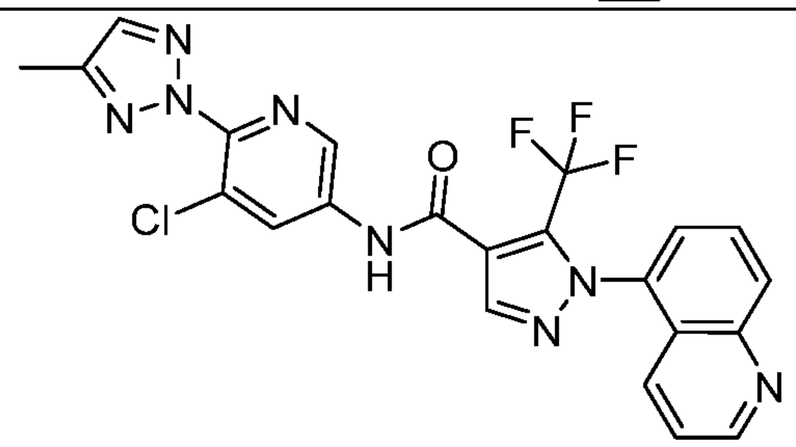
Structure	Cpd No.	Cpd Name
	**97**	*N*-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**98**	*N*-(5-chloro-6-(1-methyl-*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**99**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**100**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**101**	*N*-(6-(4-(4-aminobutyl)piperazine-1-carbonyl)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide

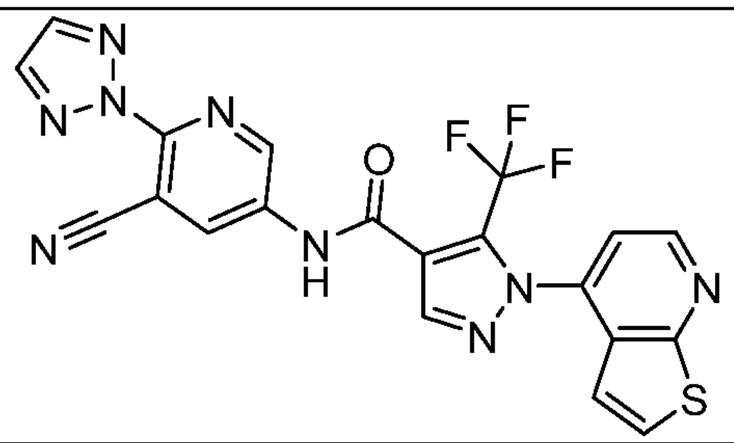
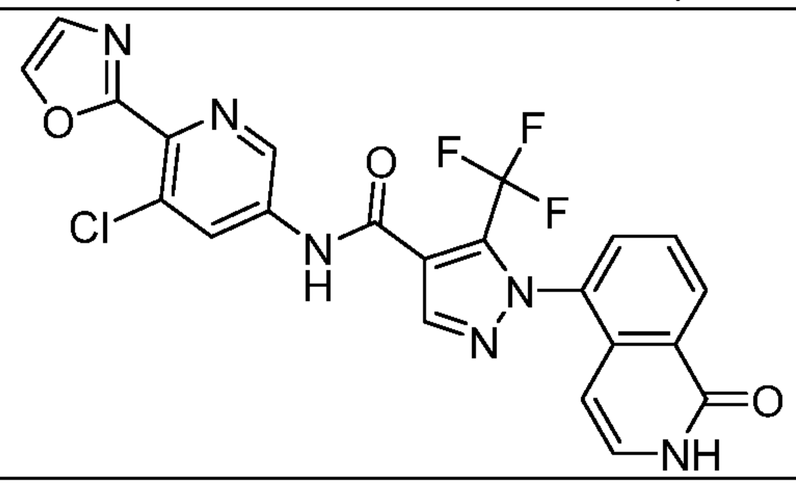
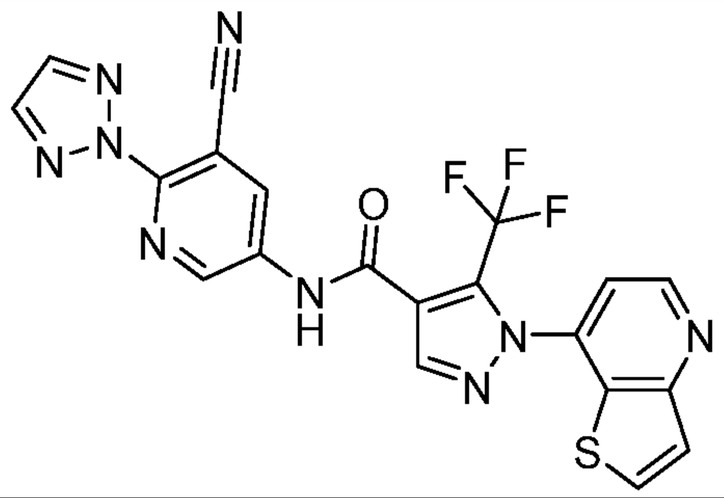
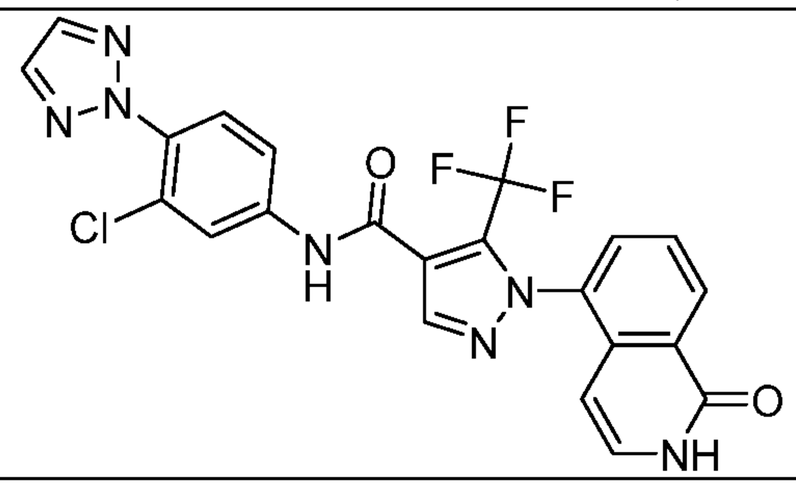
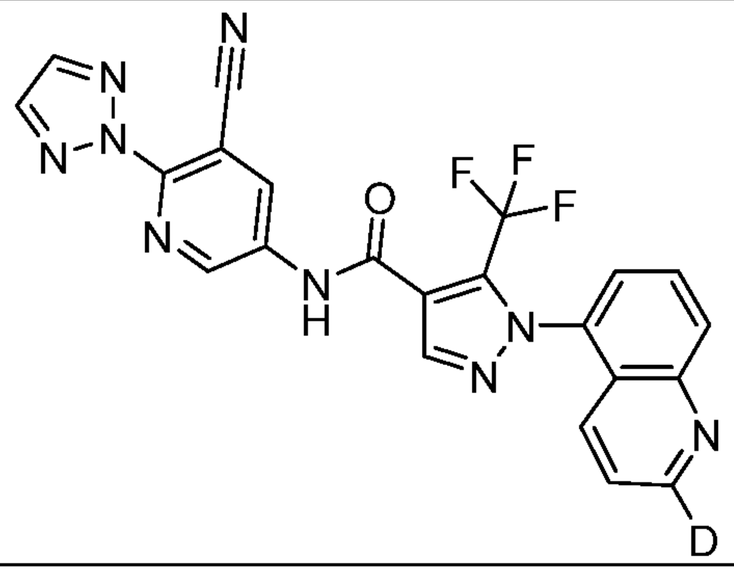
Structure	Cpd No.	Cpd Name
	**102**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(phthalazin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**103**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**104**	*N*-(5-chloro-6-(*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**105**	*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinoxalin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide
	**106**	N-(5-chloro-6-(difluoromethoxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

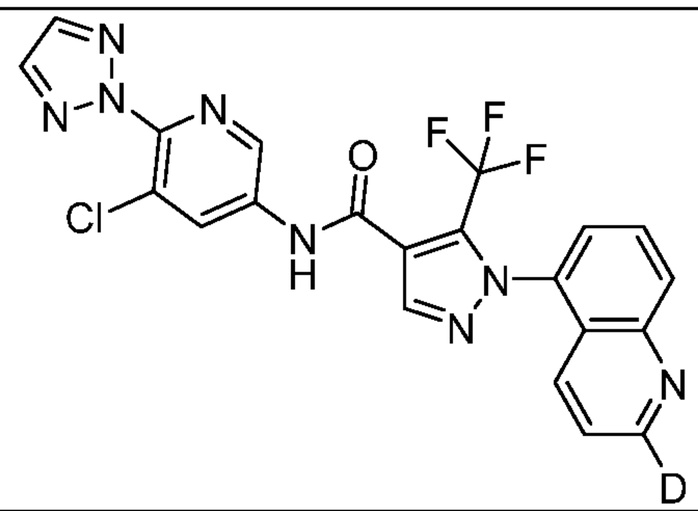
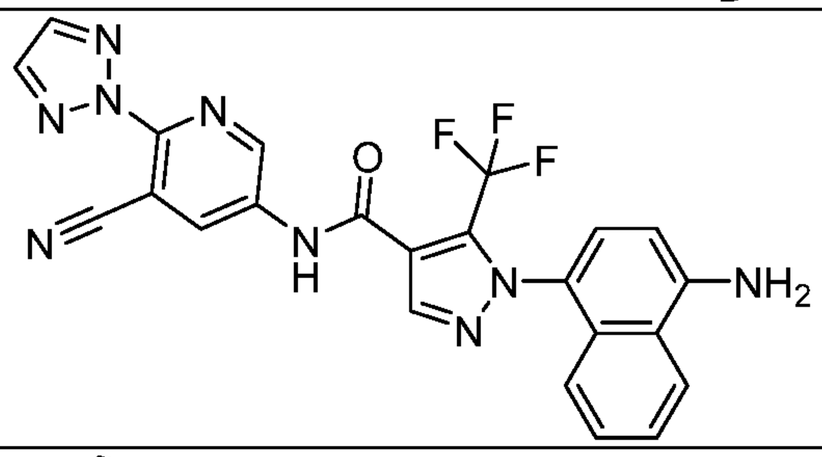
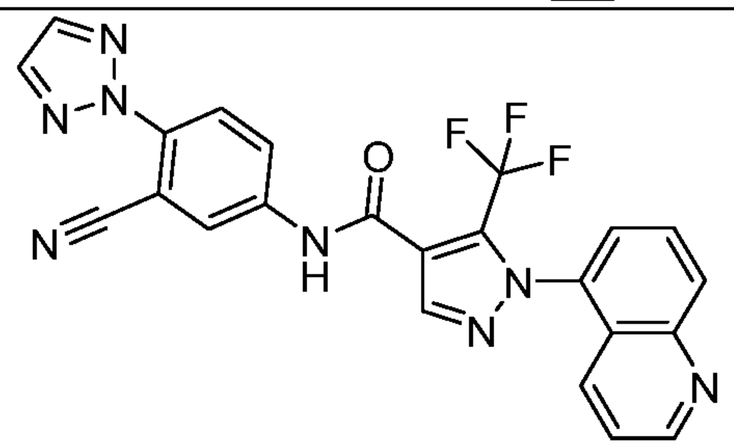
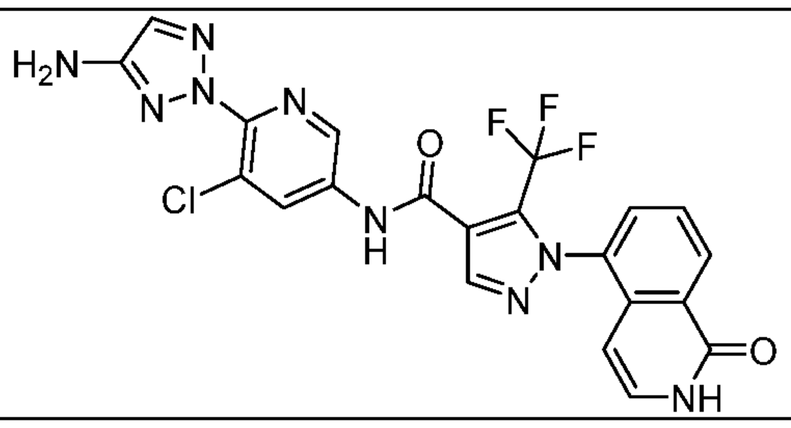
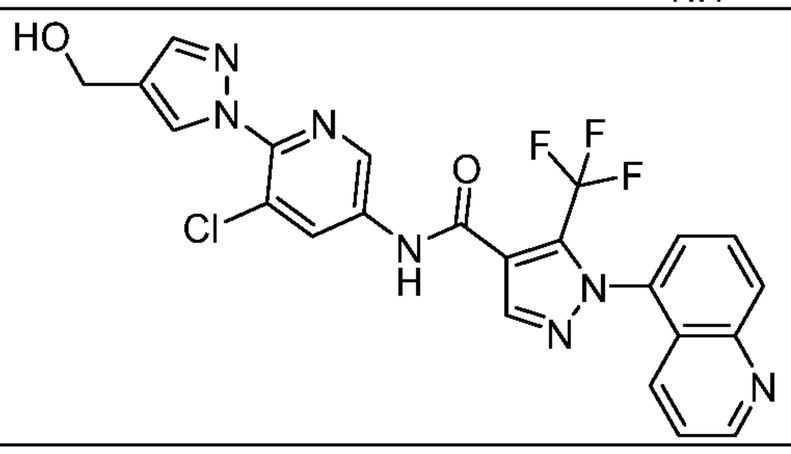
Structure	Cpd No.	Cpd Name
	**107**	N-(5-chloro-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**108**	methyl2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate
	**109**	2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid
	**110**	1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**111**	1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

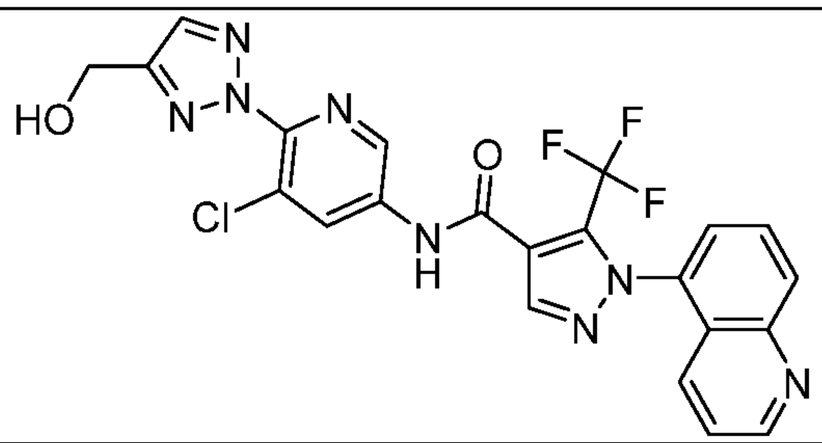
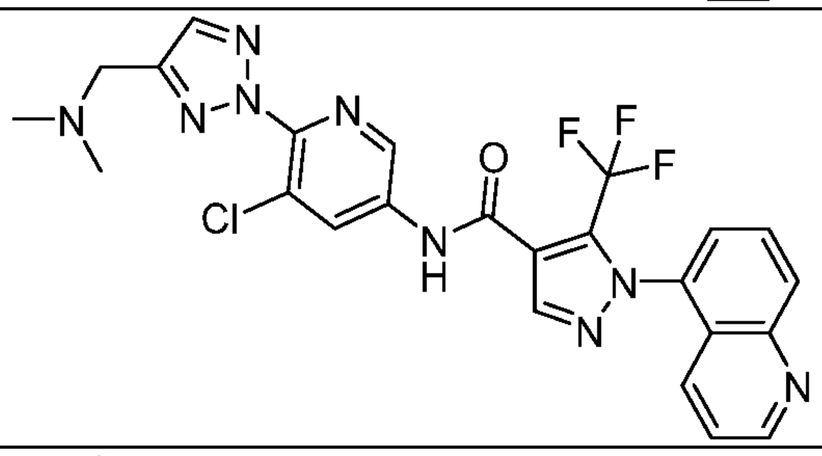
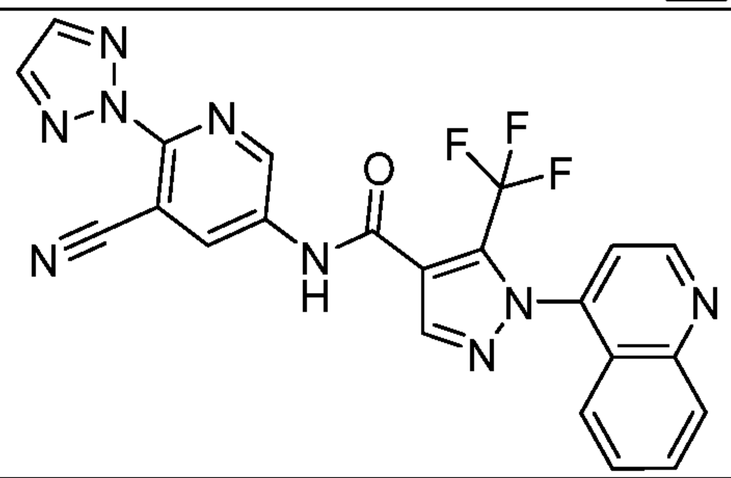
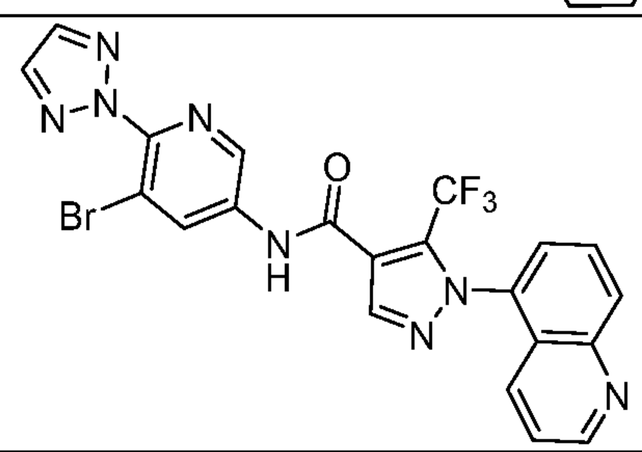
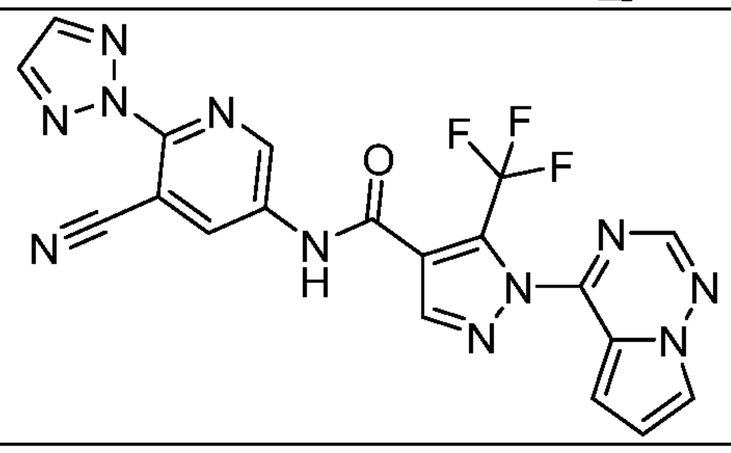
Structure	Cpd No.	Cpd Name
	**112**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**113**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**114**	1-(benzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**115**	N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**116**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

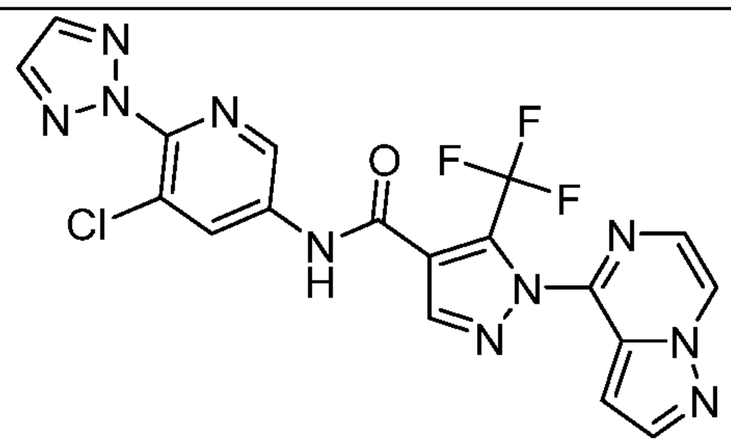
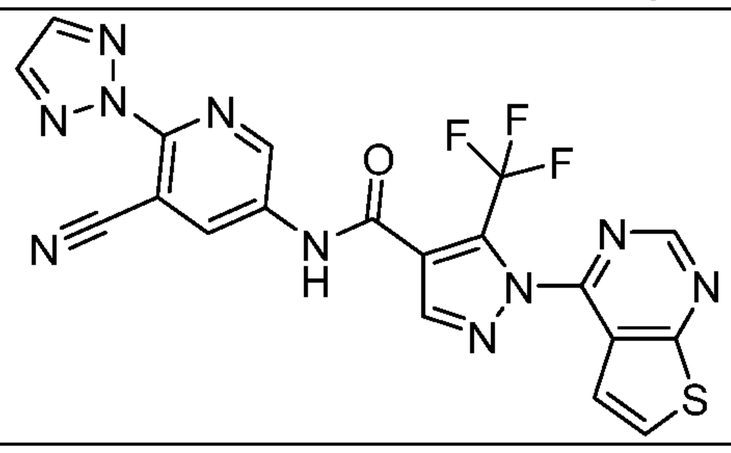
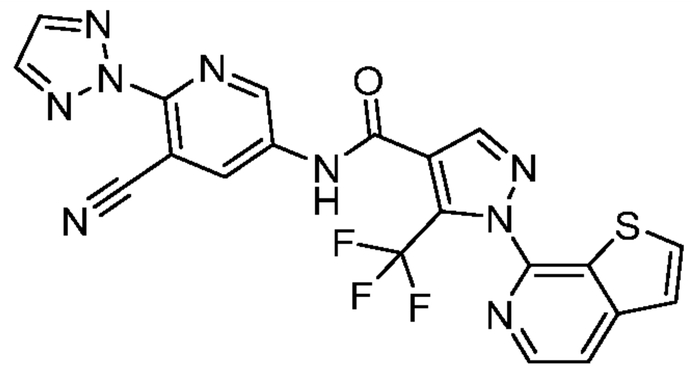
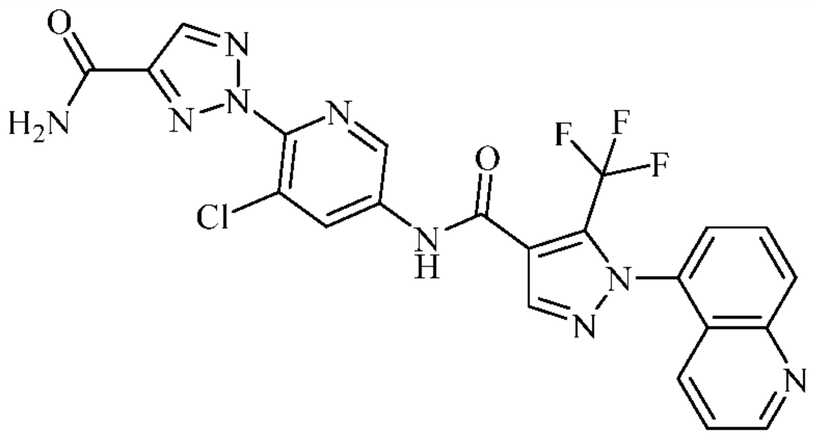
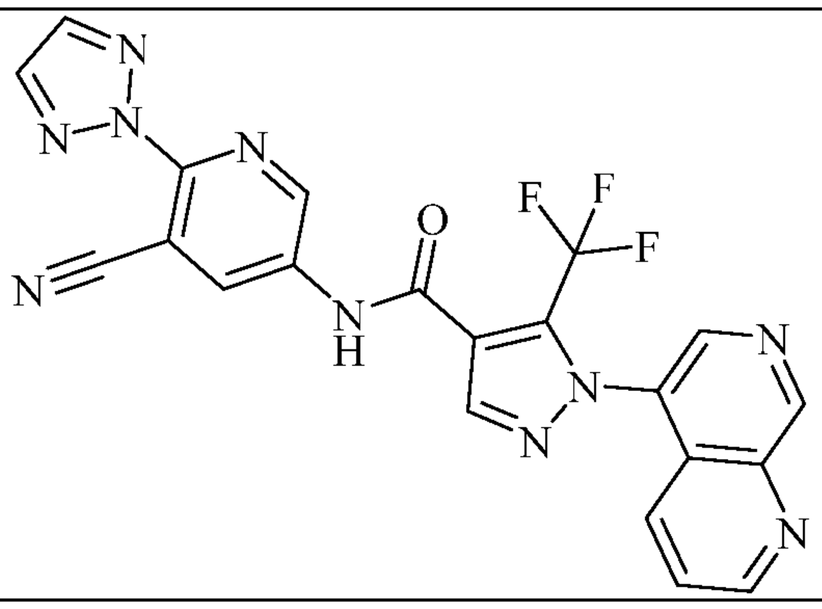
Structure	Cpd No.	Cpd Name
	**117**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**118**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**119**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**120**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

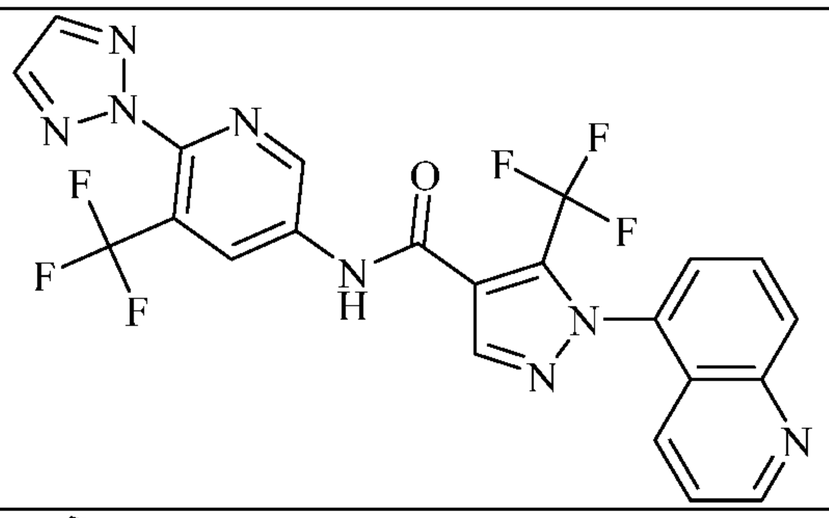
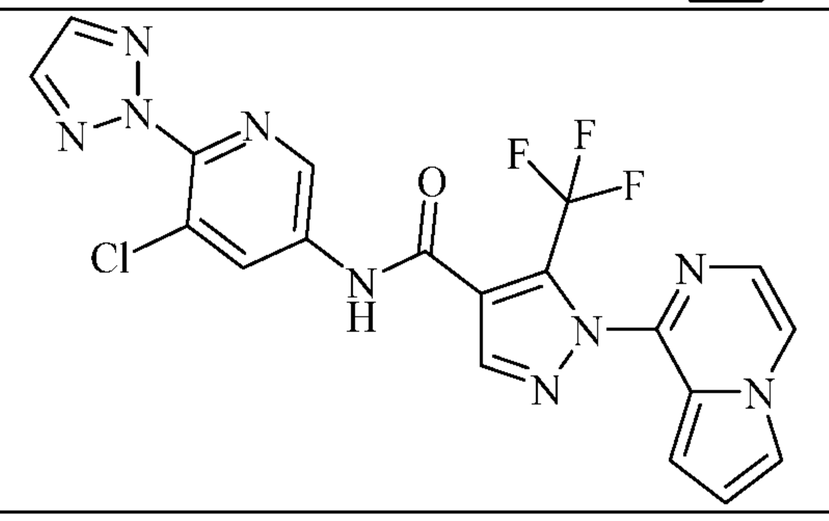
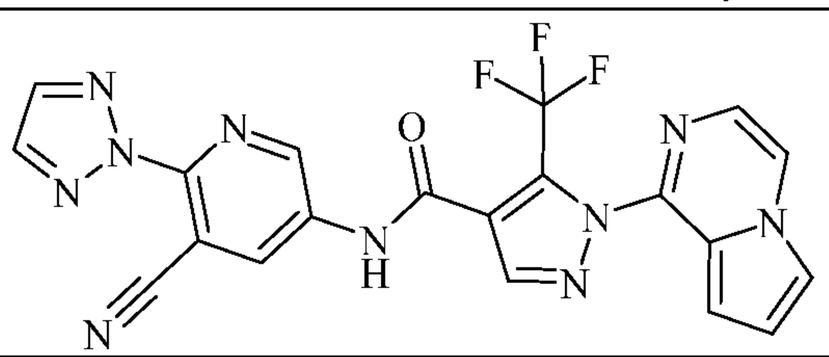
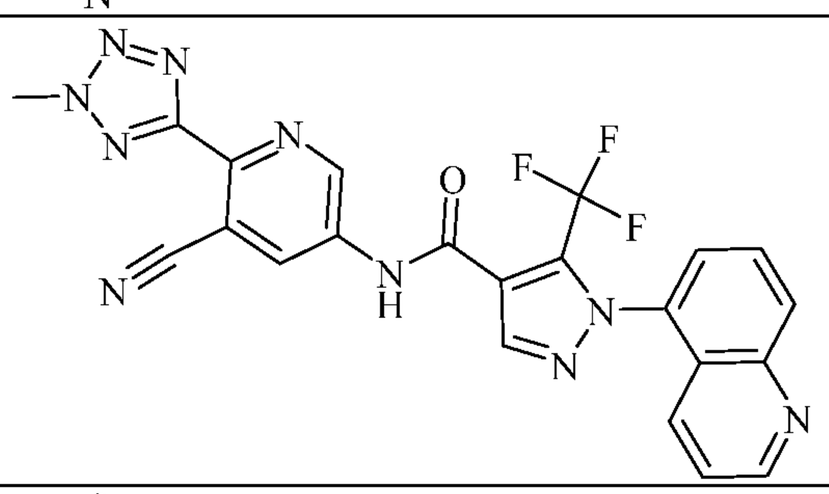
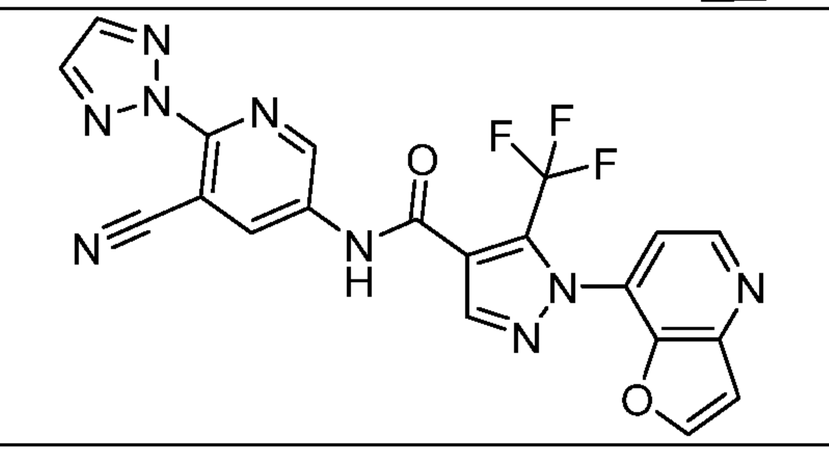
Structure	Cpd No.	Cpd Name
	**121**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**122**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**123**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**124**	N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**125**	N-(5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

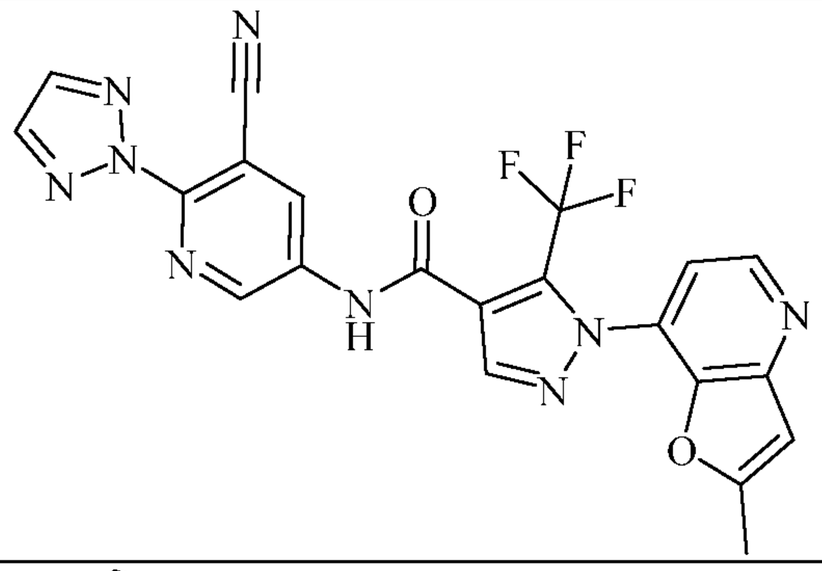
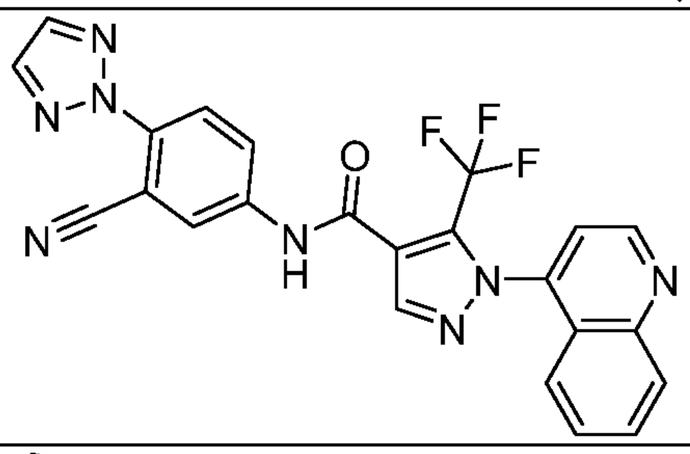
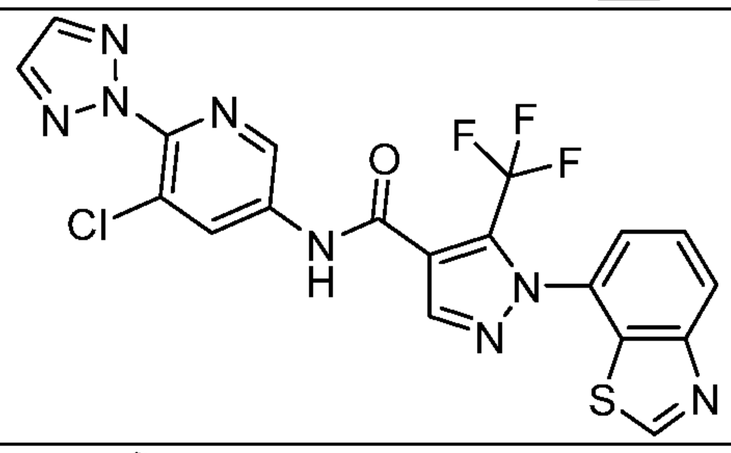
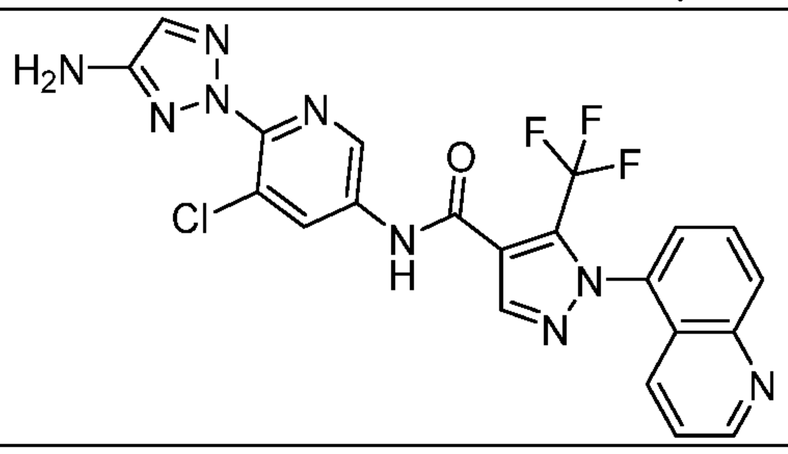
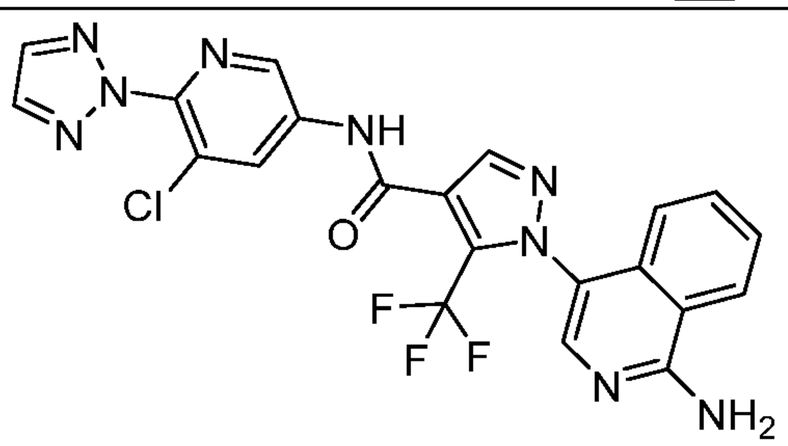
Structure	Cpd No.	Cpd Name
	**126**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**127**	N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**128**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**129**	N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**130**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

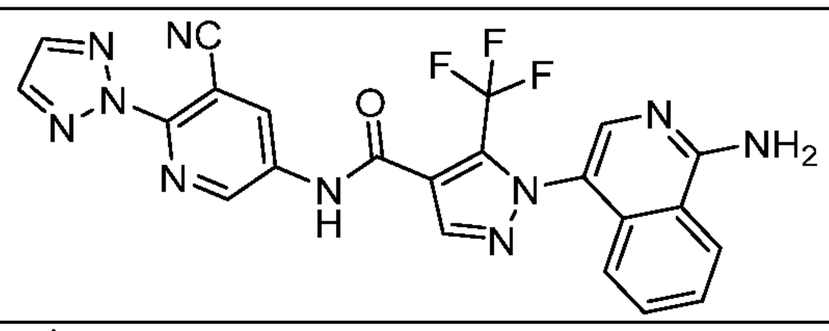
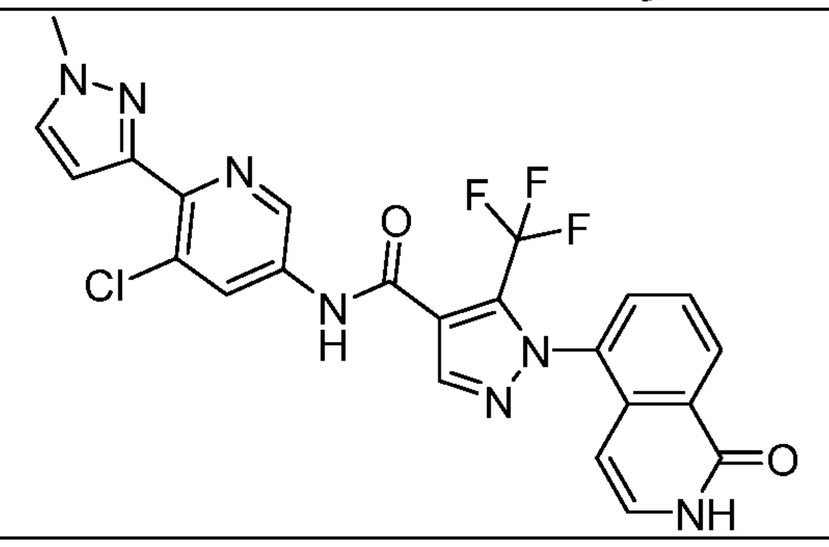
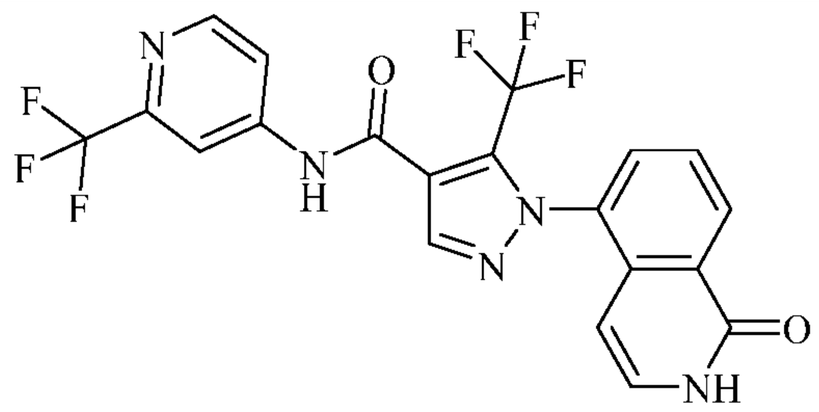
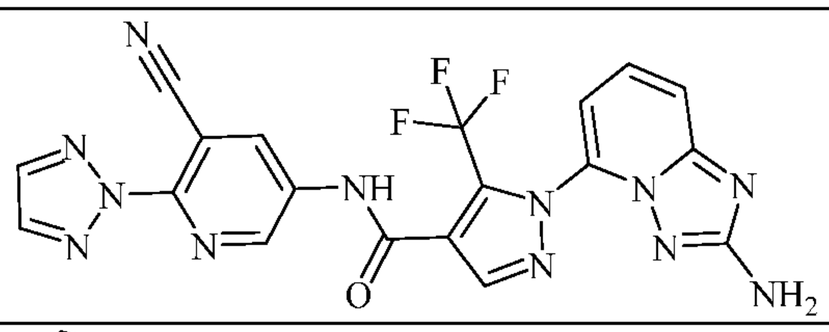
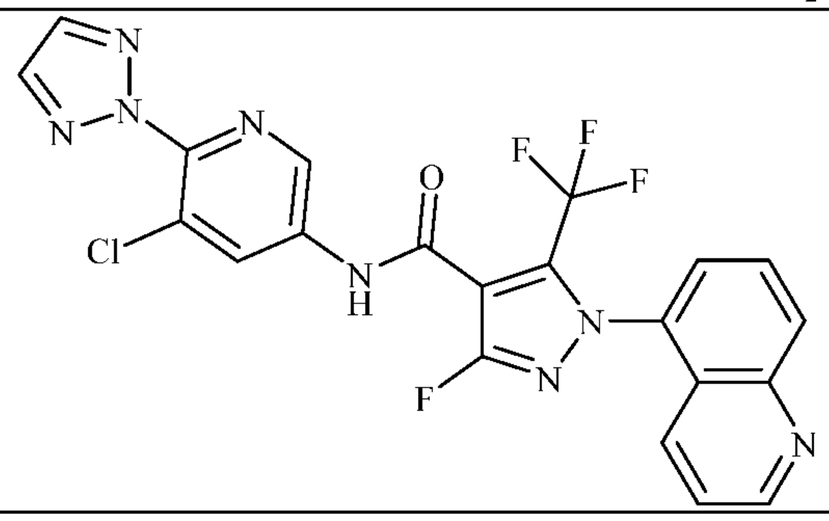
Structure	Cpd No.	Cpd Name
	**131**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-Dquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**132**	1-(4-aminonaphthalen-1-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**133**	N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**134**	N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**135**	N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

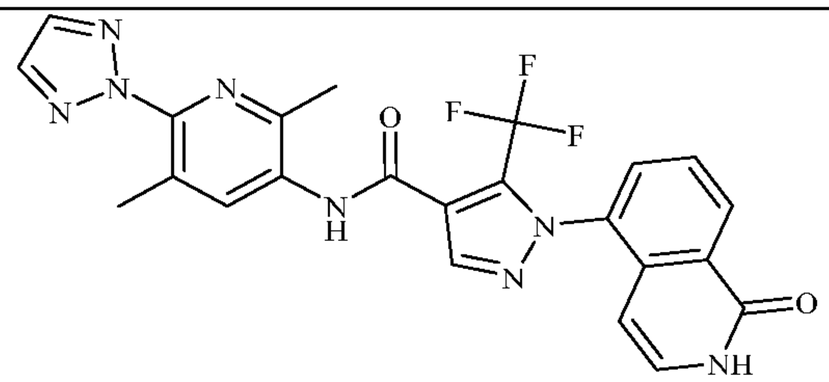
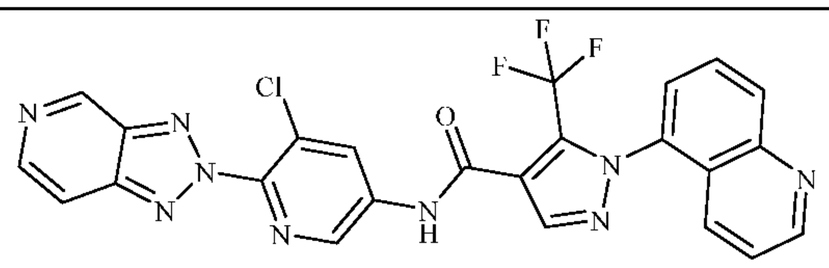
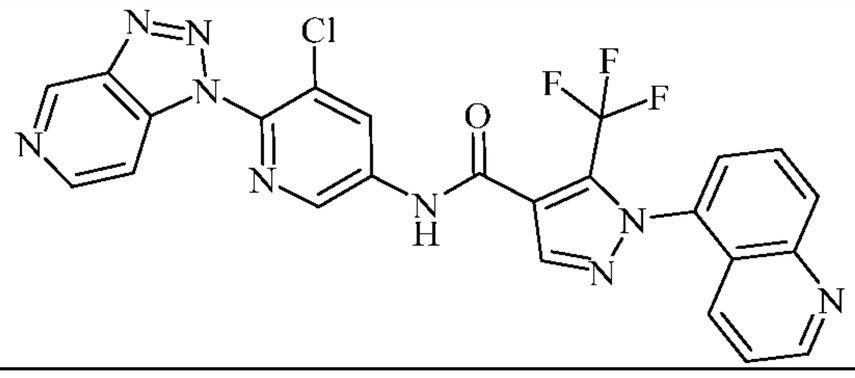
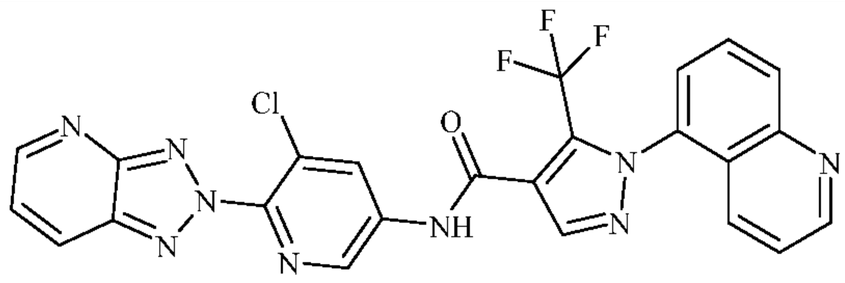
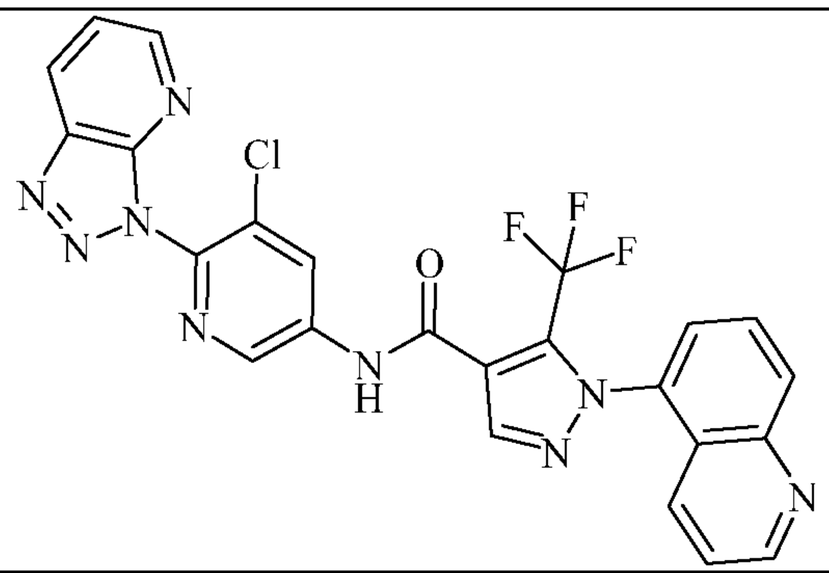
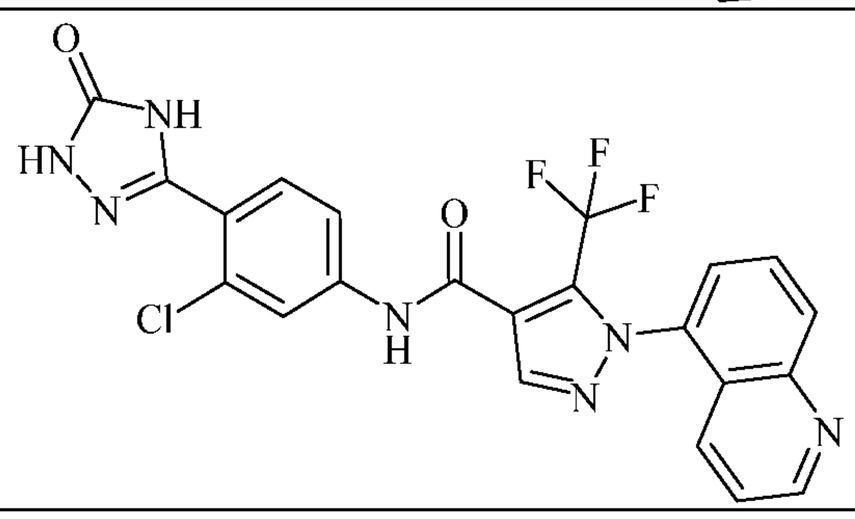
Structure	Cpd No.	Cpd Name
	**136**	N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**137**	N-(5-chloro-6-(4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**138**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**139**	N-(5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**140**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

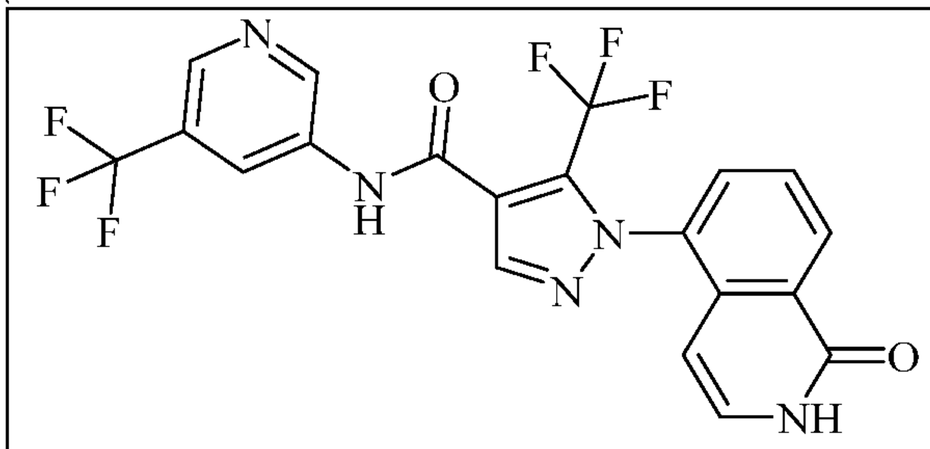
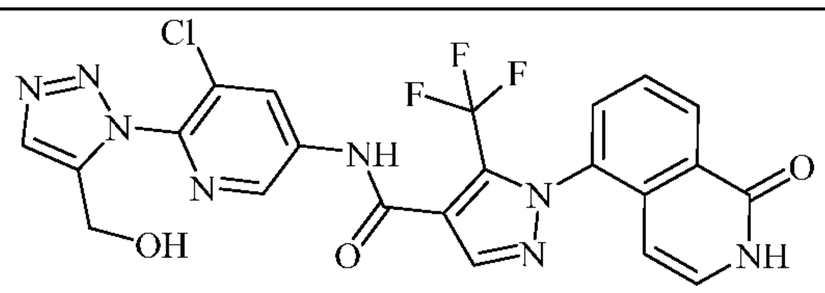
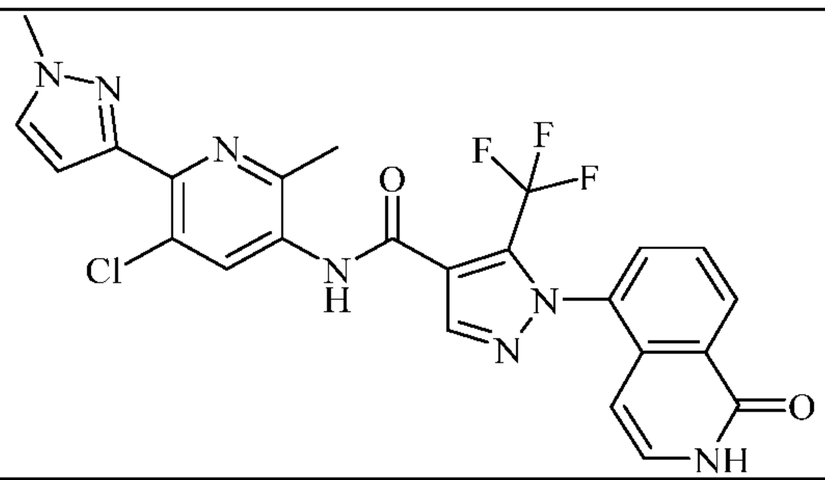
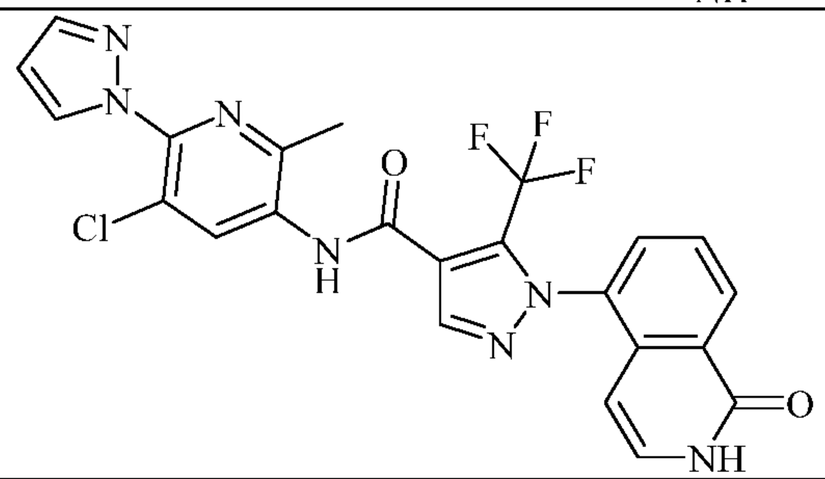
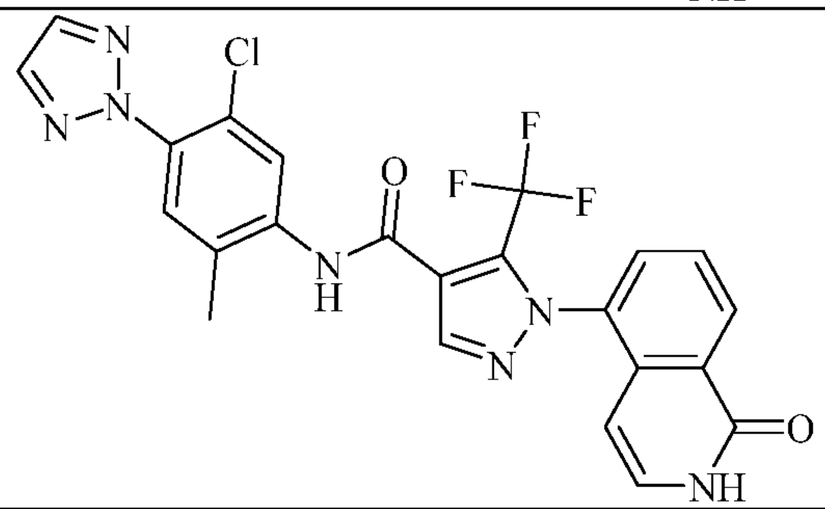
Structure	Cpd No.	Cpd Name
	**141**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**142**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**143**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**144**	2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide
	**145**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

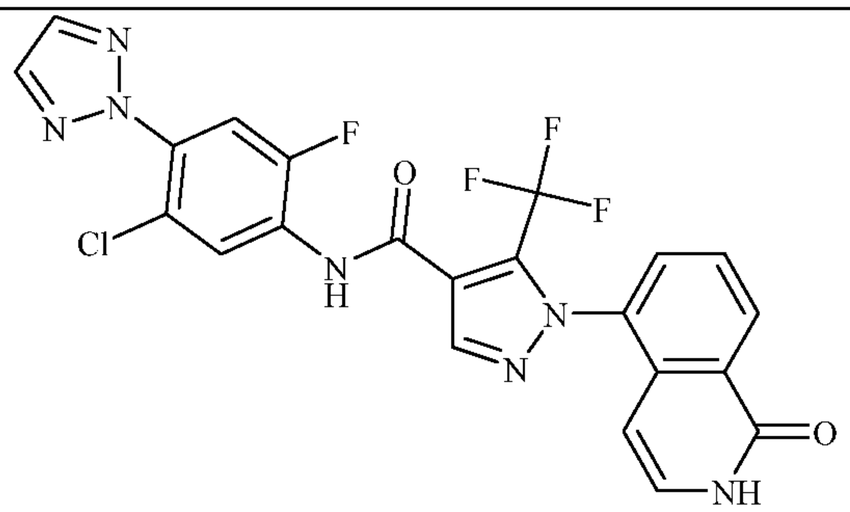
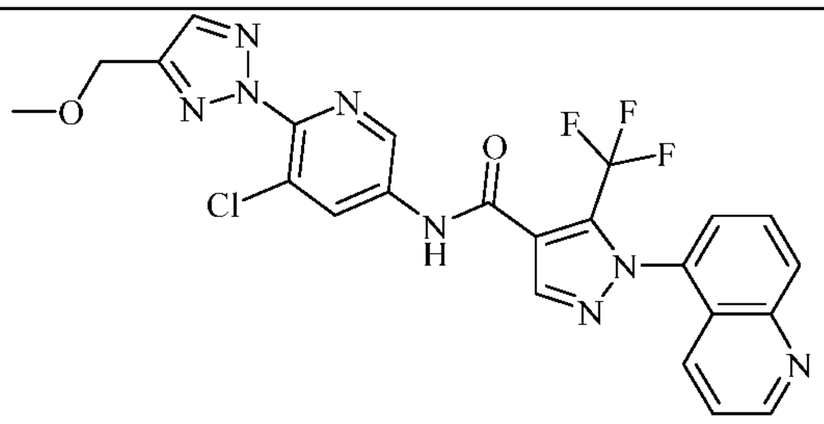
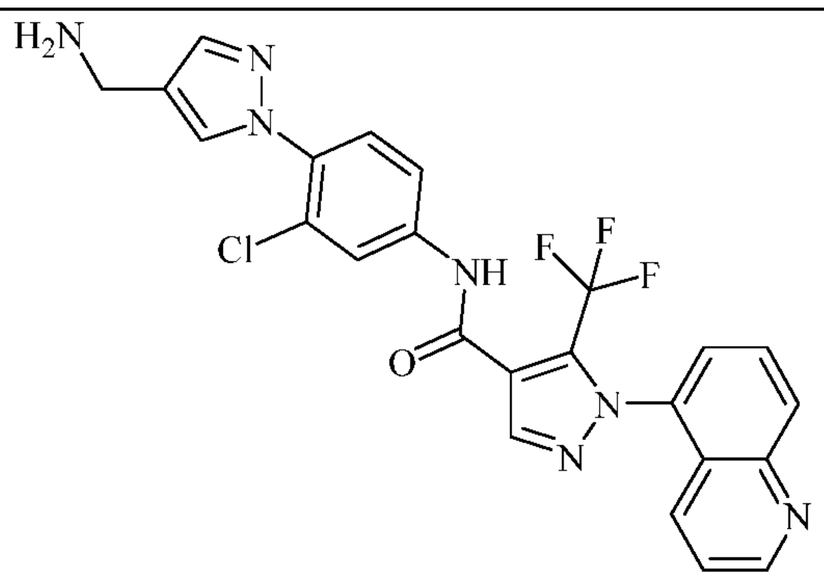
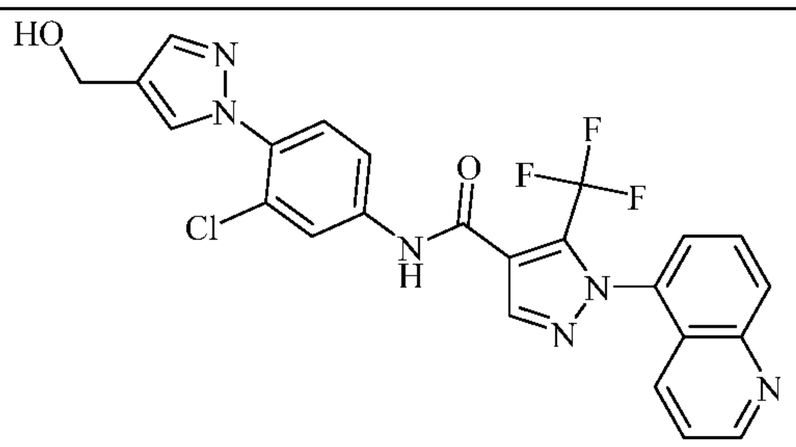
Structure	Cpd No.	Cpd Name
	**146**	N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**147**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**148**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**149**	N-(5-cyano-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**150**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

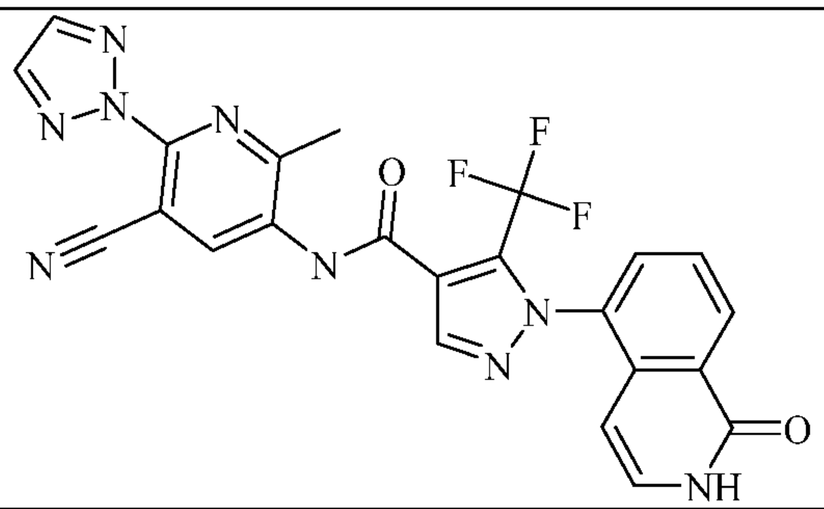
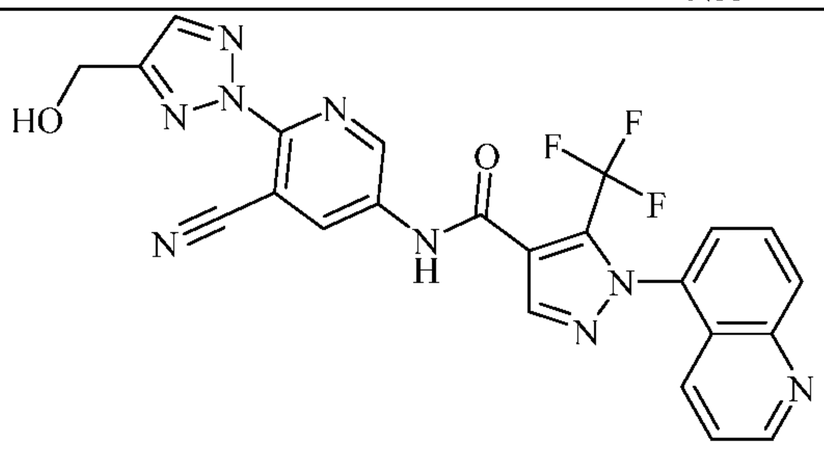
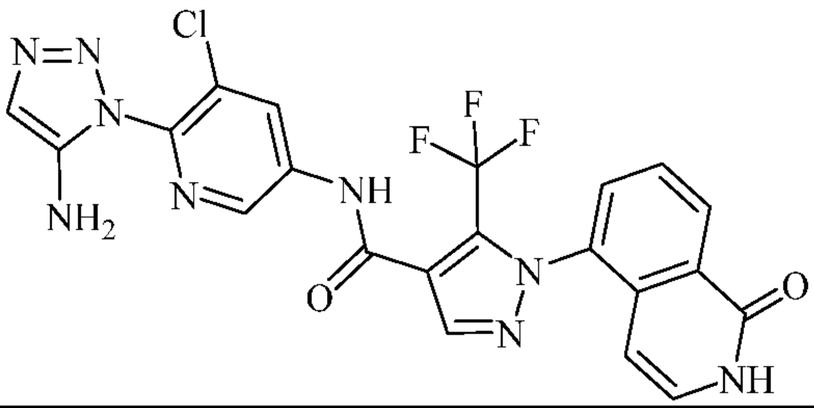
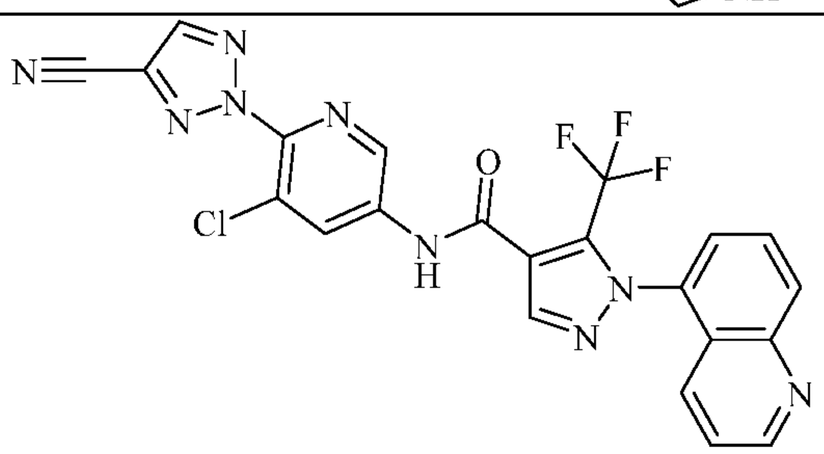
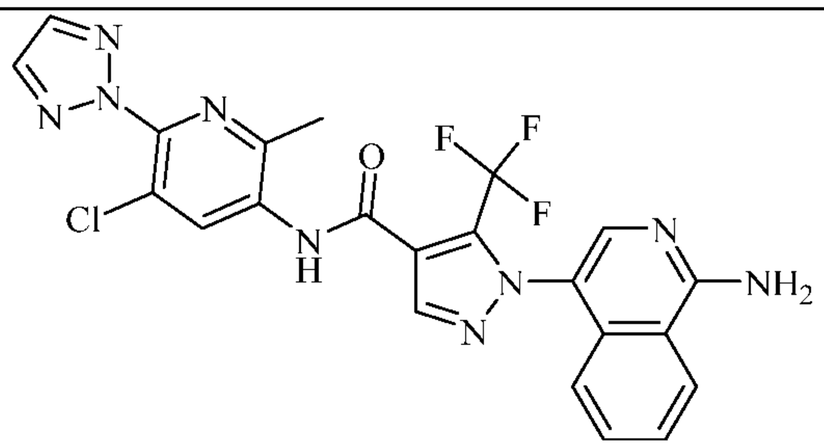
Structure	Cpd No.	Cpd Name
	**151**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**152**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoro-2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**153**	1-(benzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**154**	N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**155**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

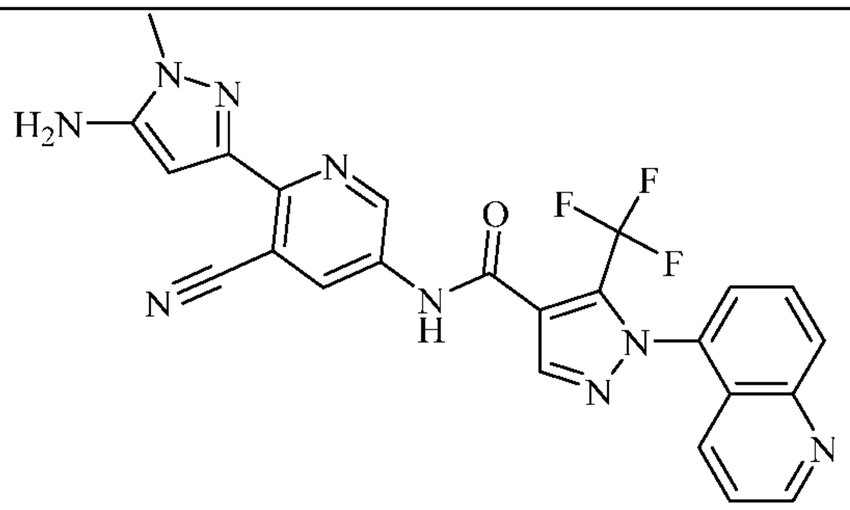
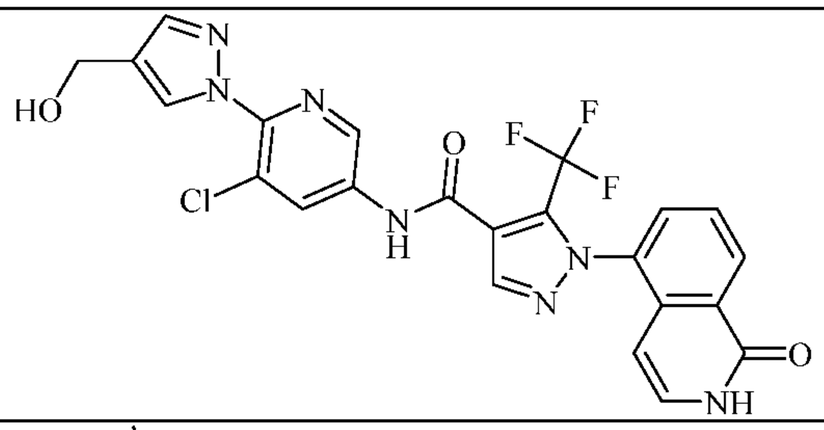
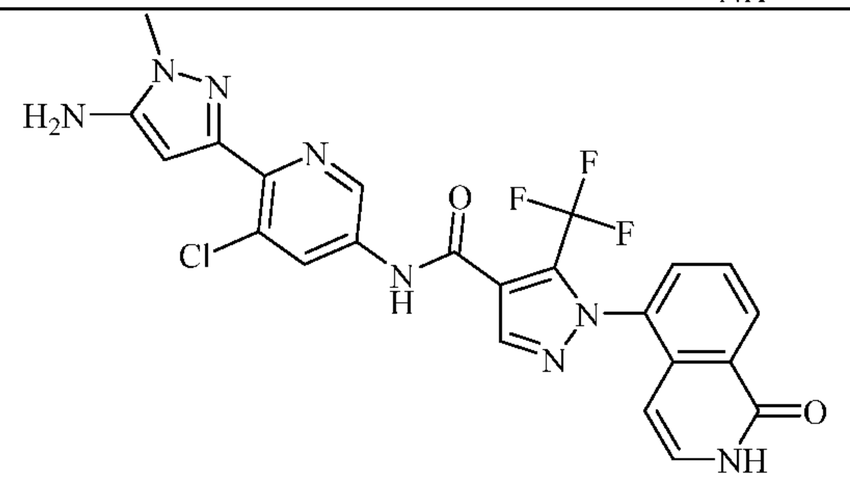
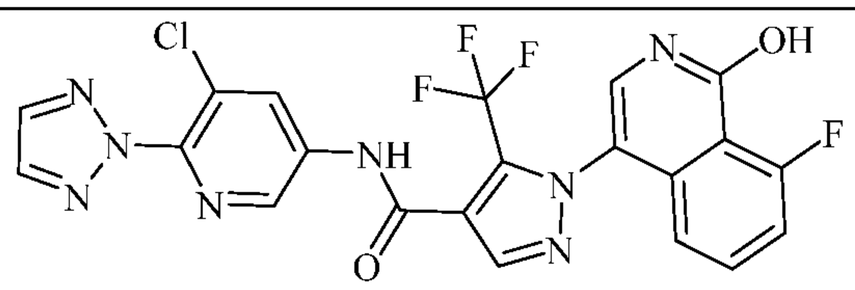
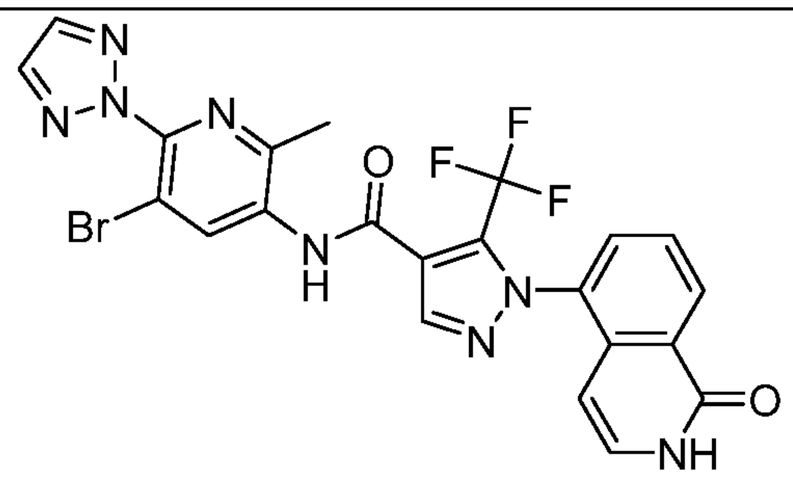
Structure	Cpd No.	Cpd Name
	**156**	1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**157**	N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**158**	1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**159**	1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**160**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

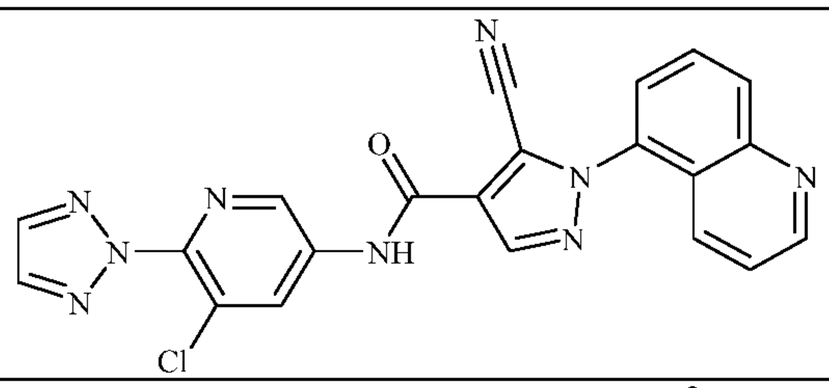
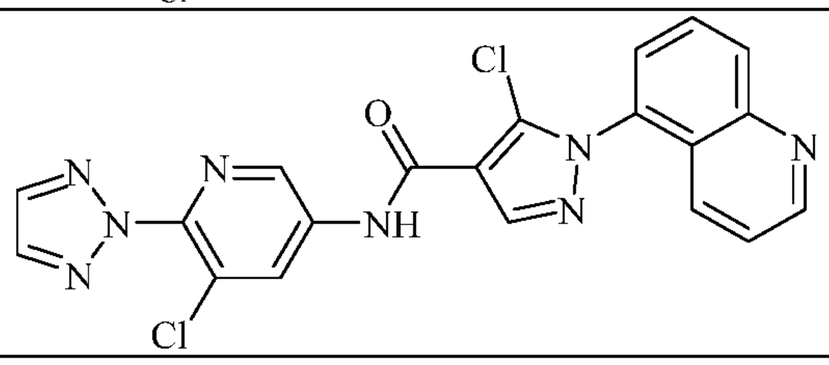
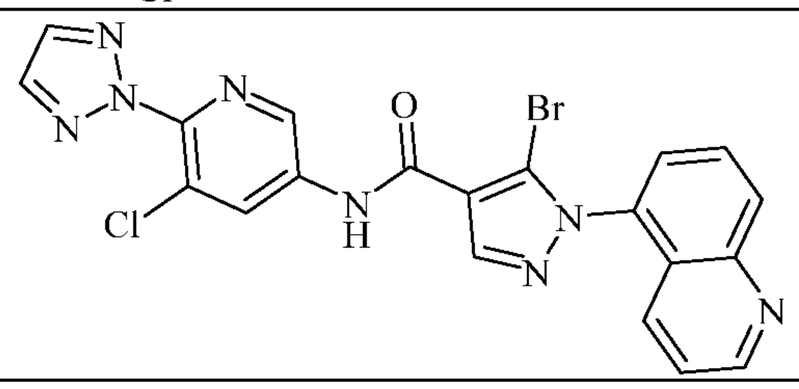
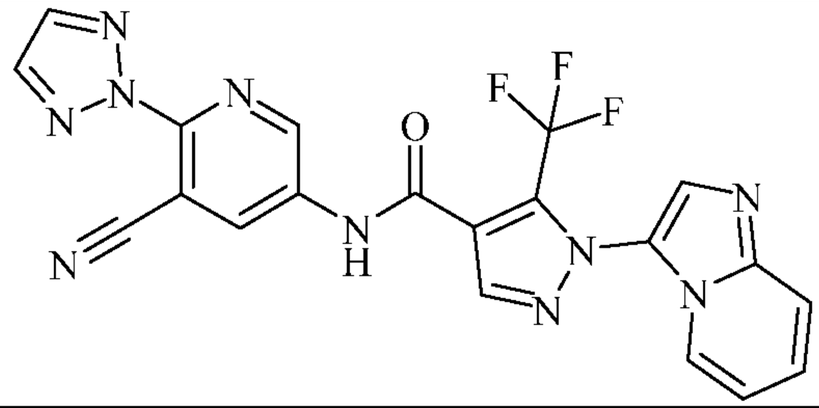
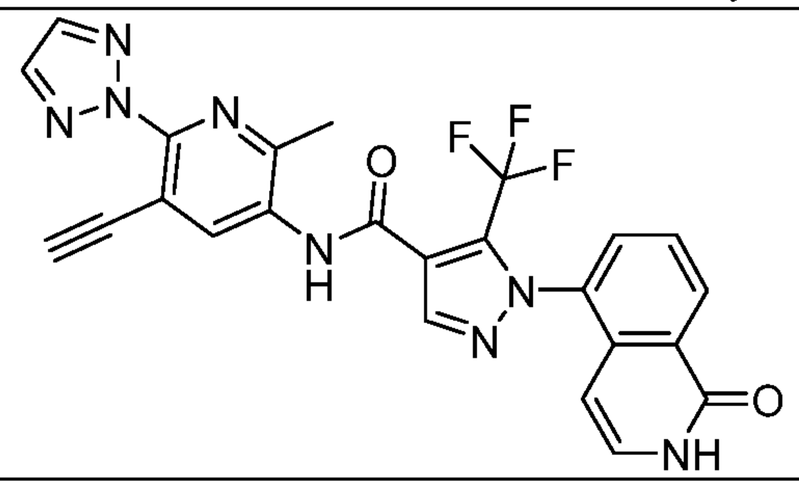
Structure	Cpd No.	Cpd Name
	**161**	N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**162**	N-(6-(2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**163**	N-(6-(1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**164**	N-(6-(2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**165**	N-(6-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**166**	N-(3-chloro-4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

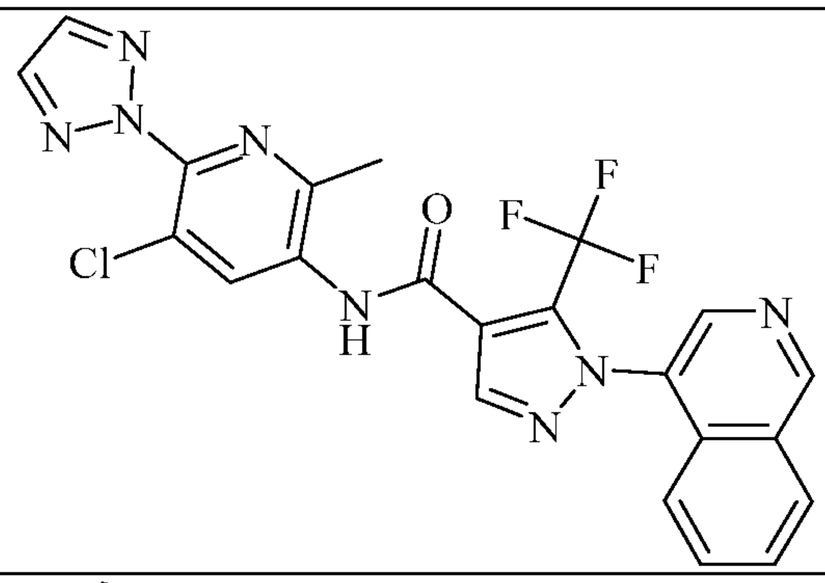
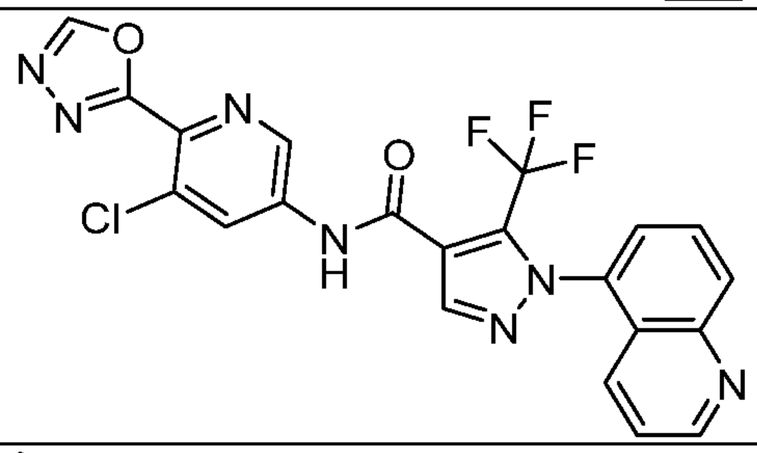
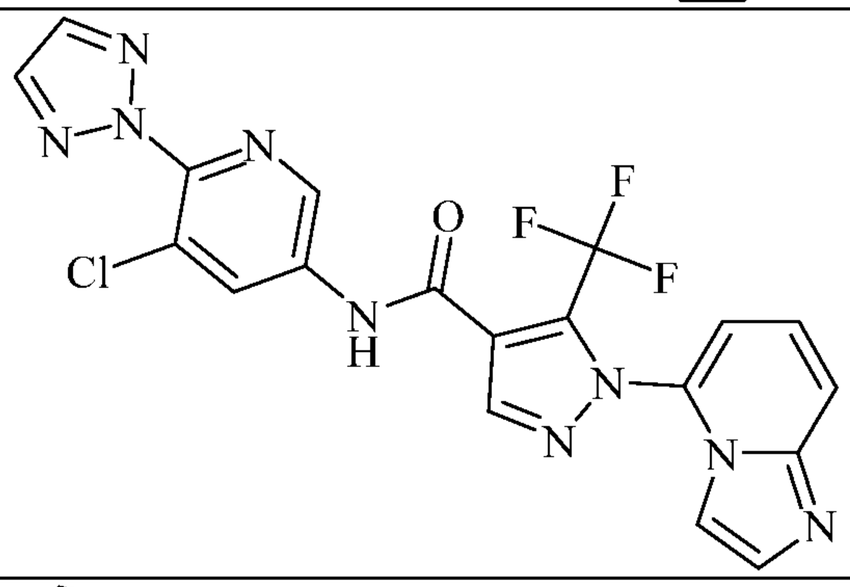
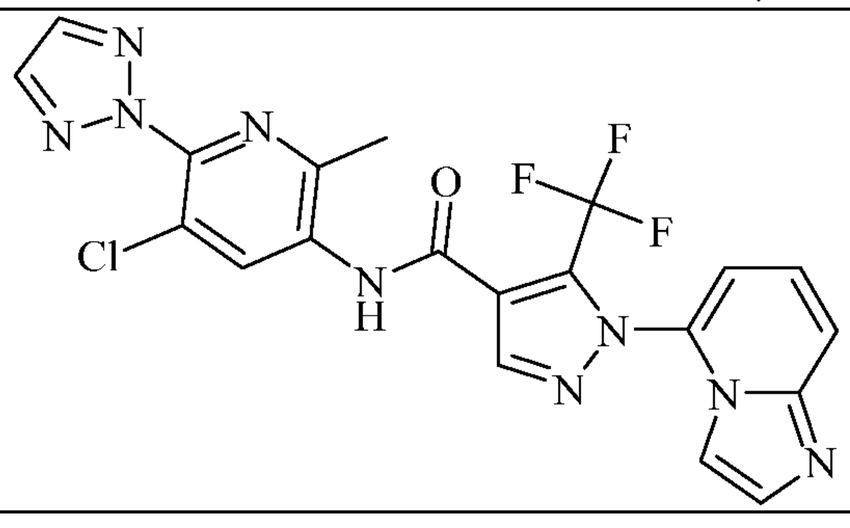
Structure	Cpd No.	Cpd Name
	**167**	1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide
	**168**	N-(5-chloro-6-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**169**	N-(5-chloro-2-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**170**	N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**171**	N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

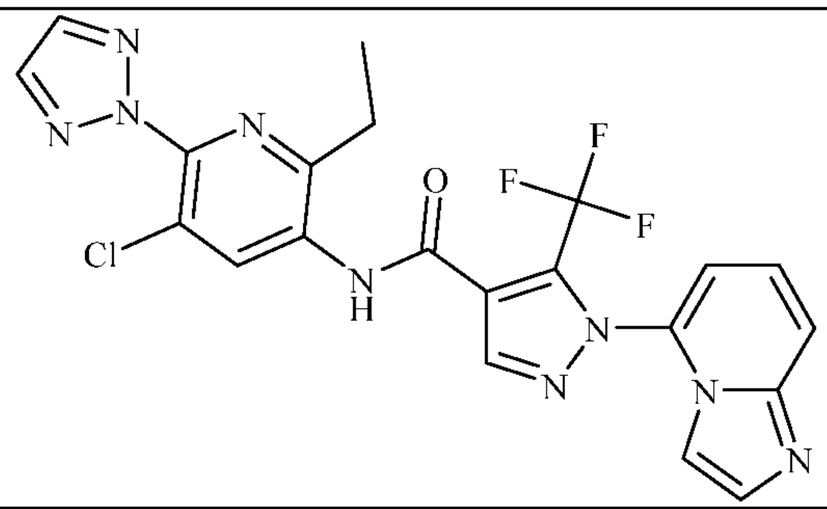
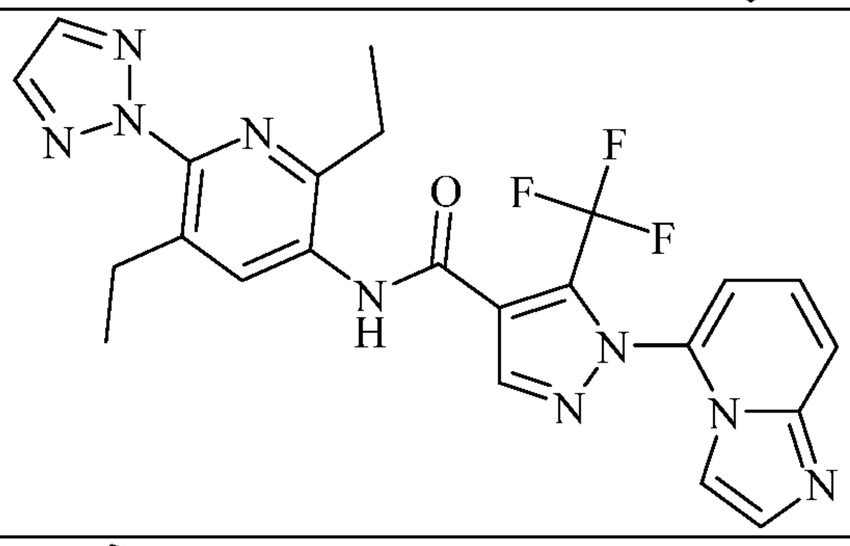
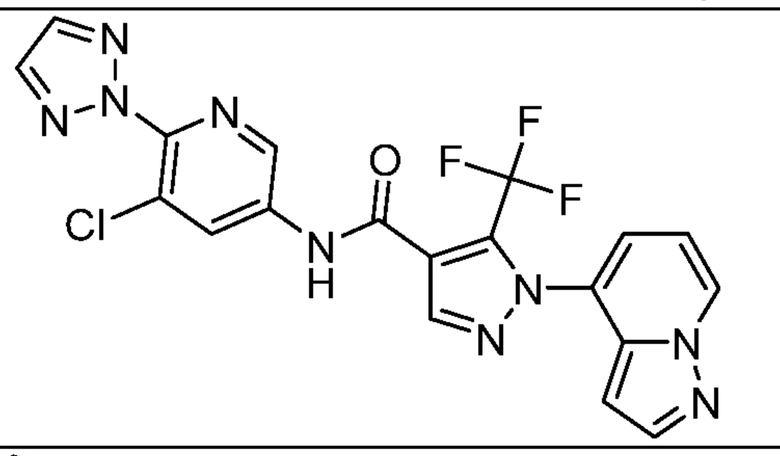
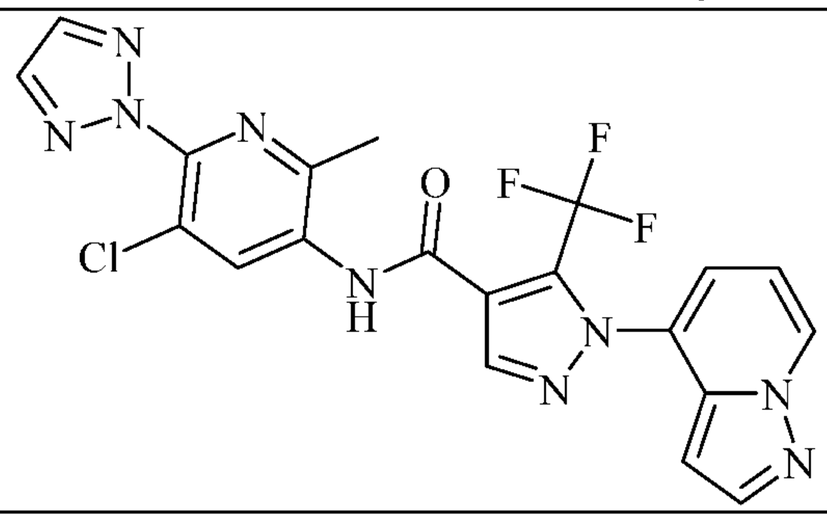
Structure	Cpd No.	Cpd Name
	**172**	N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**173**	N-(5-chloro-6-(4-(methoxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**174**	N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-chlorophenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**175**	N-(3-chloro-4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

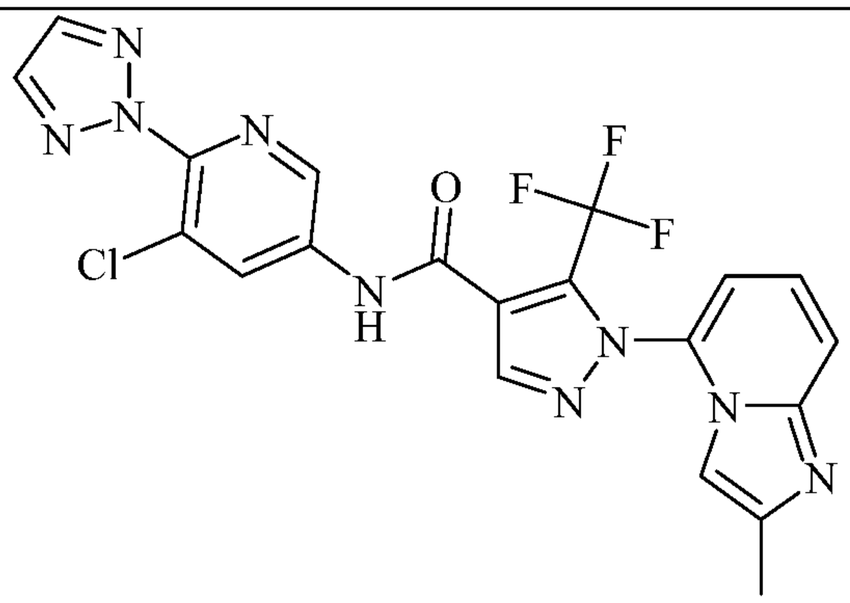
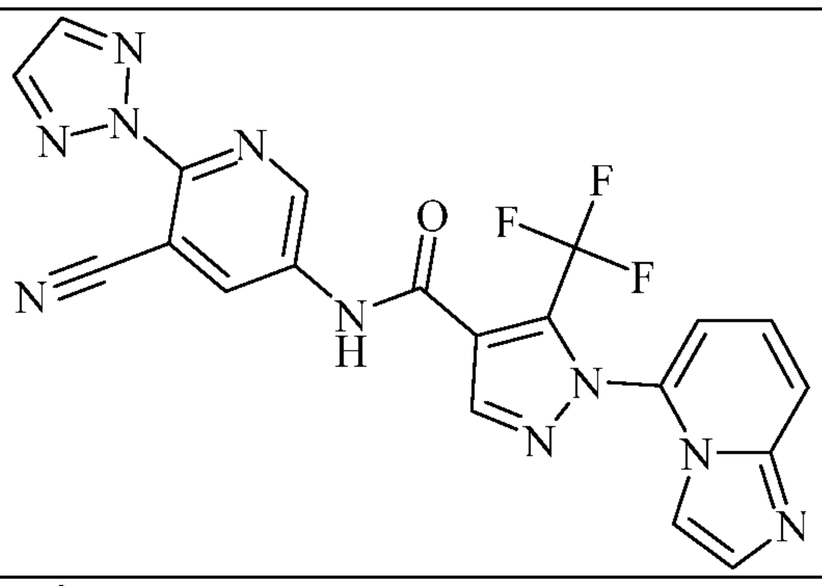
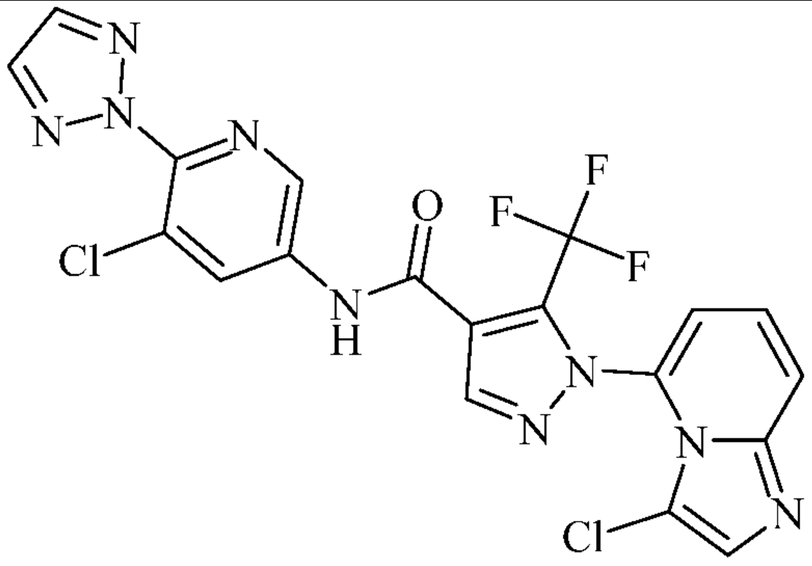
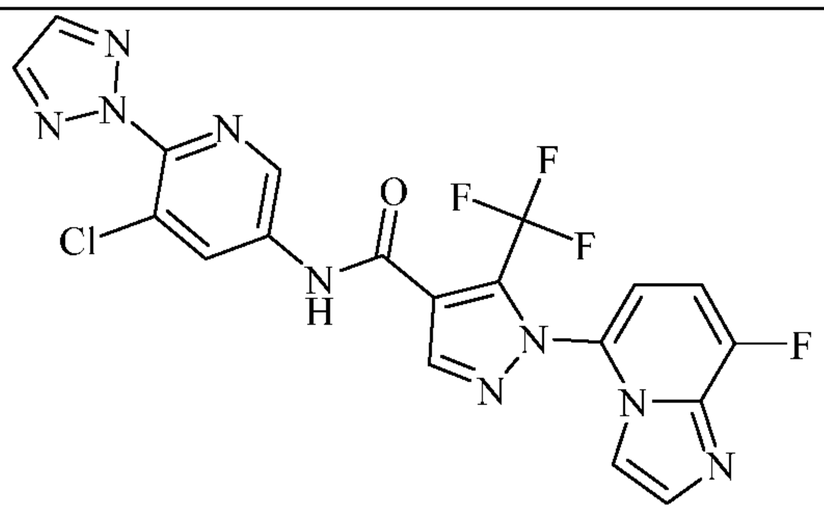
Structure	Cpd No.	Cpd Name
	**176**	N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**177**	N-(5-cyano-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**178**	N-(6-(5-amino-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**179**	N-(5-chloro-6-(4-cyano-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**180**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

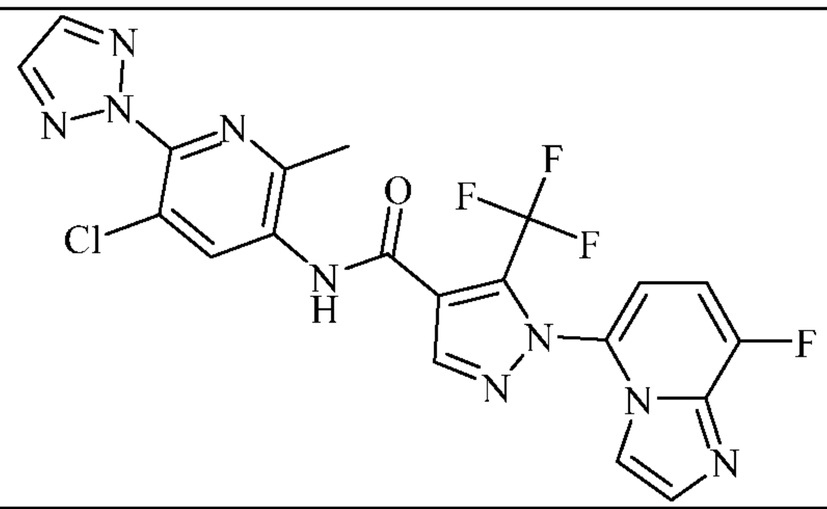
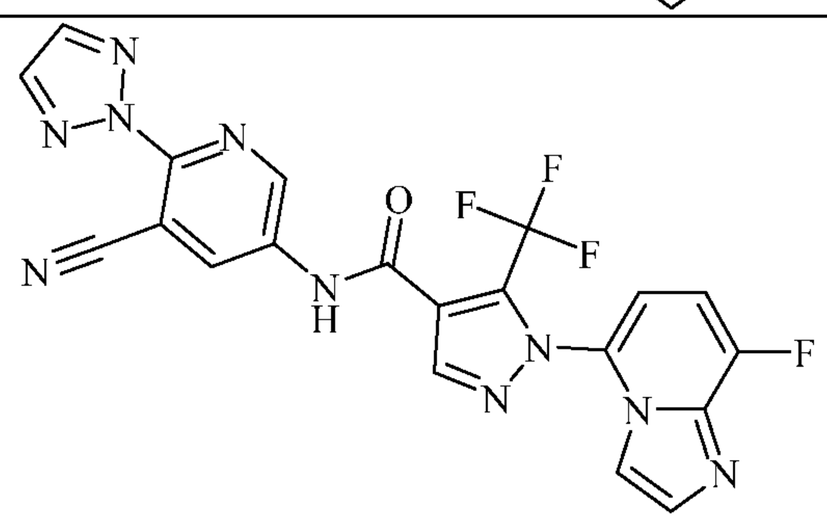
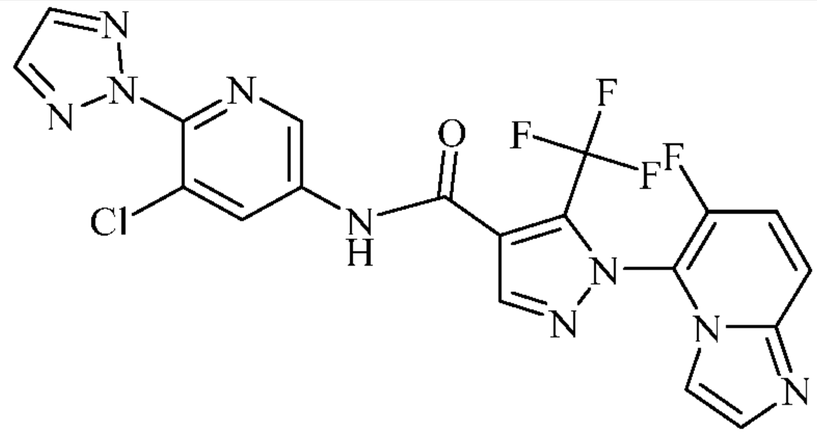
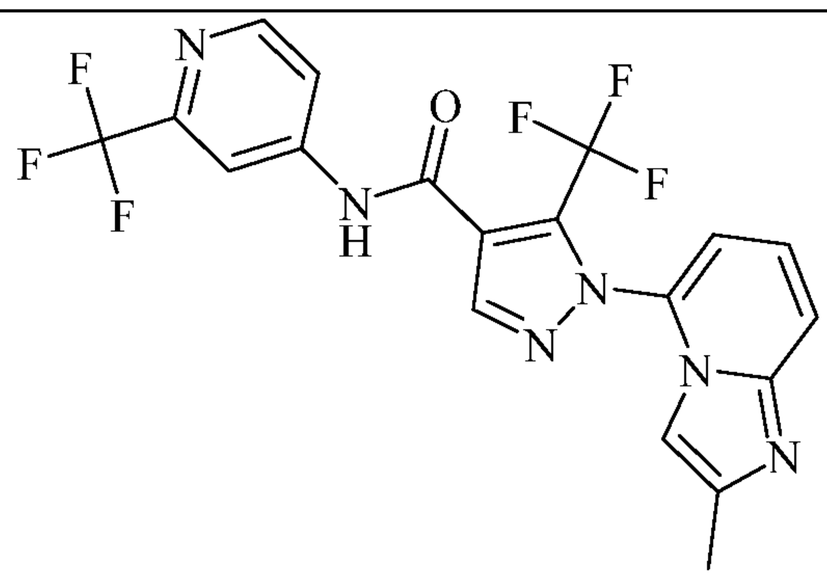
Structure	Cpd No.	Cpd Name
	**181**	N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-cyanopyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**182**	N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**183**	N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**184**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**185**	N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

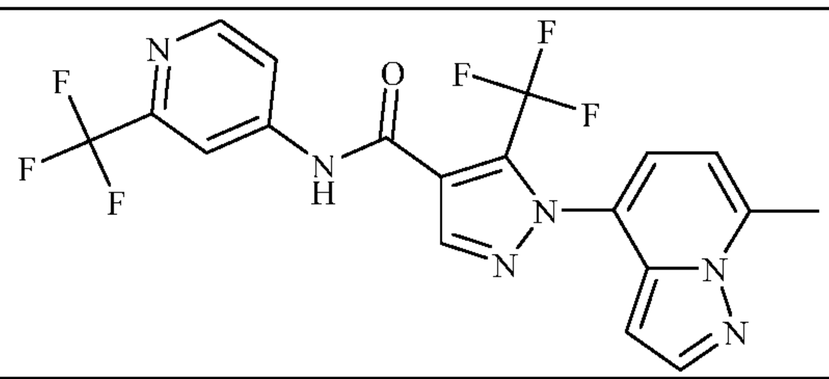
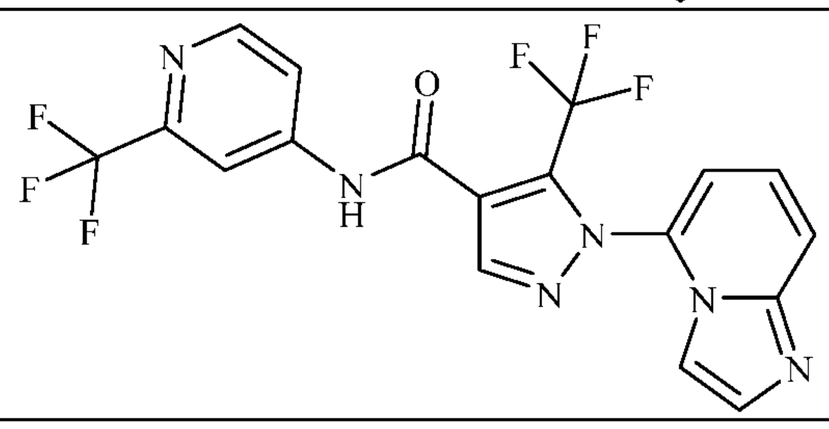
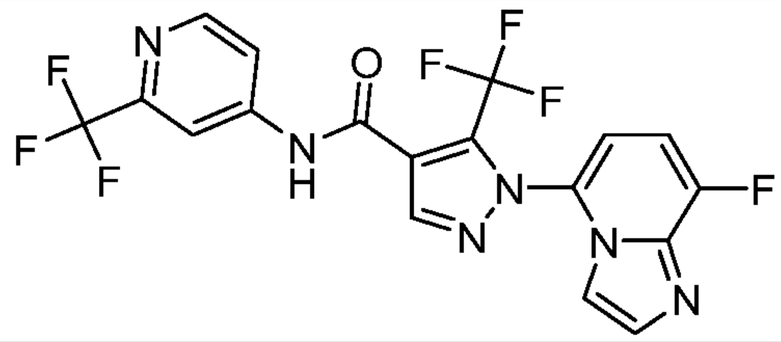
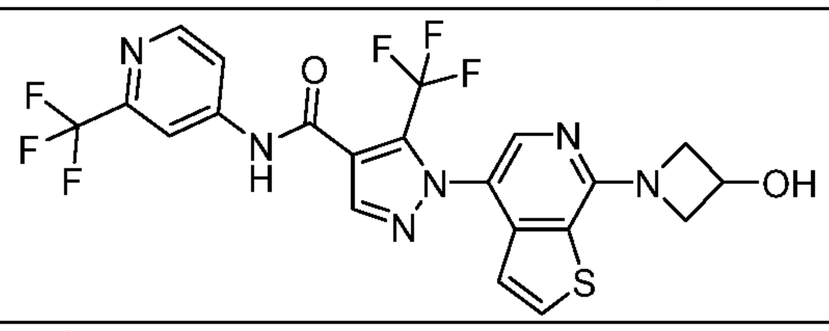
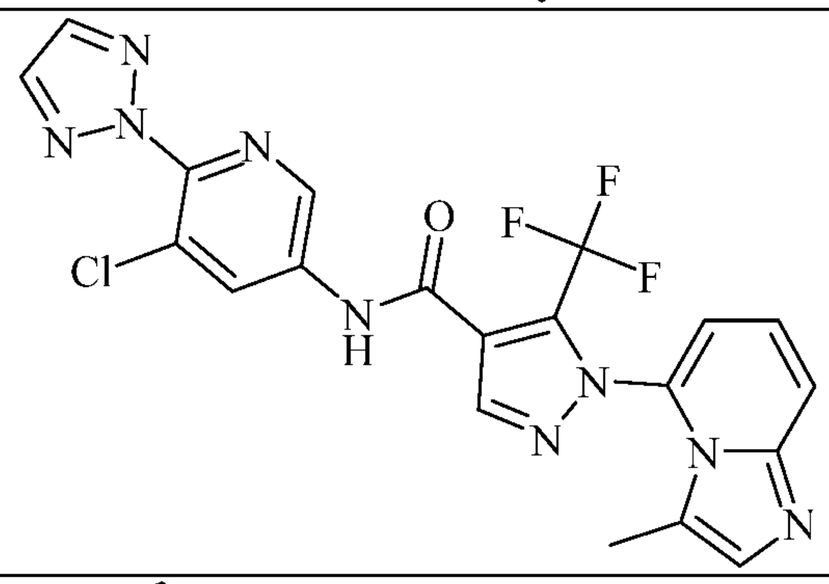
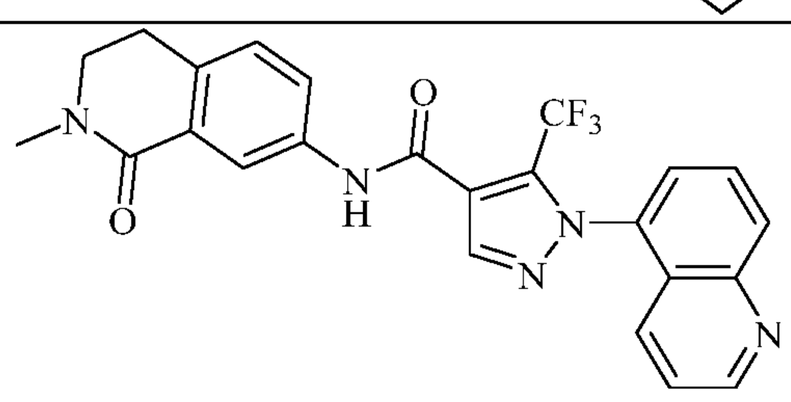
Structure	Cpd No.	Cpd Name
	**186**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-cyano-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide
	**187**	5-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide
	**188**	5-bromo-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide
	**189**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**190**	N-(5-ethynyl-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

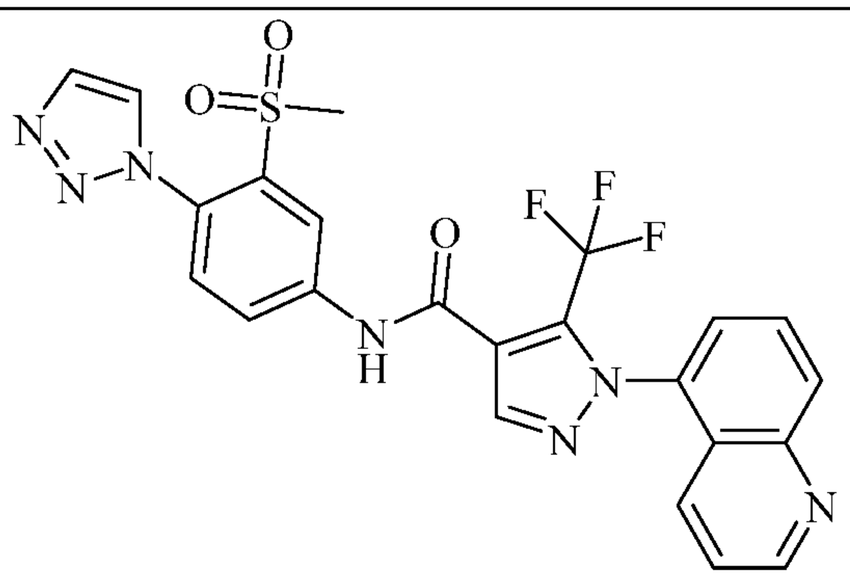
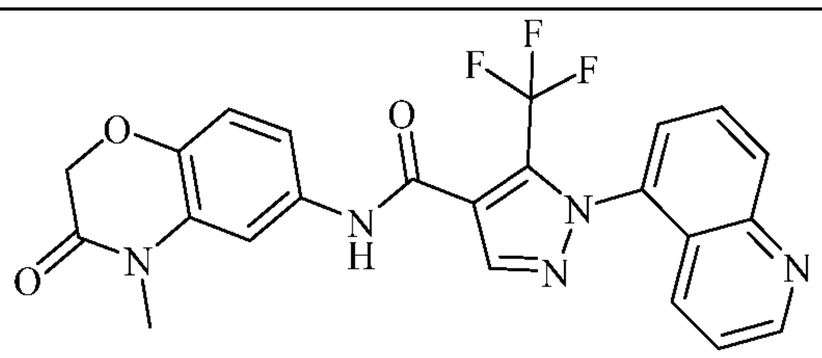
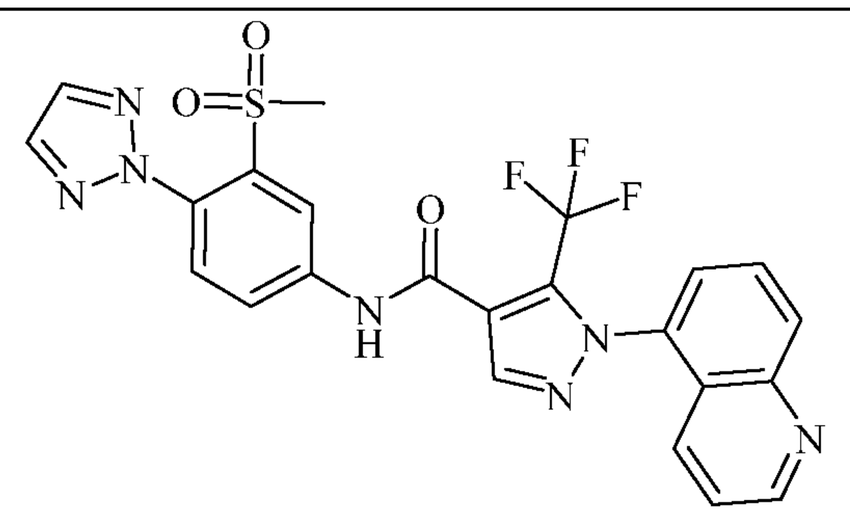
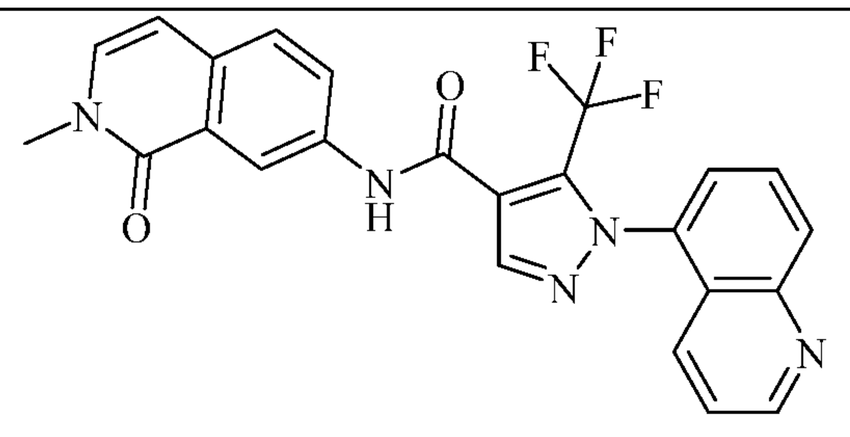
Structure	Cpd No.	Cpd Name
	**191**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**192**	N-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**193**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**194**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

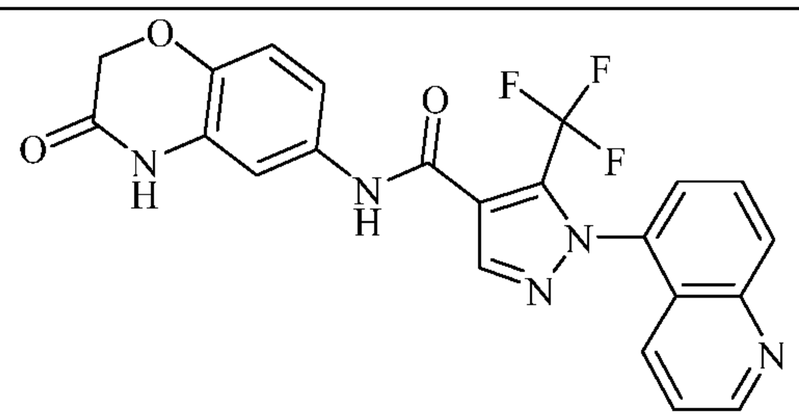
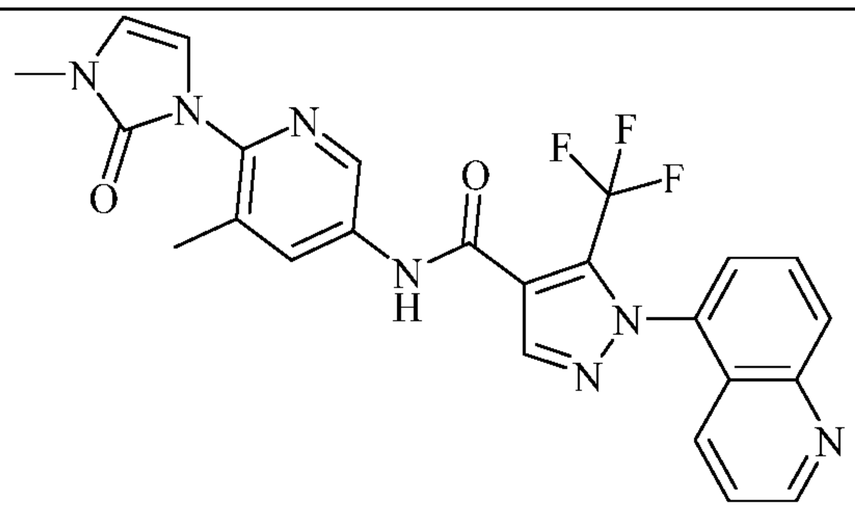
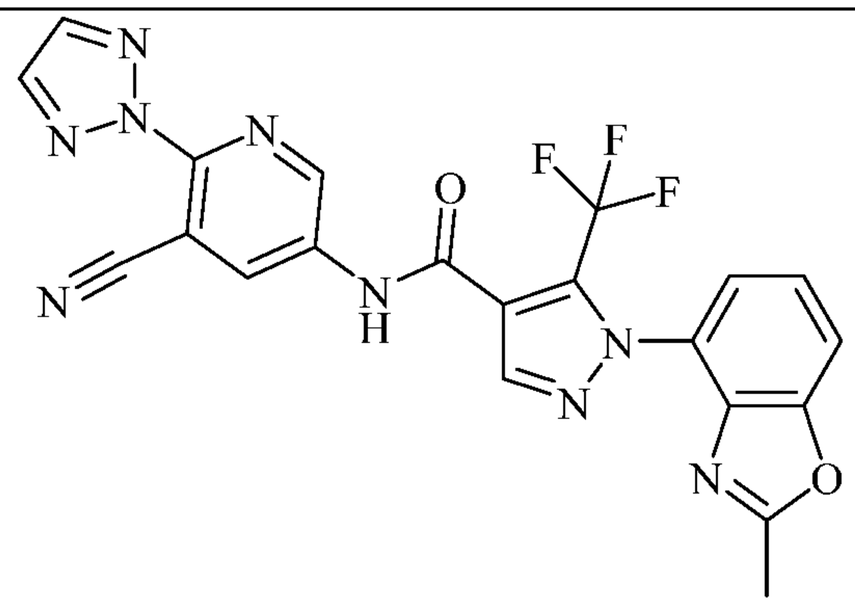
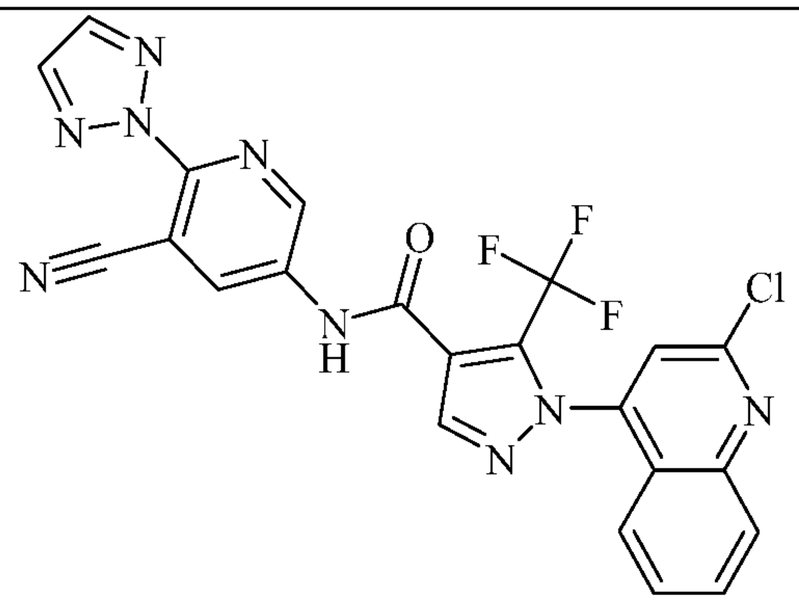
Structure	Cpd No.	Cpd Name
	**195**	N-(5-chloro-2-ethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**196**	*N* -(2,5-diethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**197**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**198**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

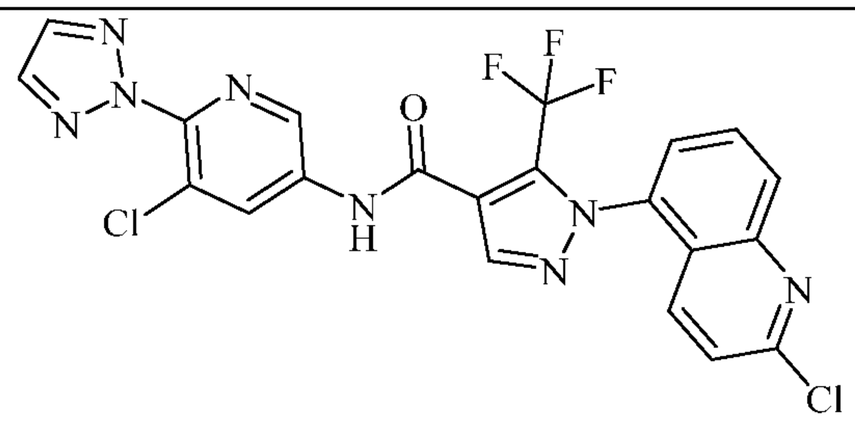
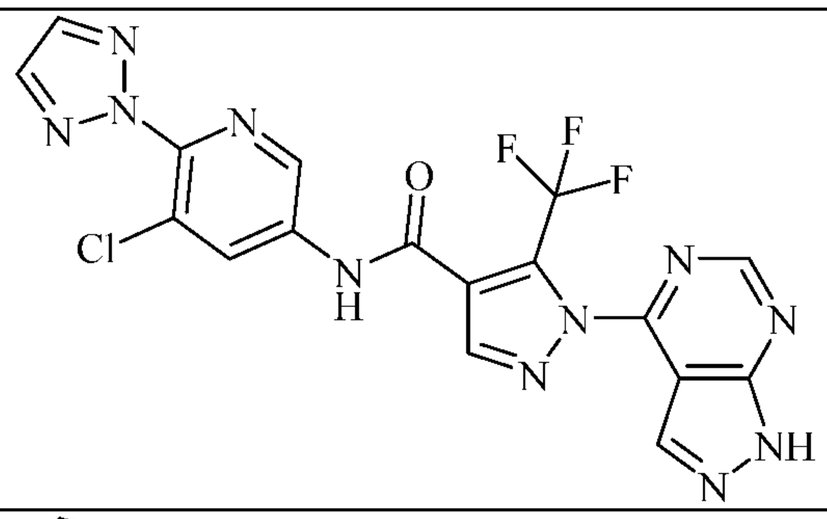
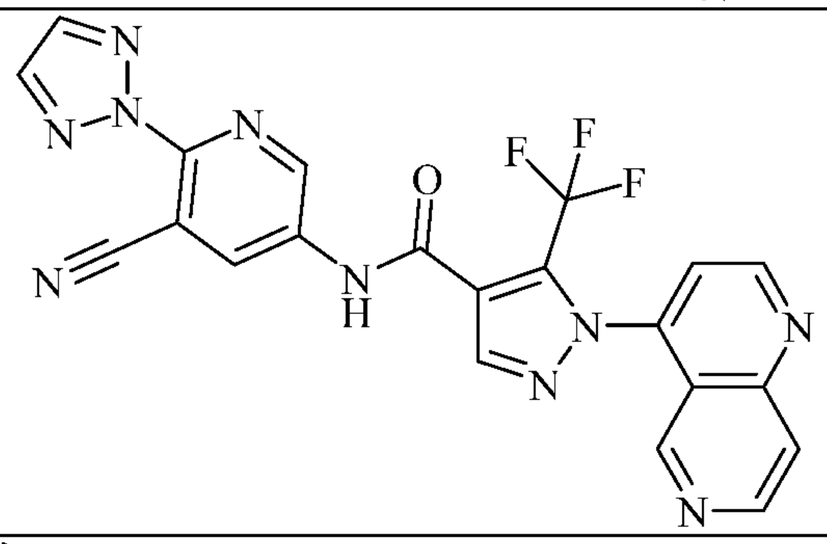
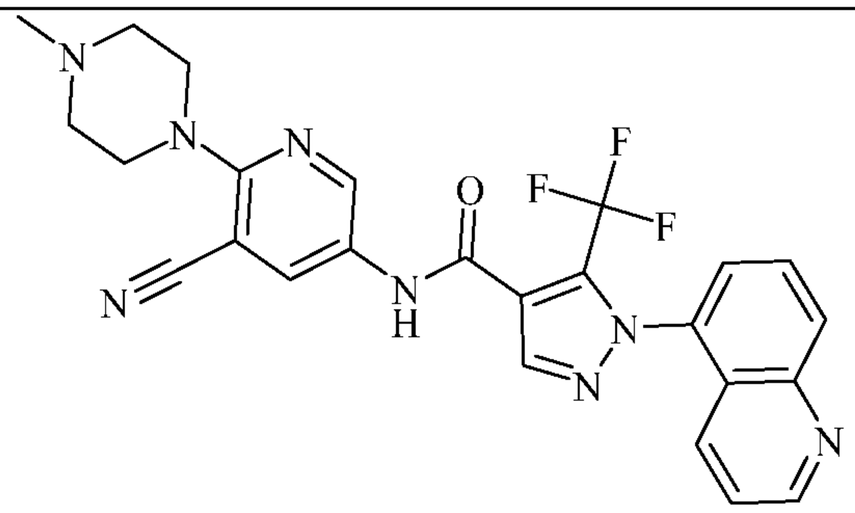
Structure	Cpd No.	Cpd Name
	**199**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**200**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**201**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-chloroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**202**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

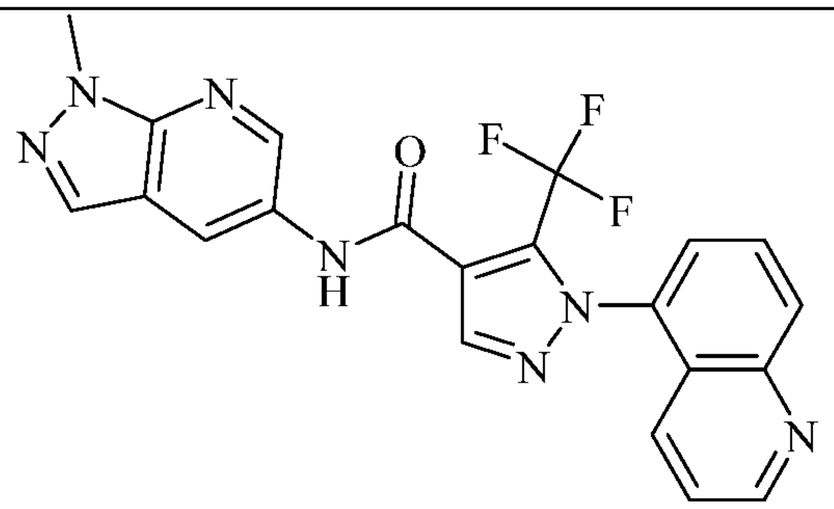
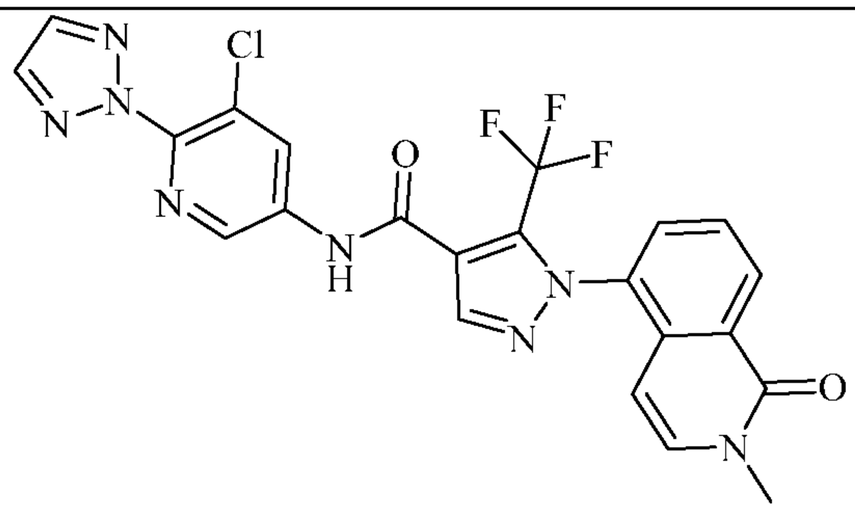
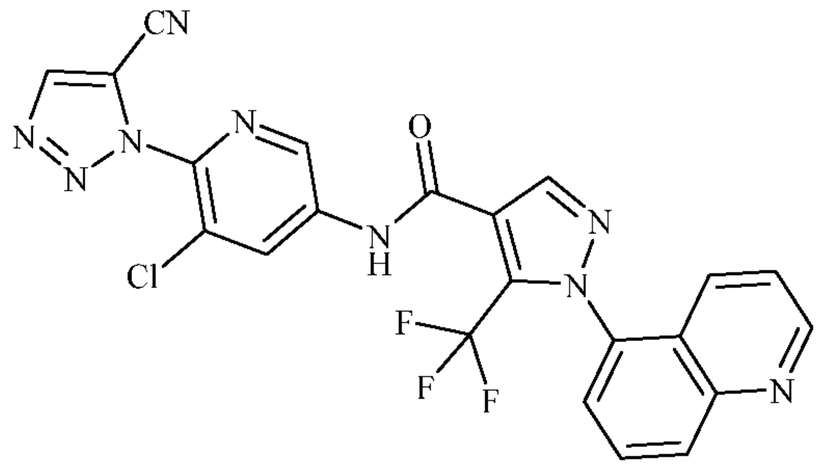
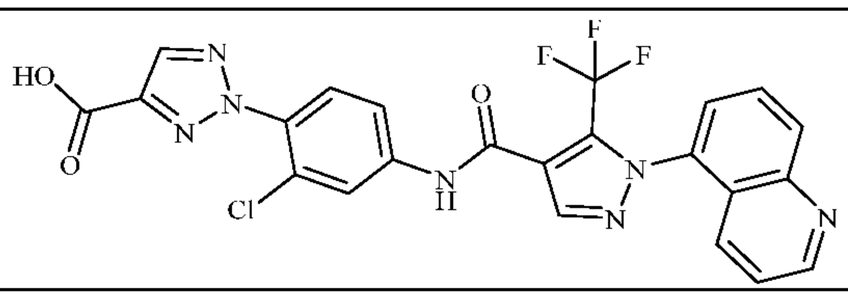
Structure	Cpd No.	Cpd Name
	**203**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**204**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**205**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**206**	1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide

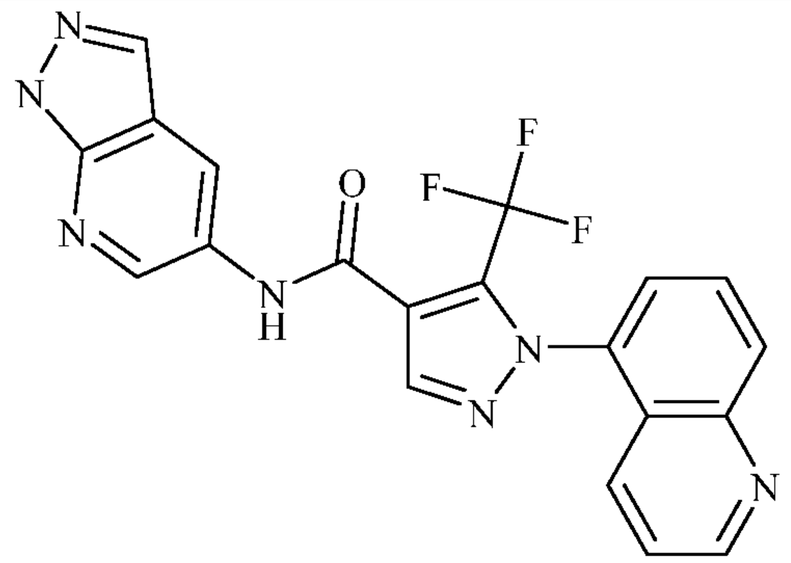
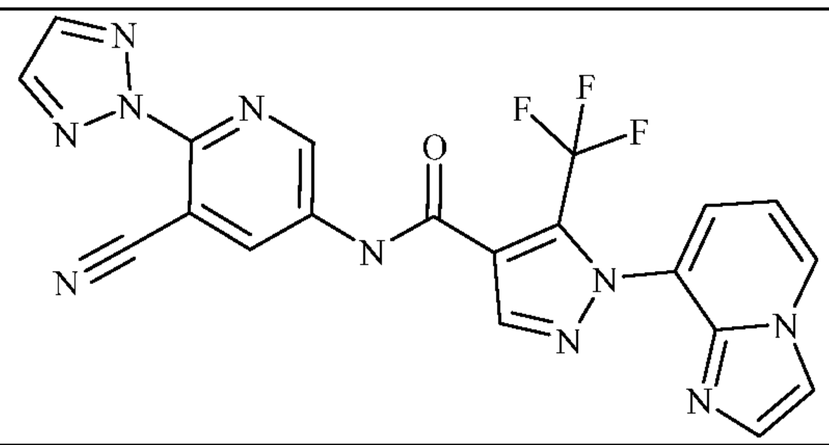
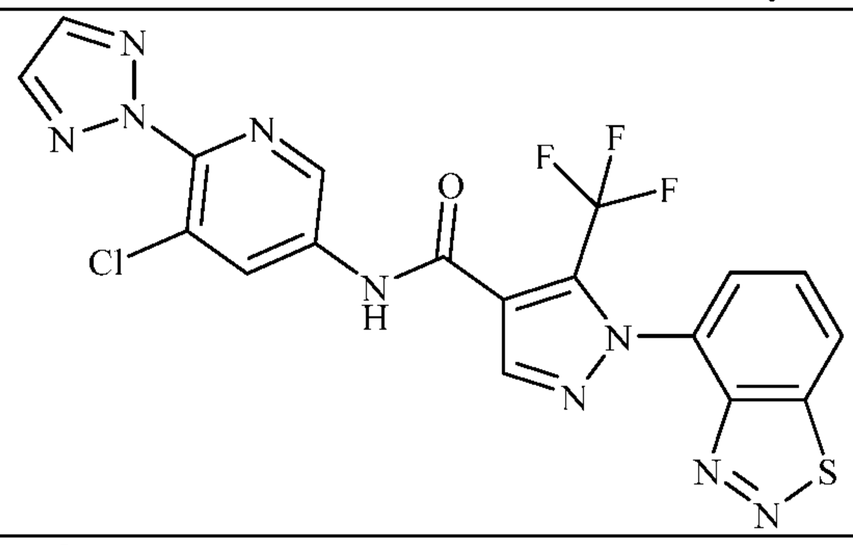
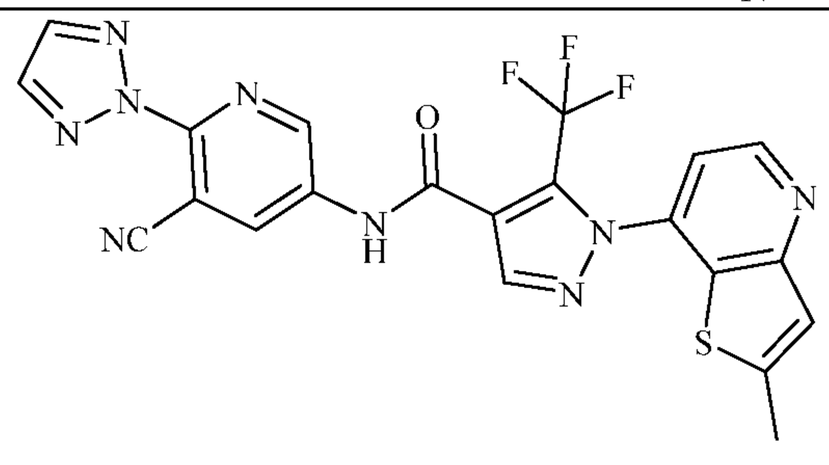
Structure	Cpd No.	Cpd Name
	**207**	1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**208**	1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**209**	1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**210**	1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**211**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**212**	*N*-(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

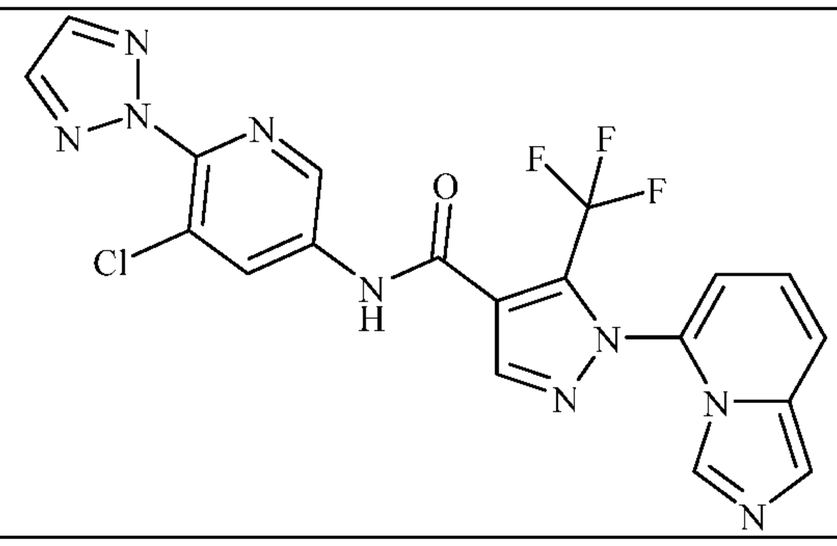
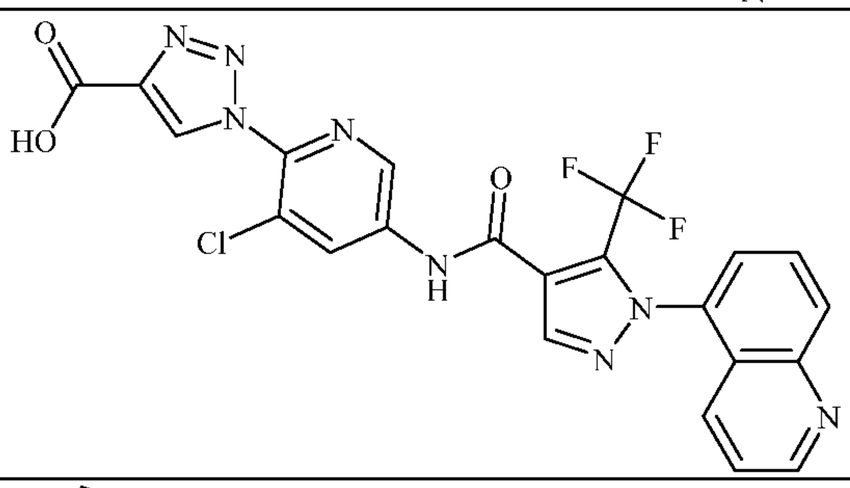
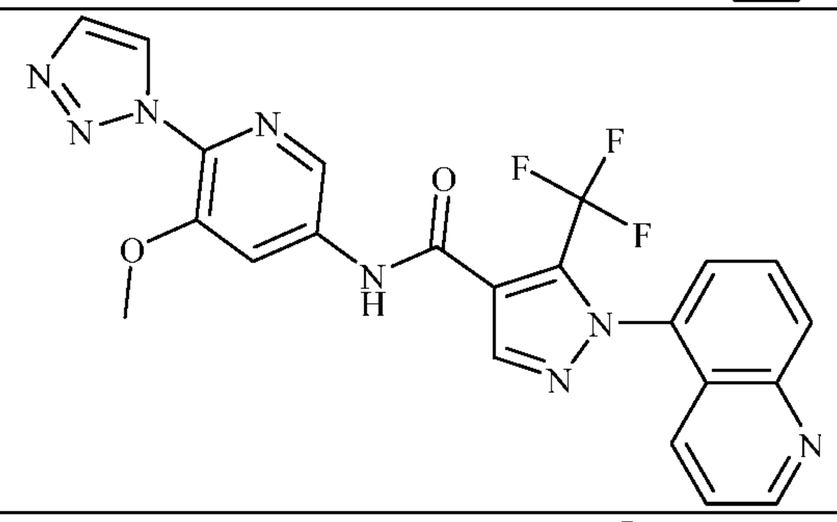
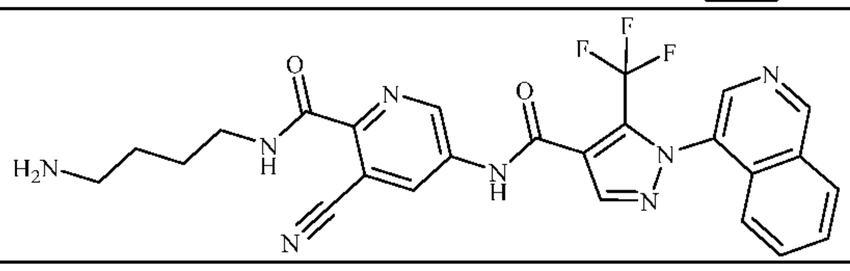
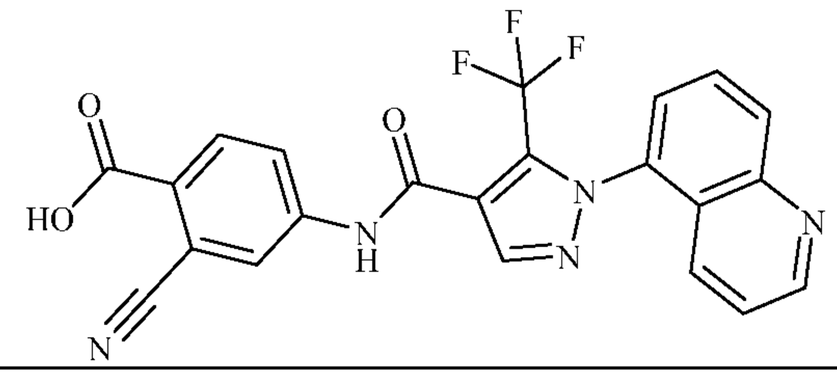
Structure	Cpd No.	Cpd Name
	**213**	*N* -(3-(methylsulfonyl)-4-(1H-1,2,3-triazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**214**	N-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**215**	*N* -(3-(methylsulfonyl)-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**216**	*N* -(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

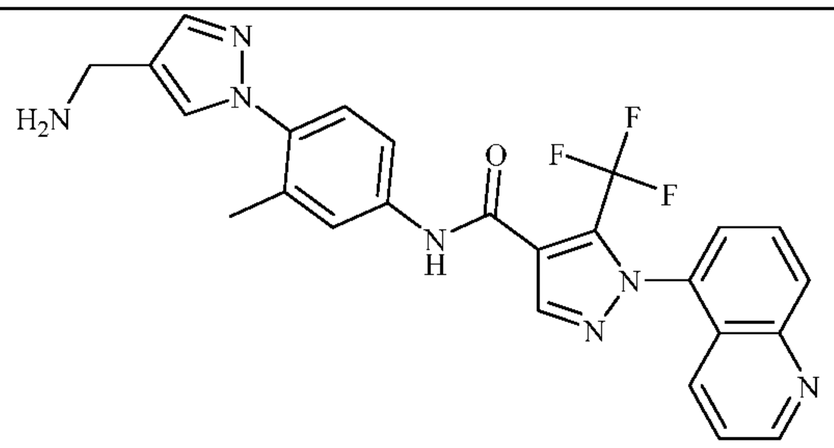
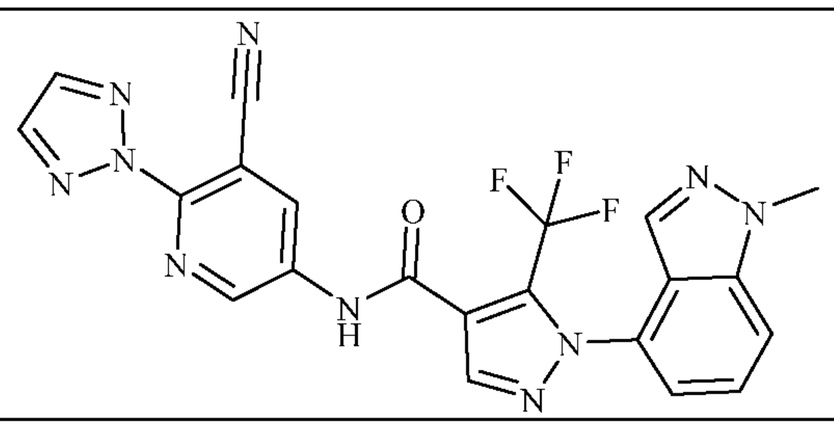
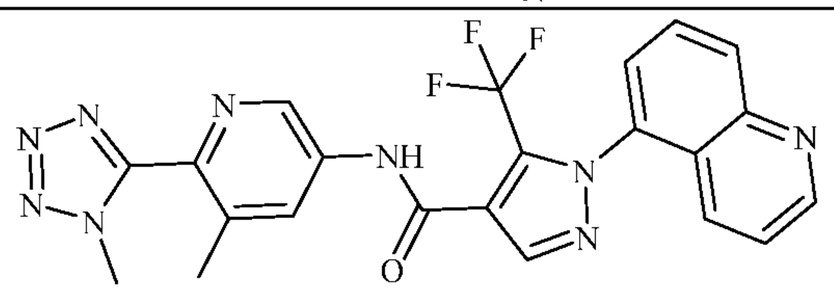
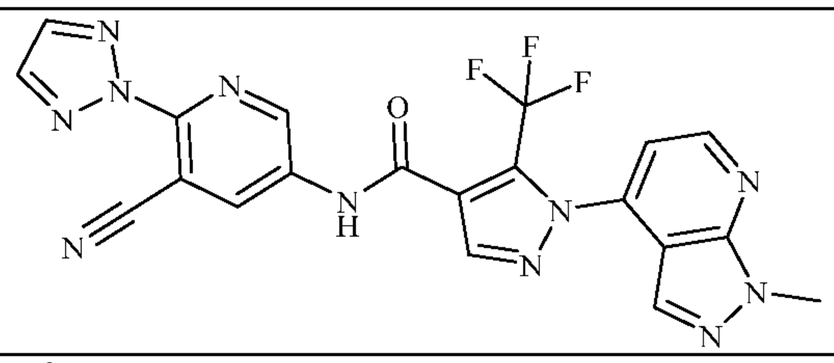
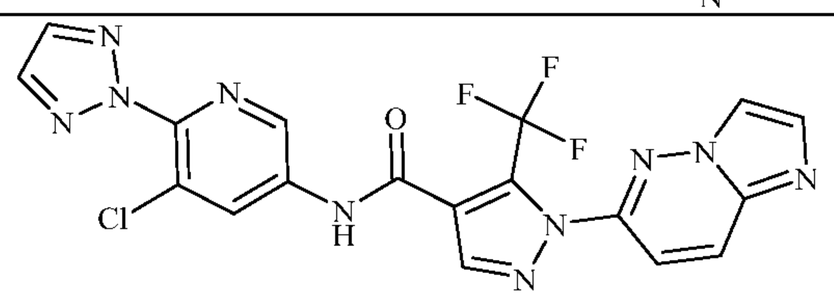
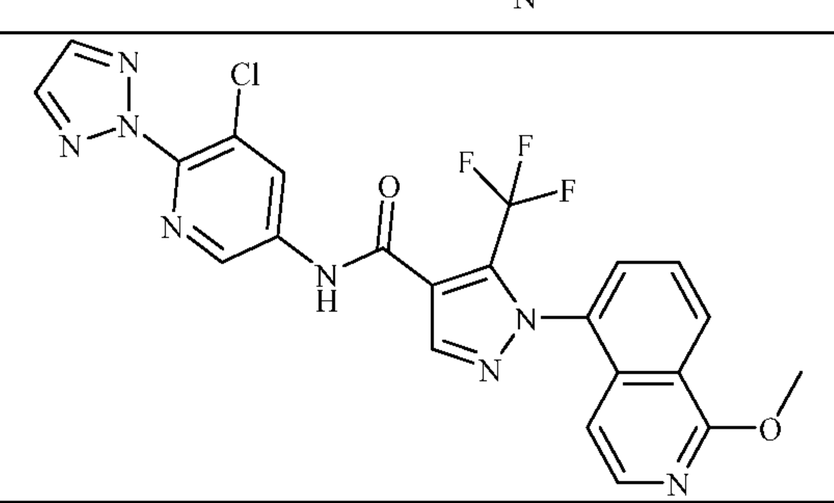
Structure	Cpd No.	Cpd Name
	**217**	N-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**218**	*N* -(5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**219**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**220**	1-(2-chloroquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

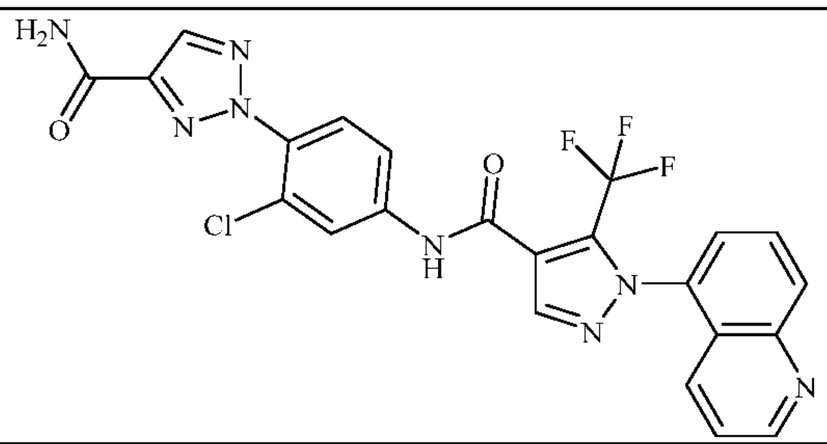
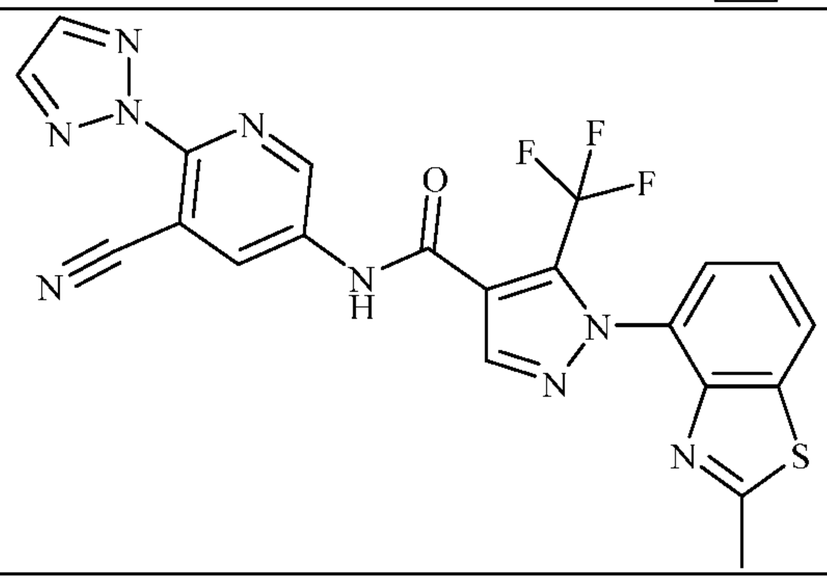
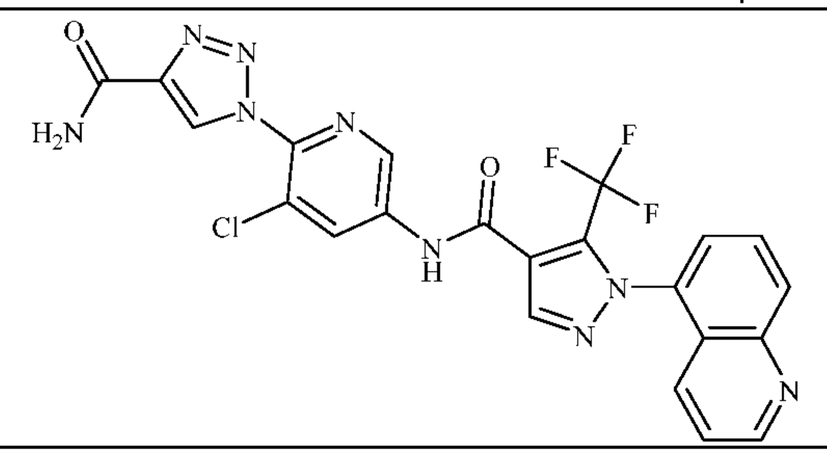
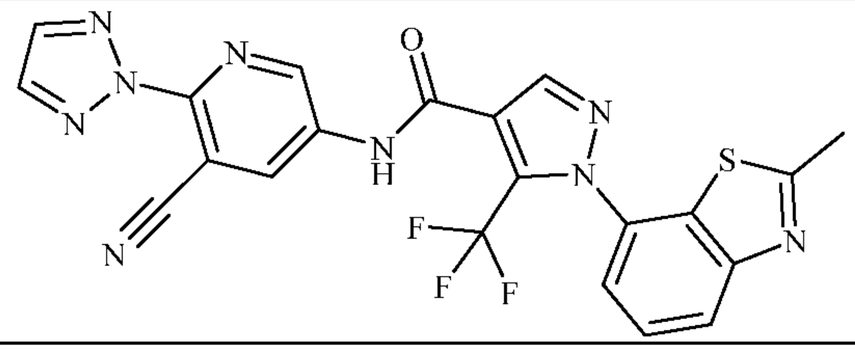
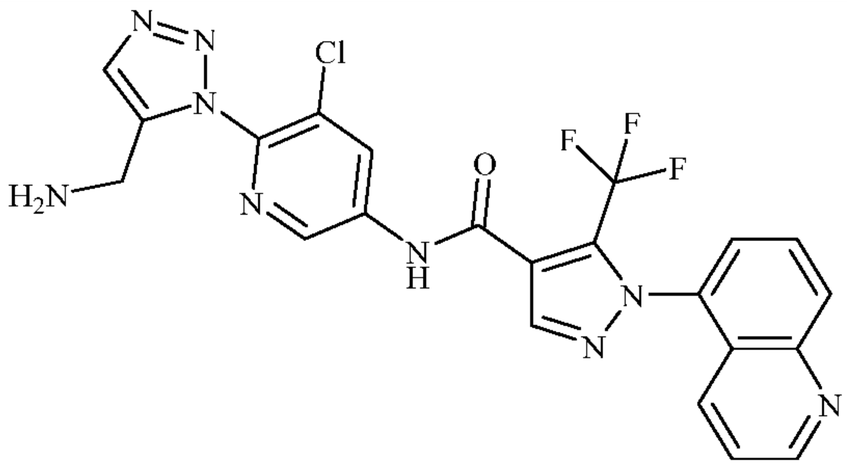
Structure	Cpd No.	Cpd Name
	**221**	*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-chloroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**222**	*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**223**	*N*-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**224**	*N*-(5-cyano-6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide

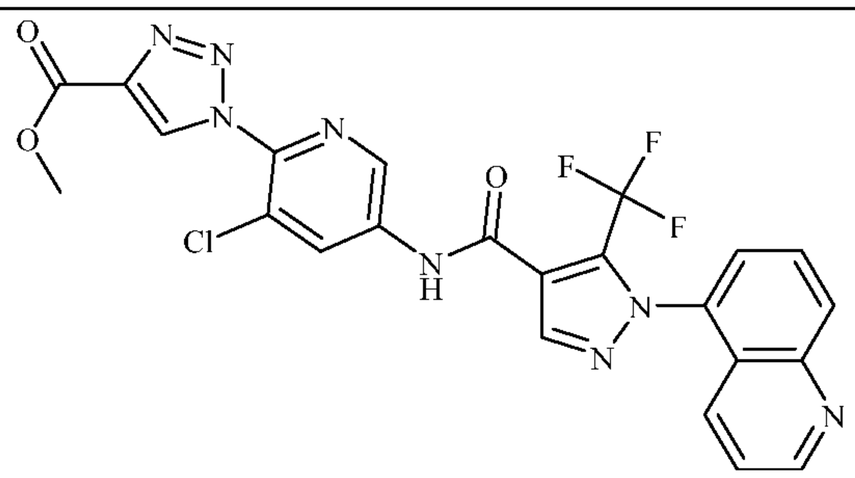
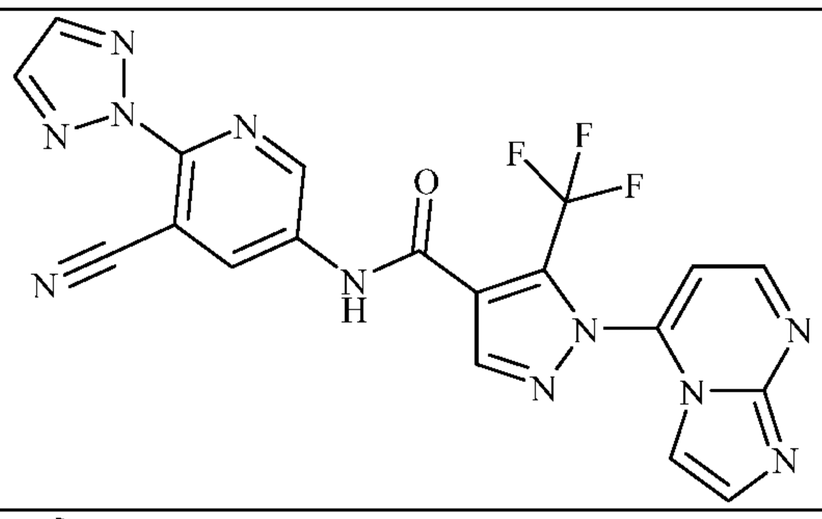
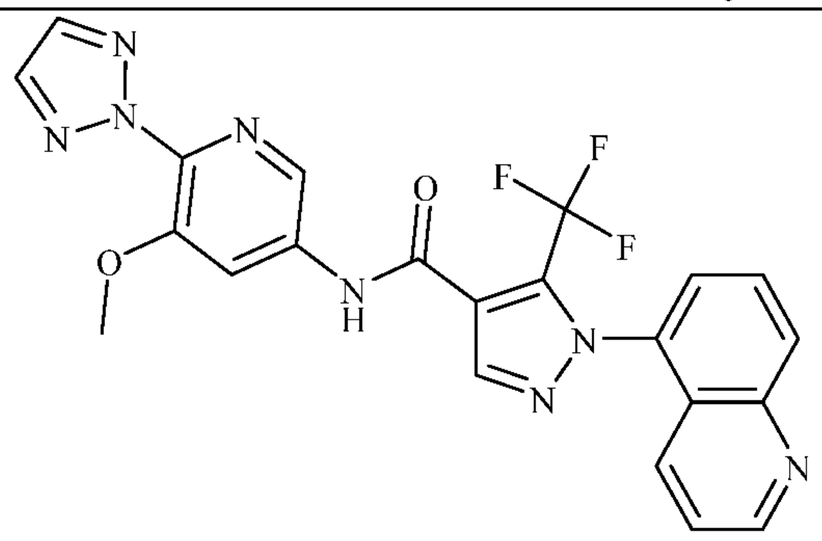
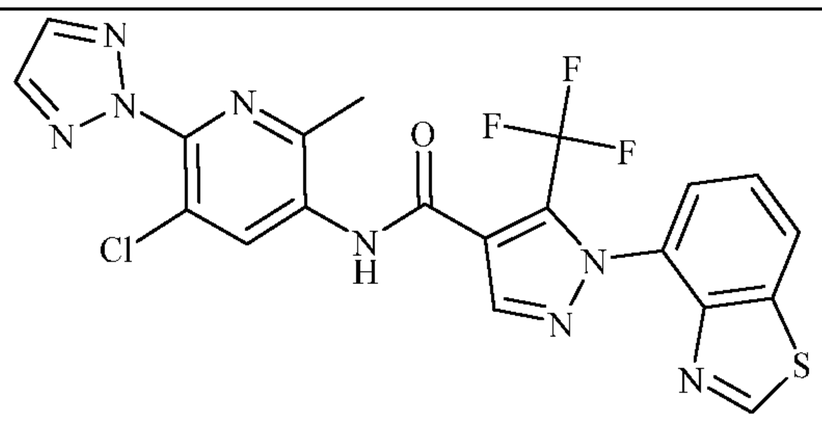
Structure	Cpd No.	Cpd Name
	**225**	N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**226**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**227**	N-(5-chloro-6-(5-cyano-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**228**	2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylic acid

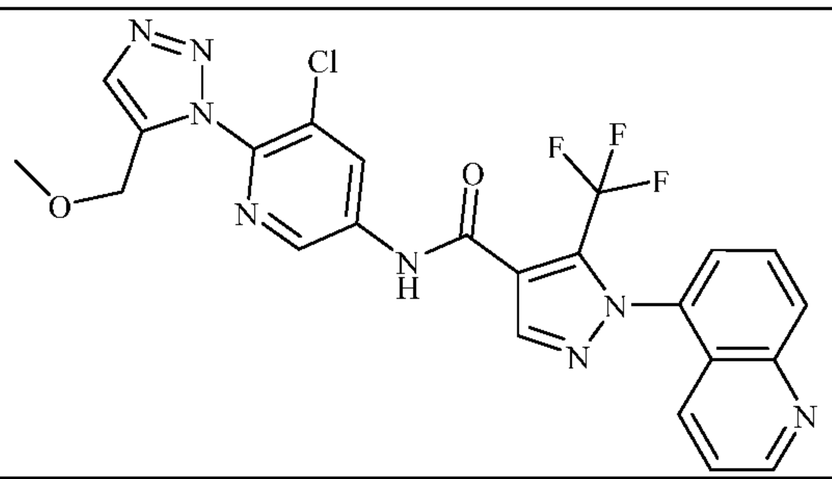
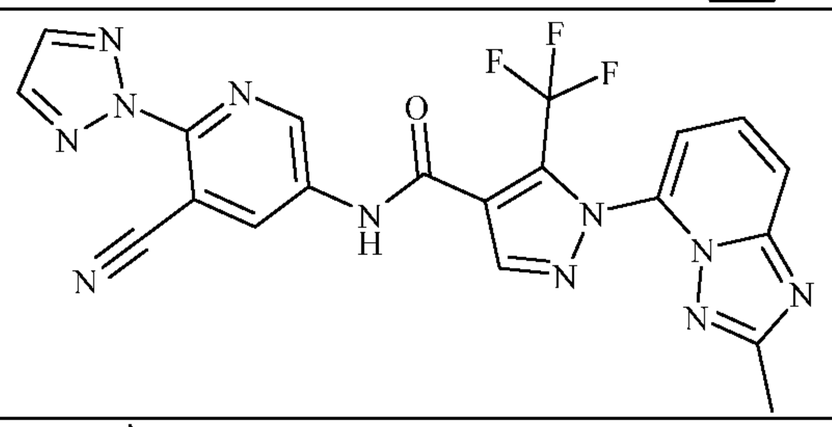
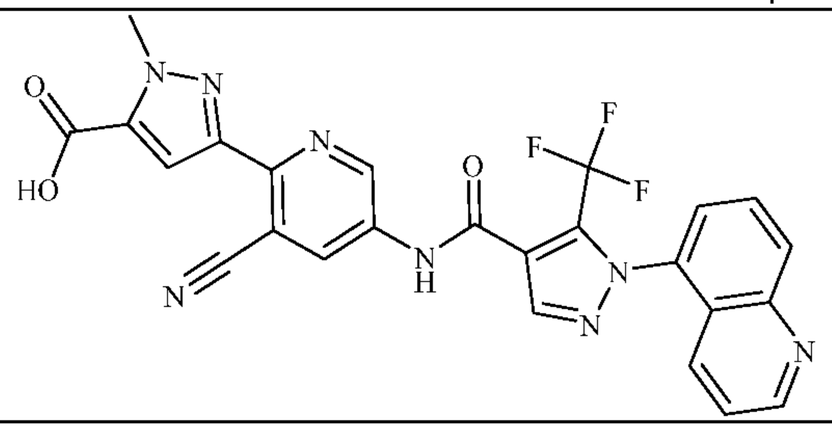
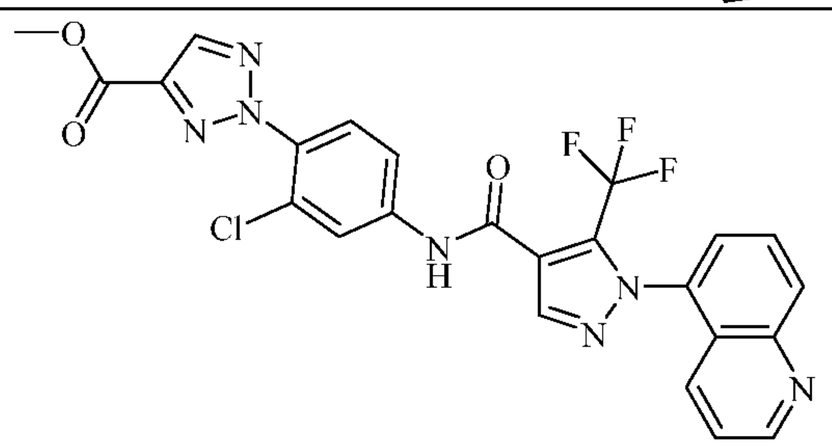
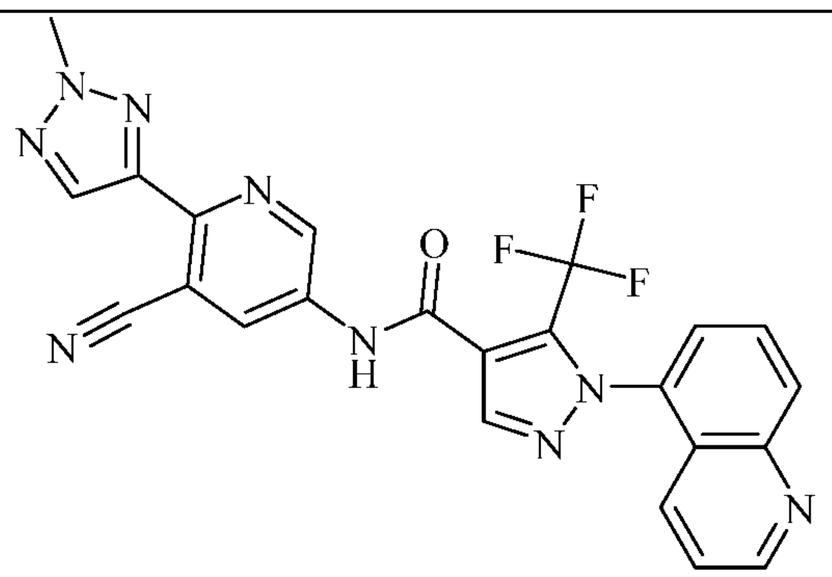
Structure	Cpd No.	Cpd Name
	**229**	N-(1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**230**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**231**	1-(benzo[d][1,2,3]thiadiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**232**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

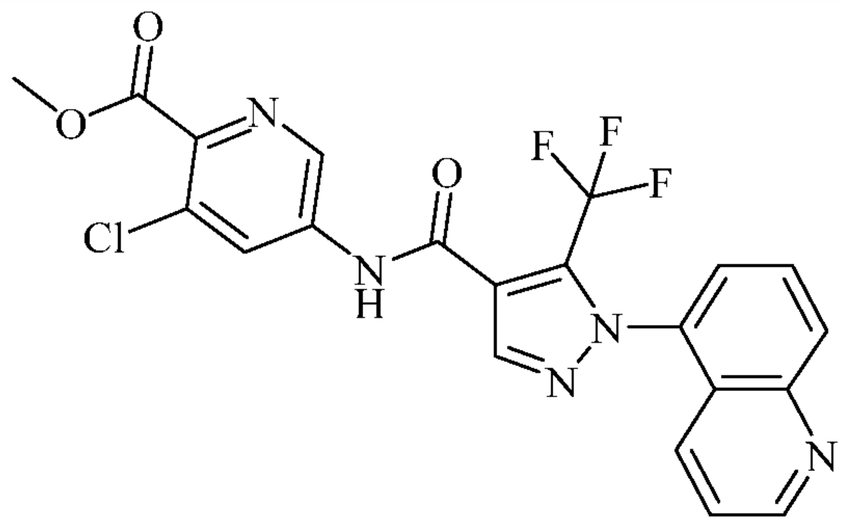
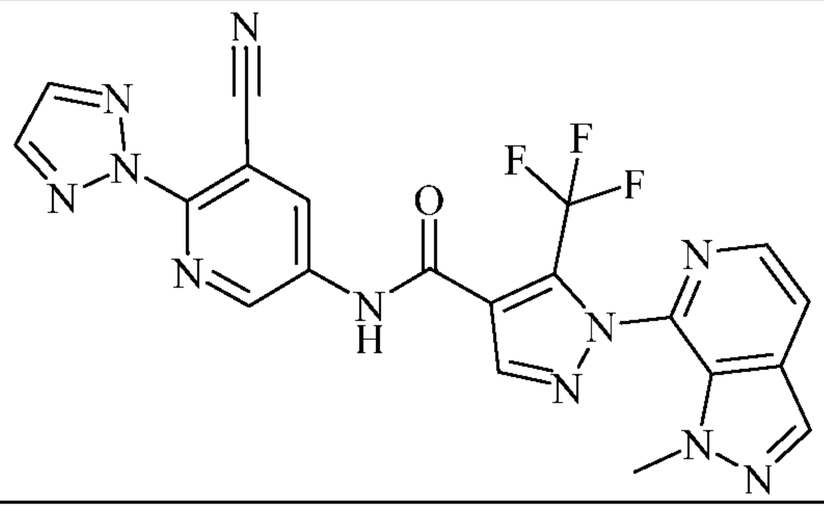
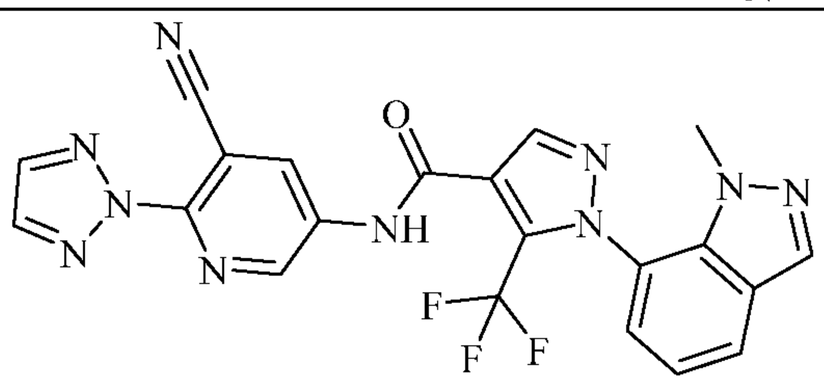
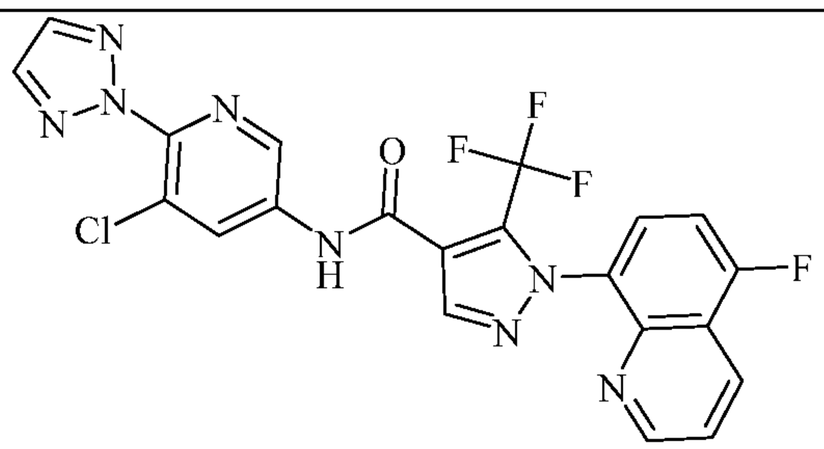
Structure	Cpd No.	Cpd Name
	**233**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**234**	1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylic acid
	**235**	N-(5-methoxy-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**236**	N-(4-aminobutyl)-3-cyano-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide
	**237**	2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoic acid

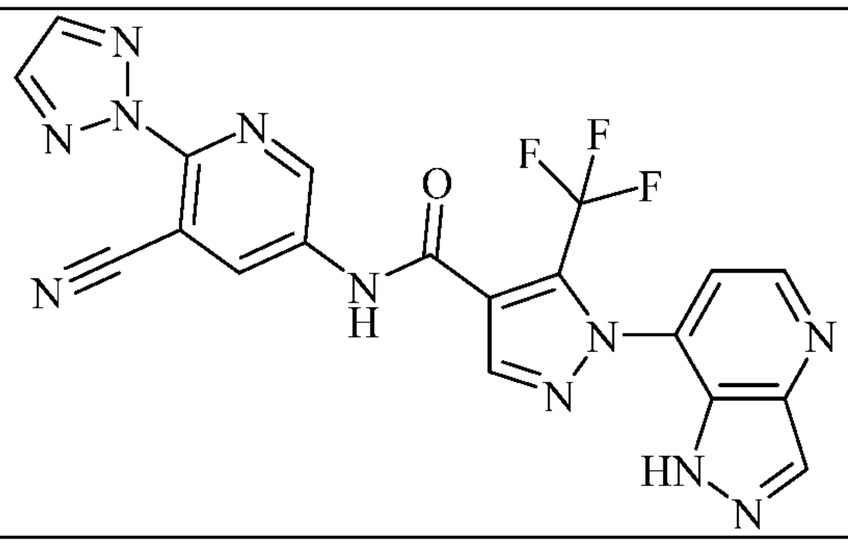
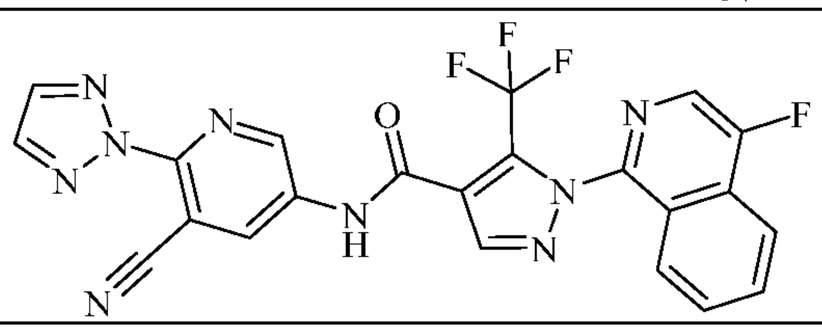
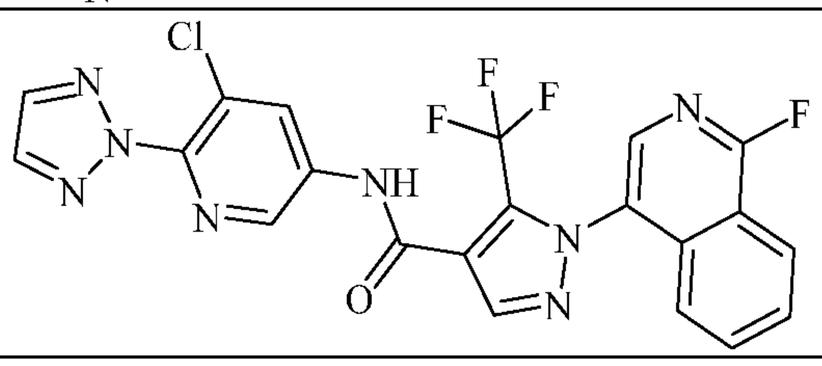
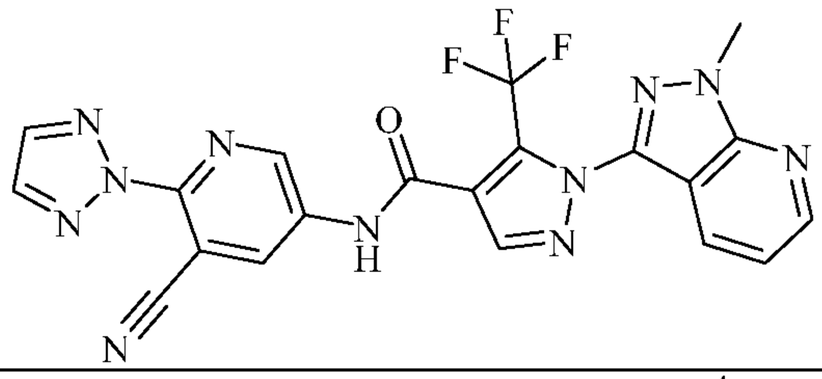
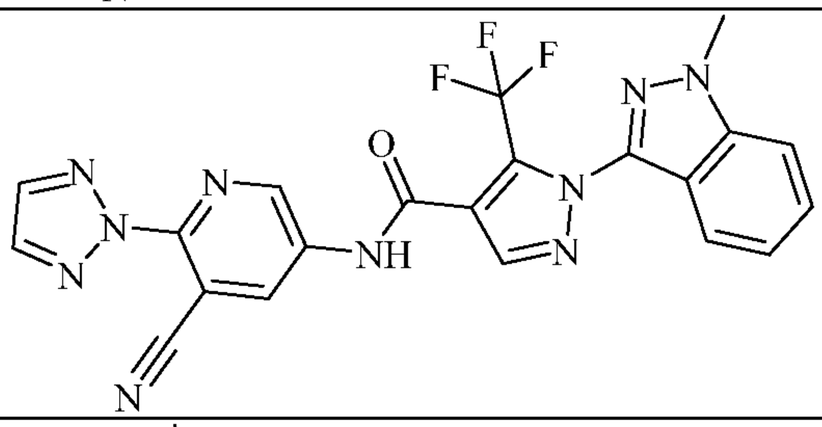
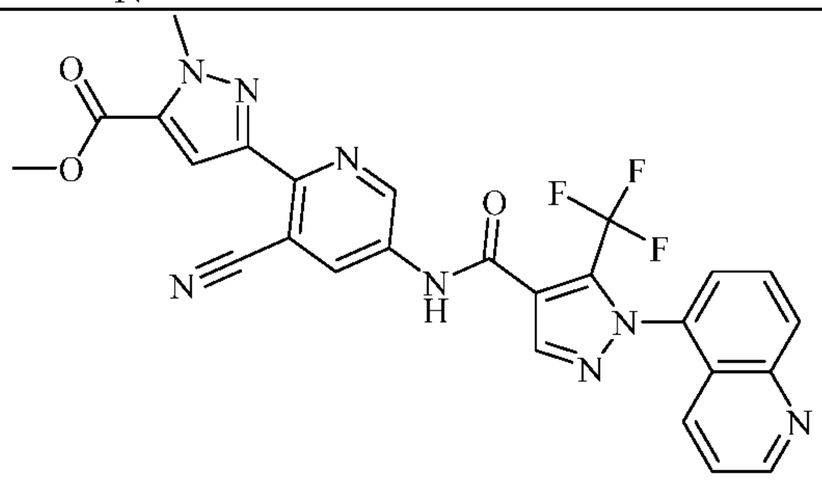
Structure	Cpd No.	Cpd Name
	**238**	N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-methylphenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**239**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**240**	N-(5-methyl-6-(1-methyl-1H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**241**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**242**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-b]pyridazin-6-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**243**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

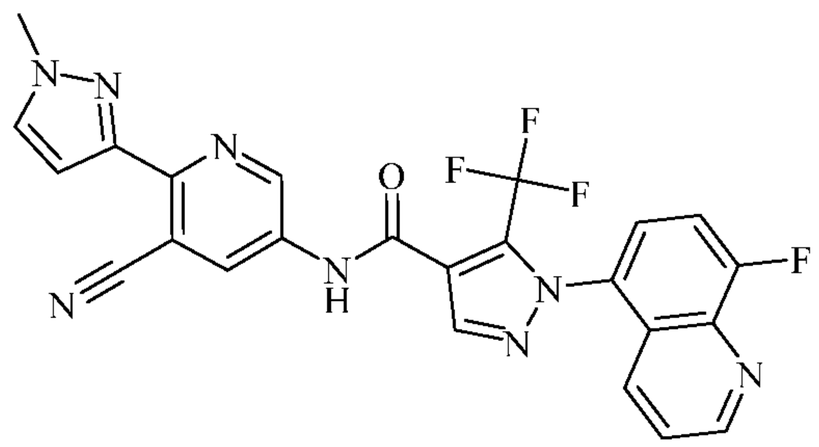
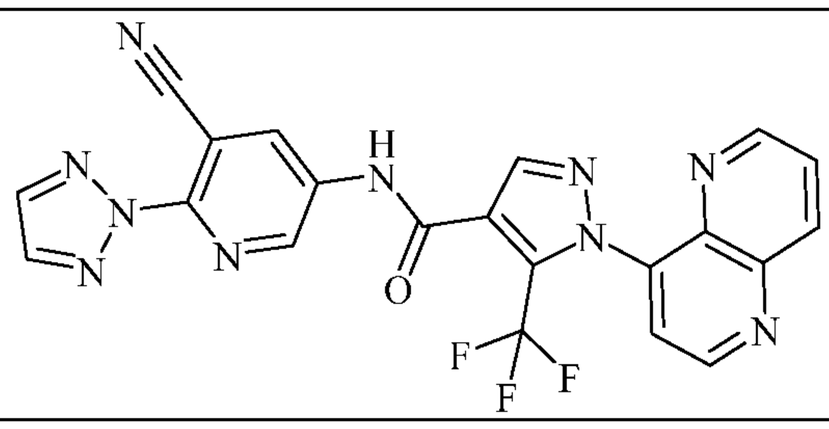
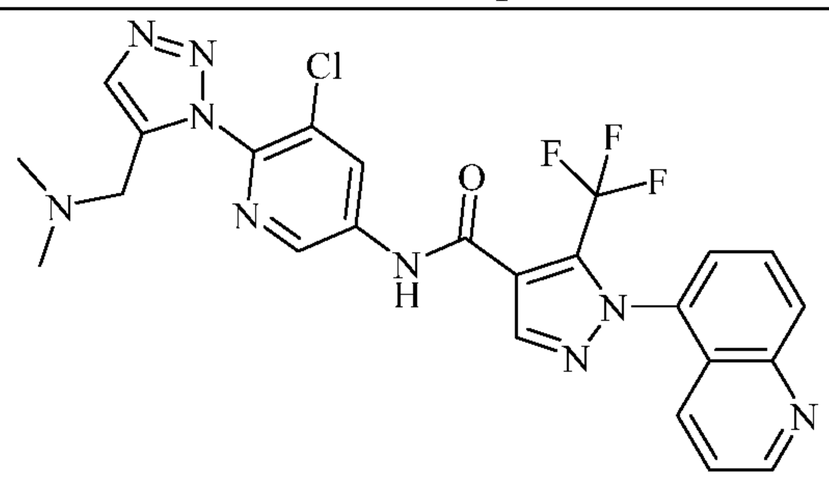
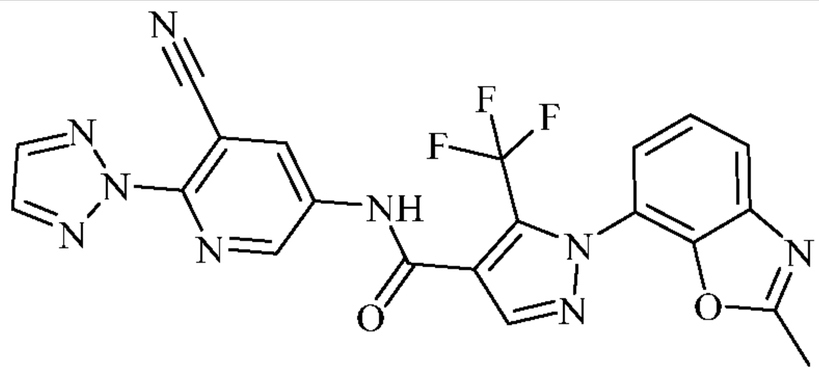
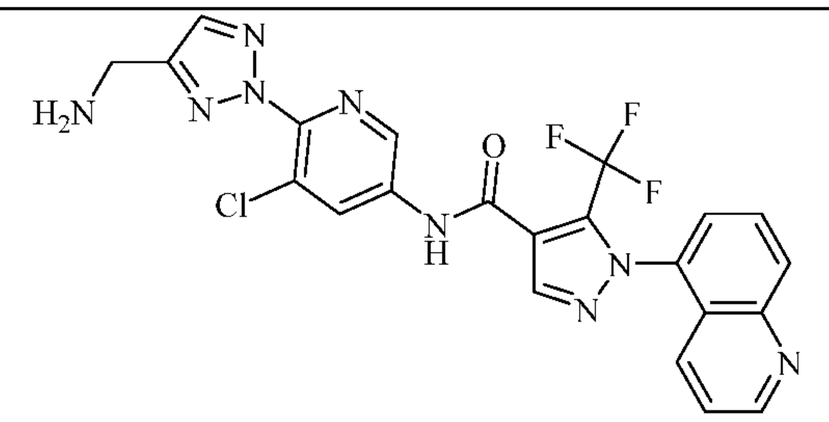
Structure	Cpd No.	Cpd Name
	**244**	2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxamide
	**245**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**246**	1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxamide
	**247**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**248**	N-(6-(5-(aminomethyl)-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

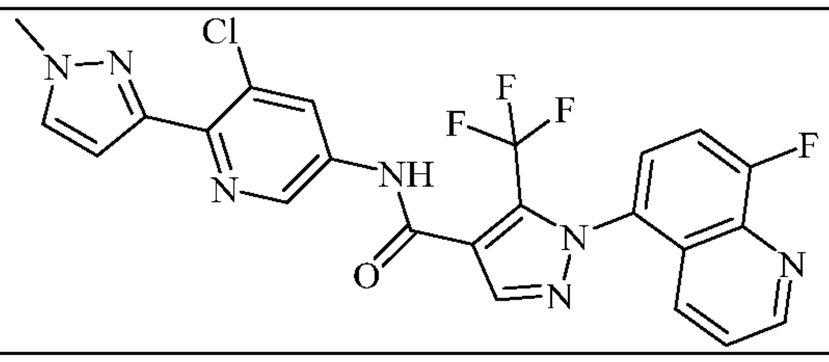
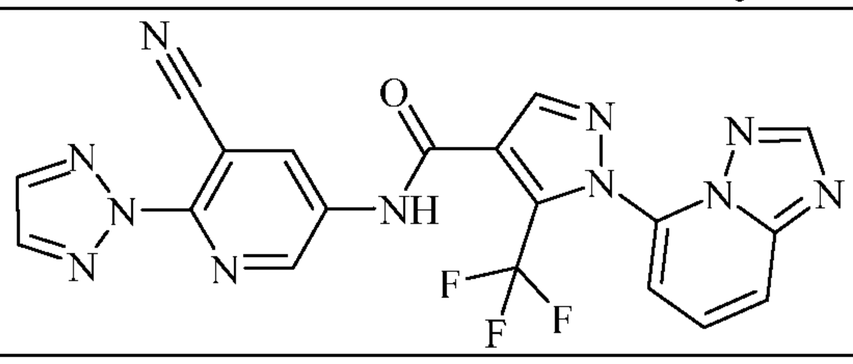
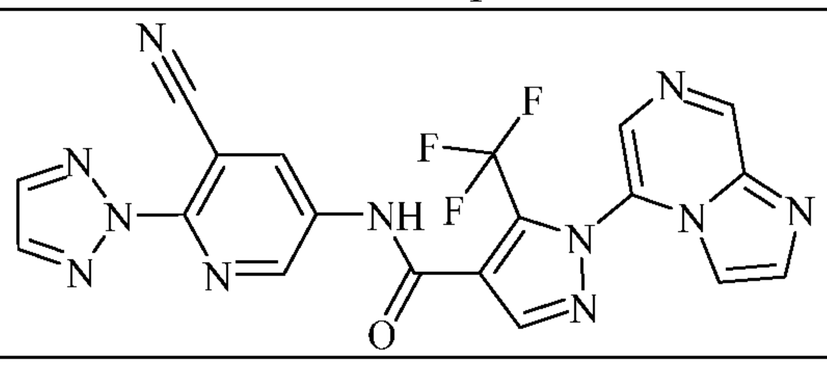
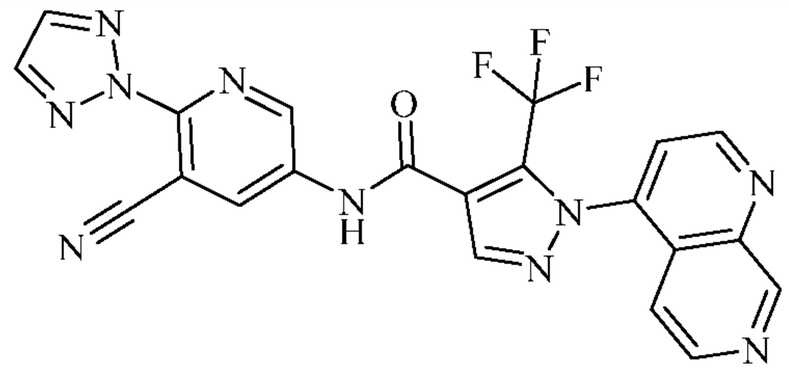
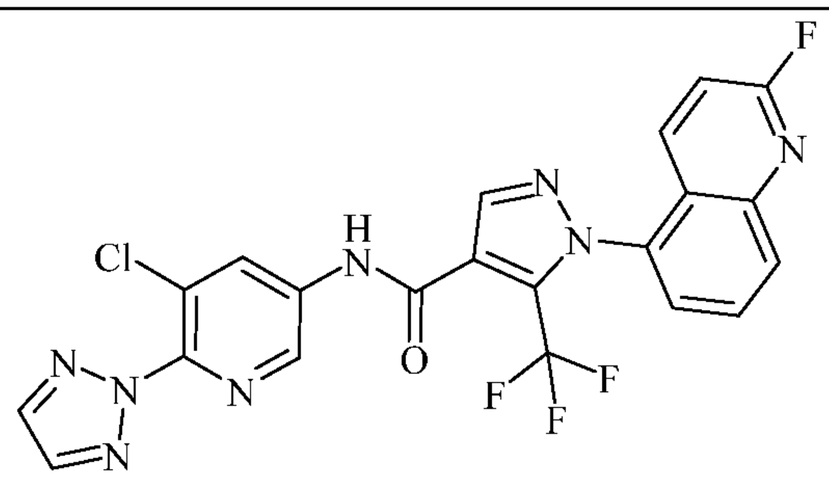
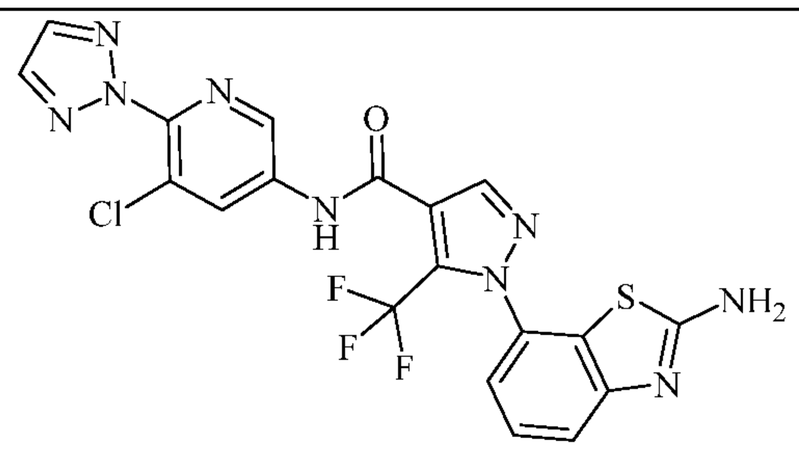
Structure	Cpd No.	Cpd Name
	**249**	methyl 1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate
	**250**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrimidin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**251**	N-(5-methoxy-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**252**	1-(benzo[d]thiazol-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

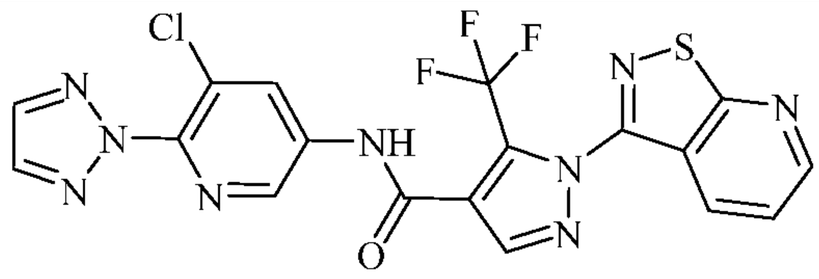
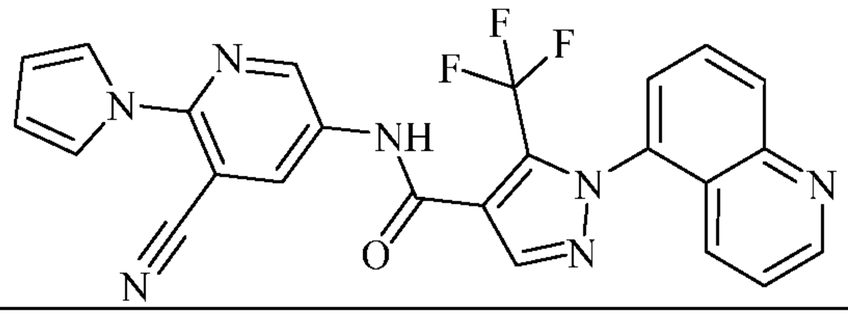
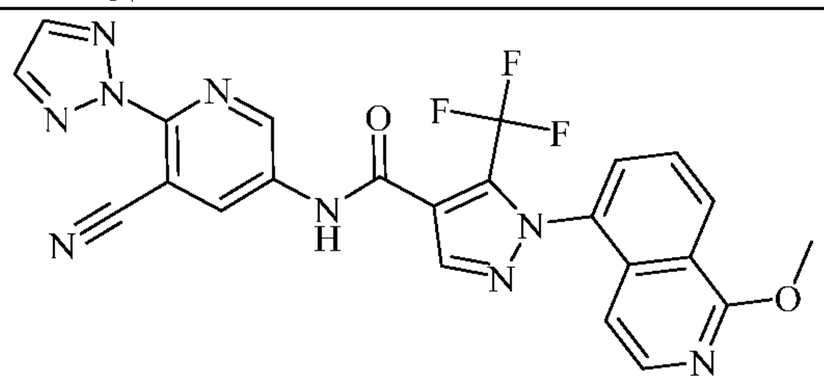
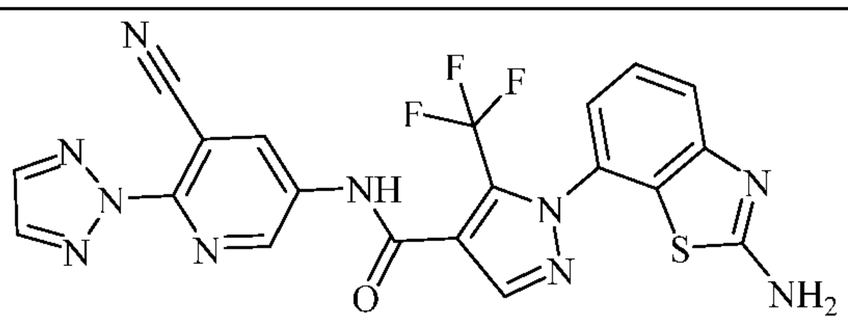
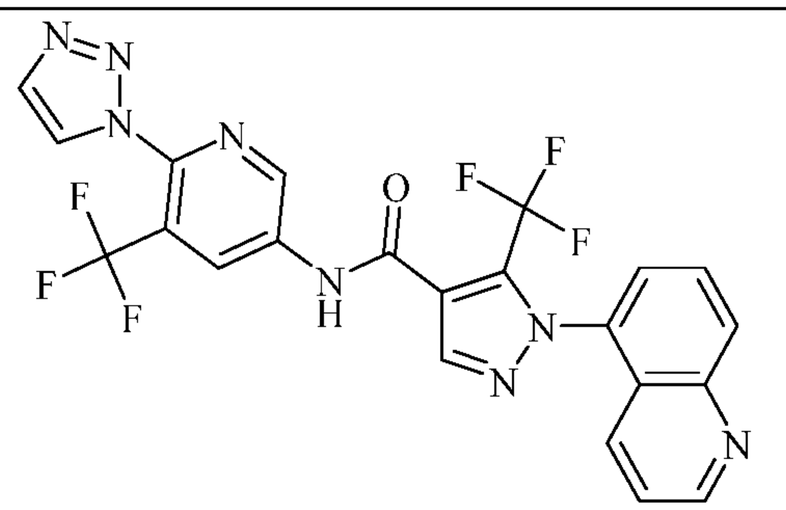
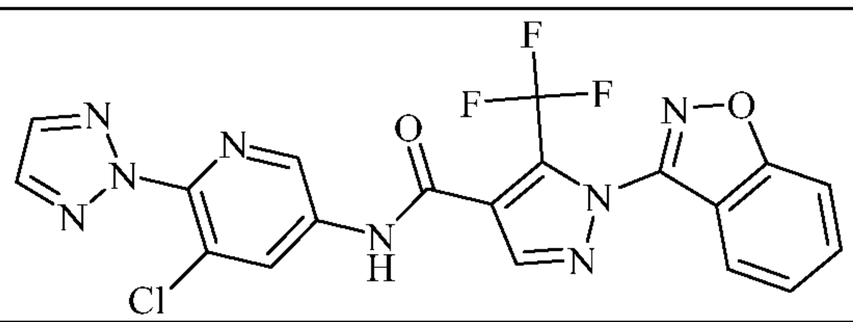
Structure	Cpd No.	Cpd Name
	**253**	N-(5-chloro-6-(5-(methoxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**254**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**255**	3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylic acid
	**256**	methyl 2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylate
	**257**	N-(5-cyano-6-(2-methyl-2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

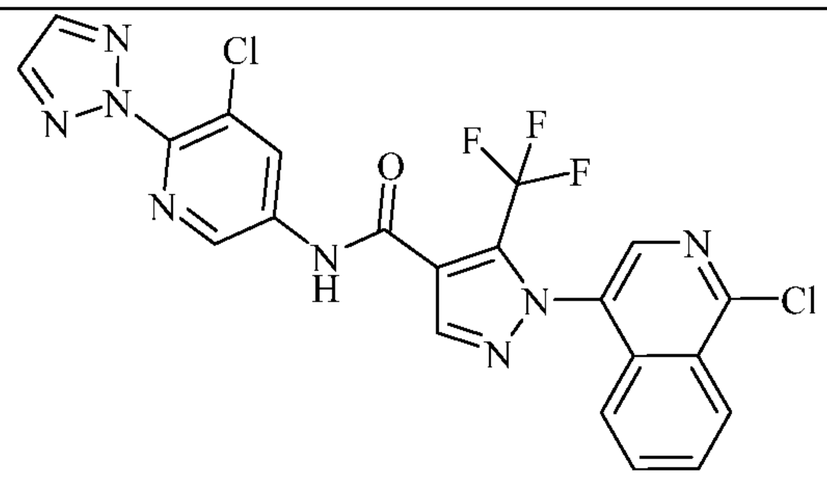
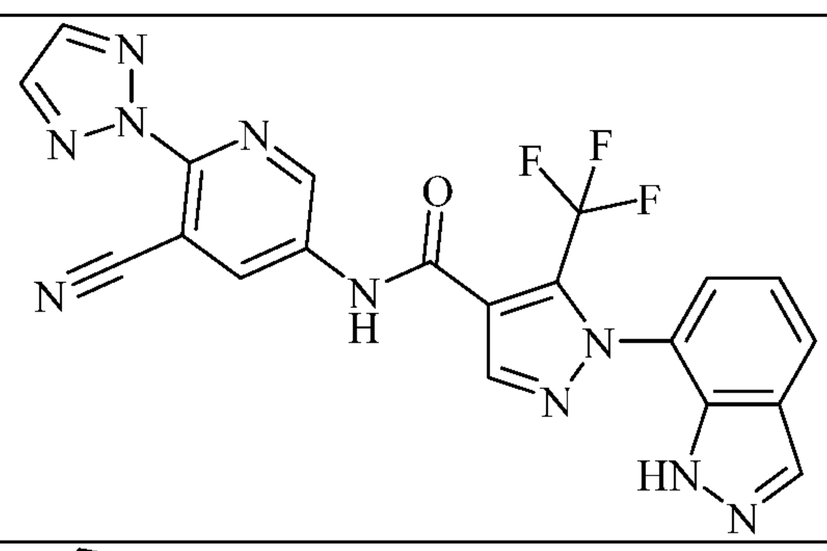
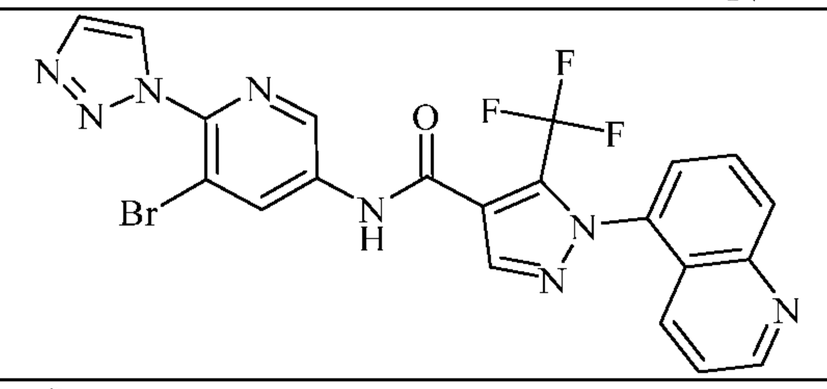
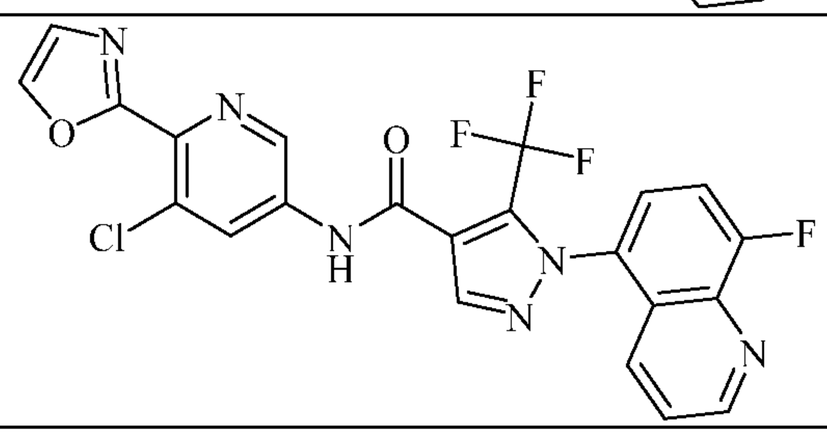
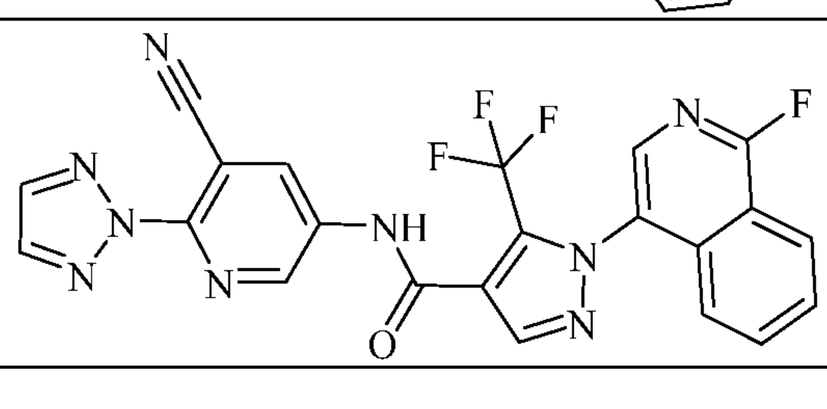
Structure	Cpd No.	Cpd Name
	**258**	methyl 3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate
	**259**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**260**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**261**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoroquinolin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

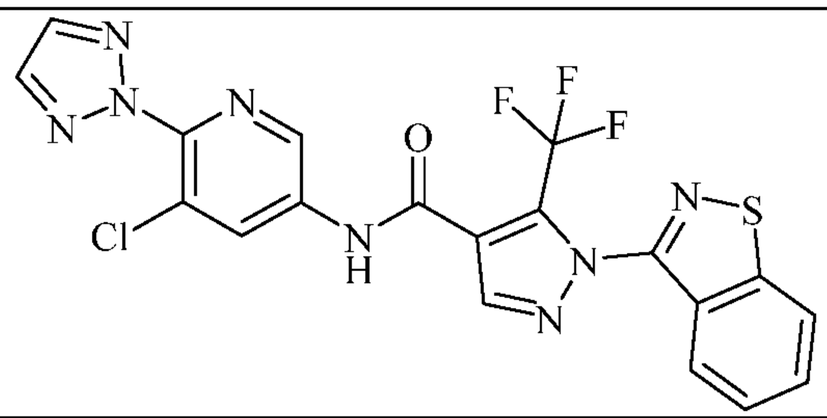
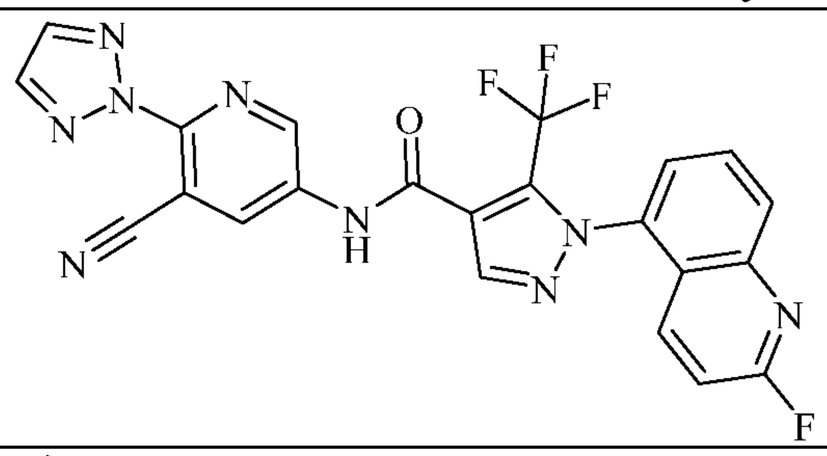
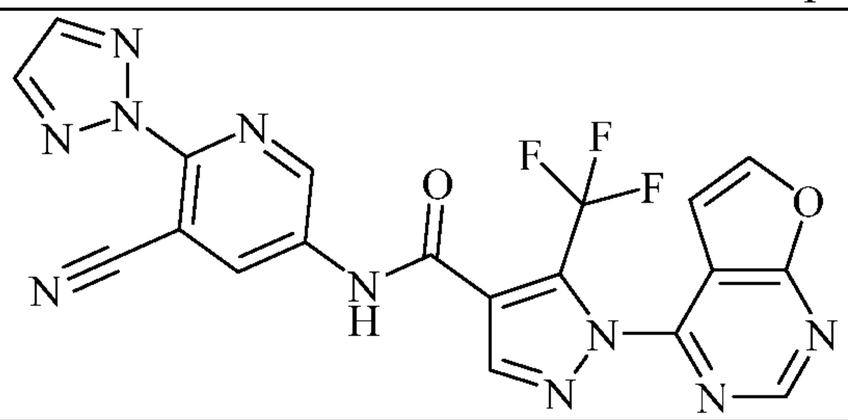
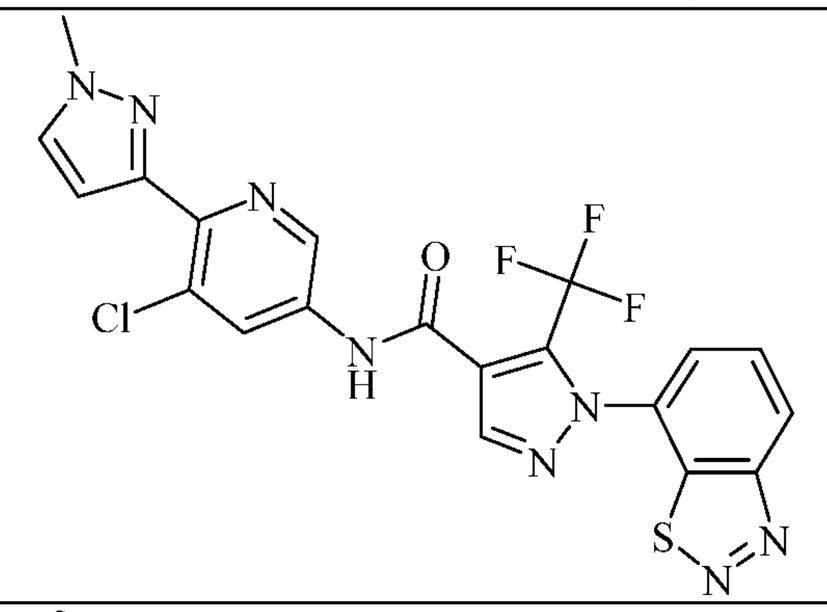
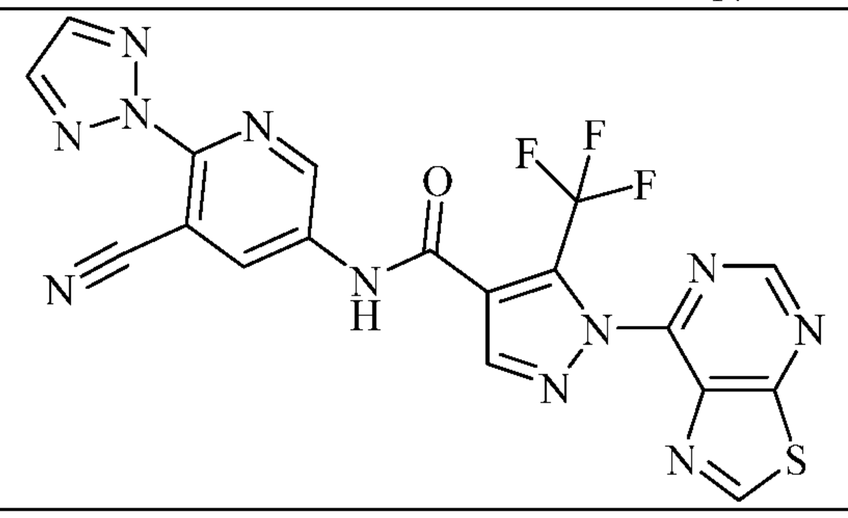
Structure	Cpd No.	Cpd Name
	**262**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[4,3-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**263**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoroisoquinolin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**264**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**265**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**266**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**267**	methyl 3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylate

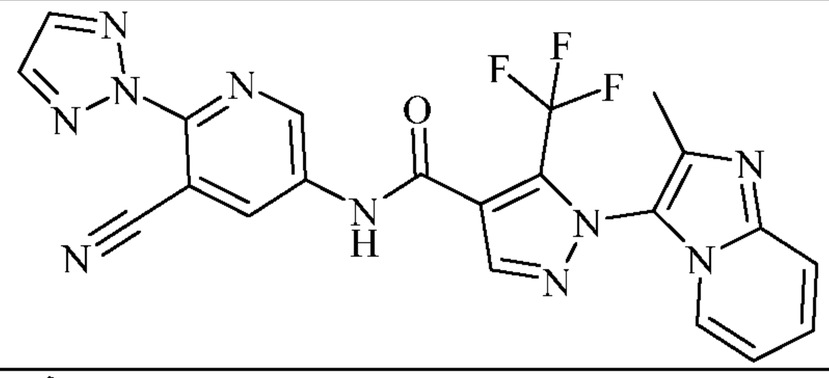
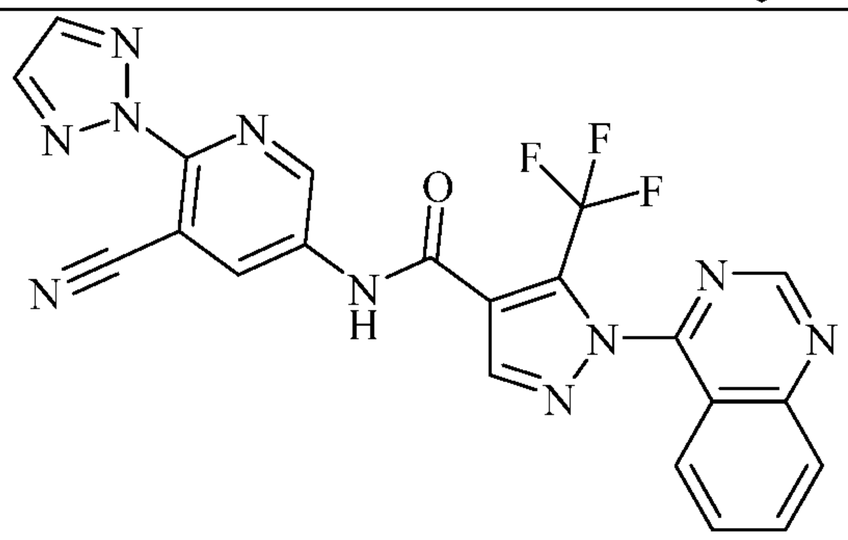
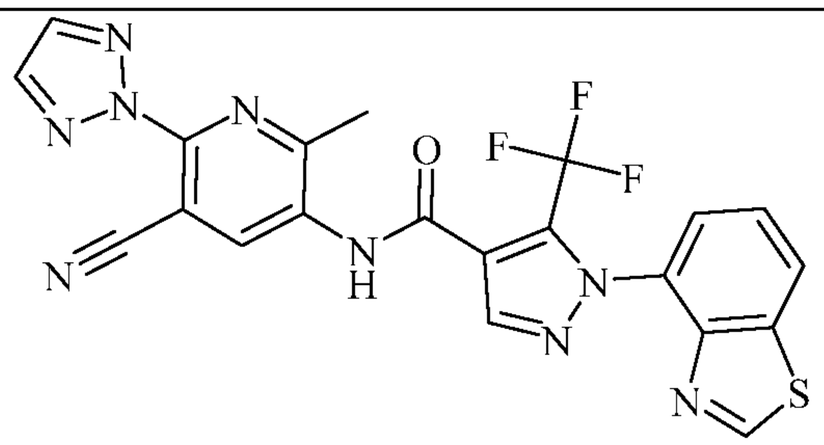
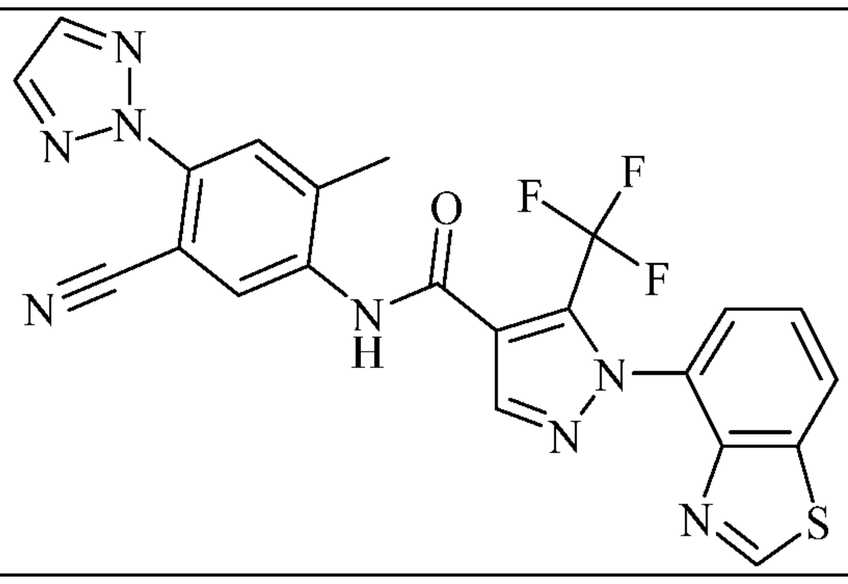
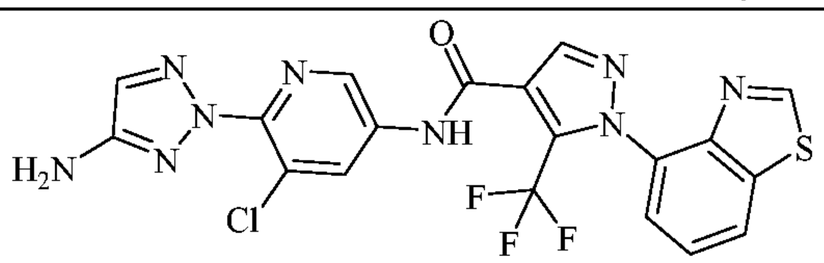
Structure	Cpd No.	Cpd Name
	**268**	N-(5-cyano-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**269**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,5-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**270**	N-(5-chloro-6-(5-((dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**271**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**272**	N-(6-(4-(aminomethyl)-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

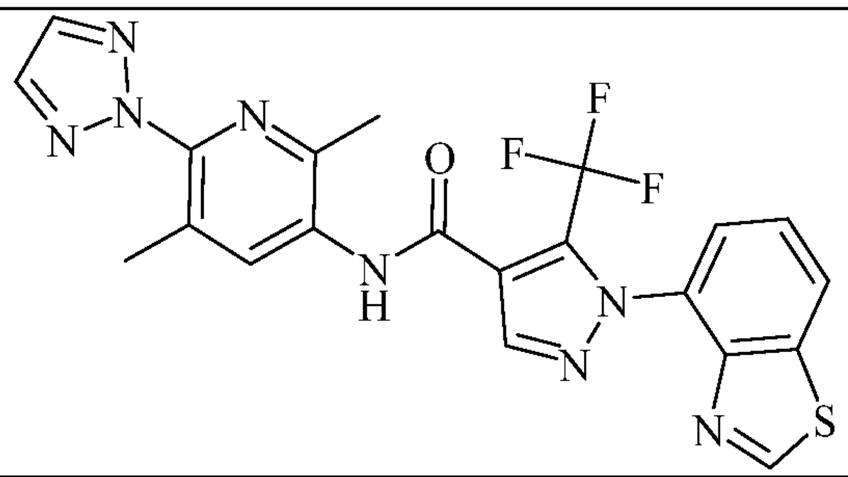
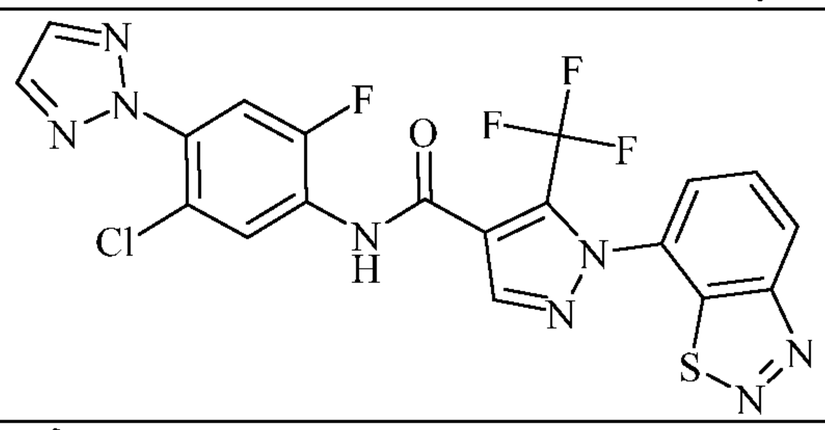
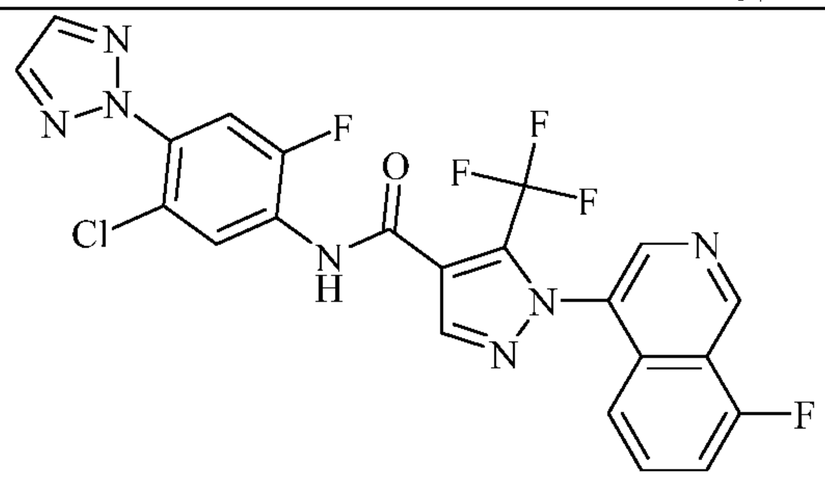
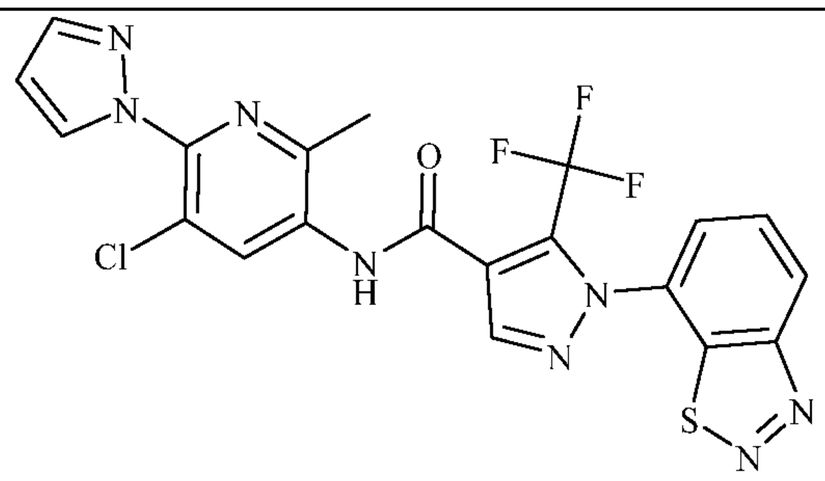
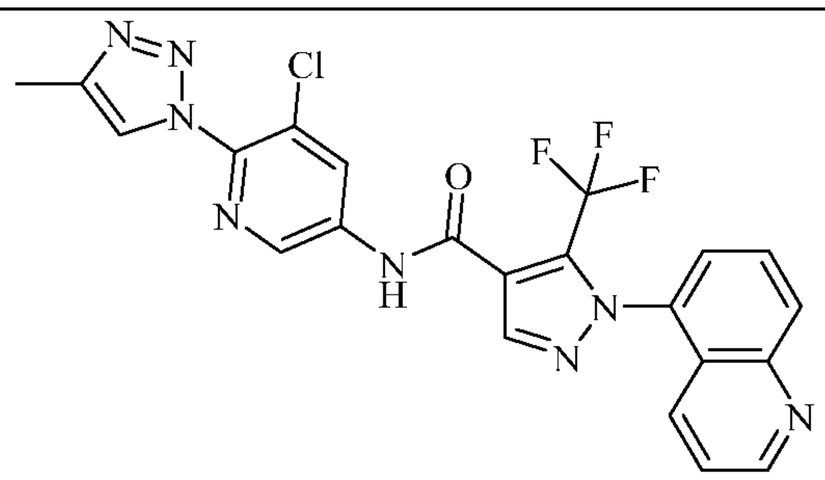
Structure	Cpd No.	Cpd Name
	**273**	N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**274**	1-([1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**275**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**276**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**277**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**278**	1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

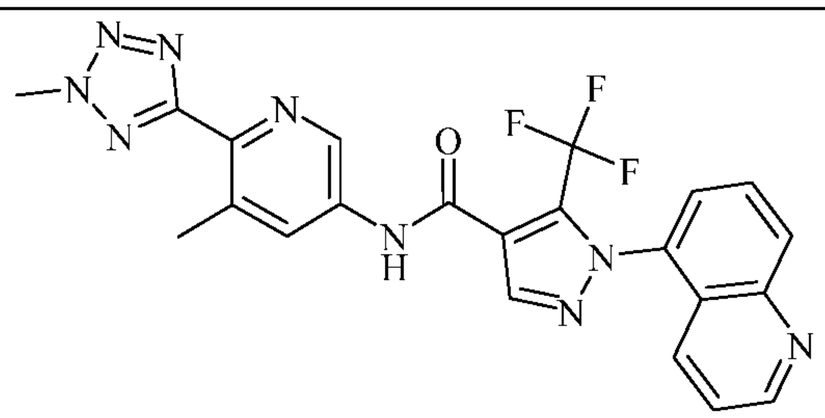
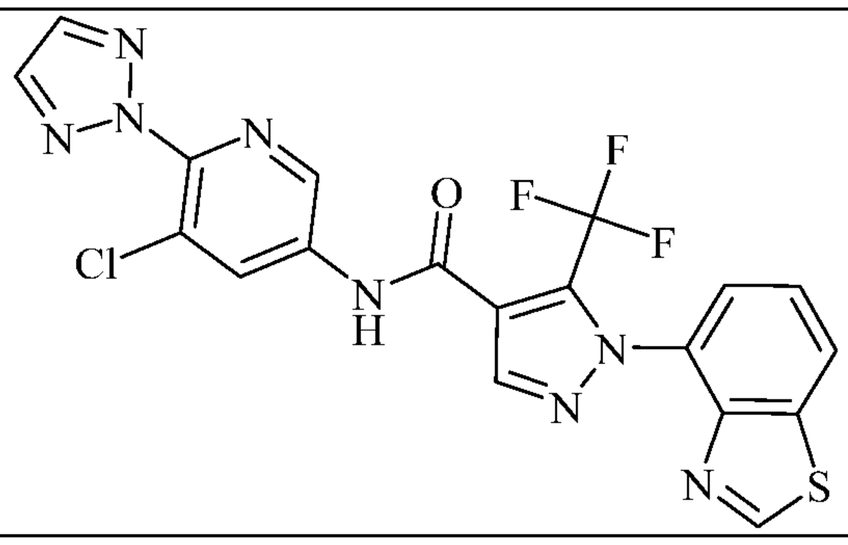
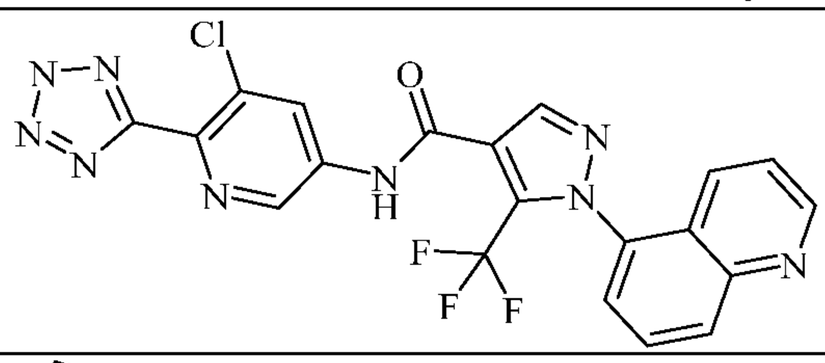
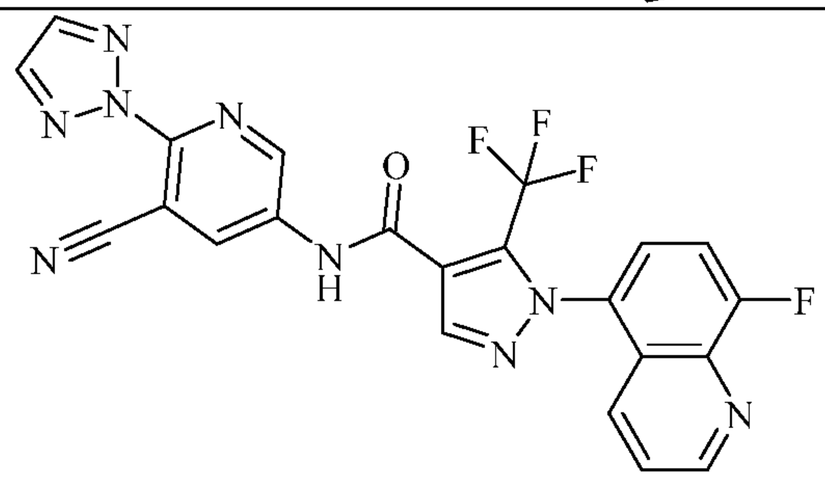
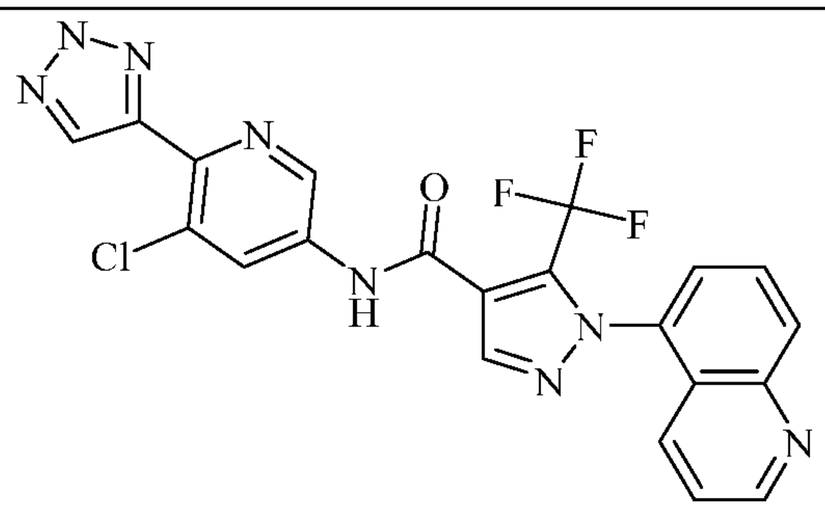
Structure	Cpd No.	Cpd Name
	**279**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isothiazolo[5,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**280**	N-(5-cyano-6-(1H-pyrrol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**281**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**282**	1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**283**	N-(6-(1H-1,2,3-triazol-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**284**	1-(benzo[d]isoxazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

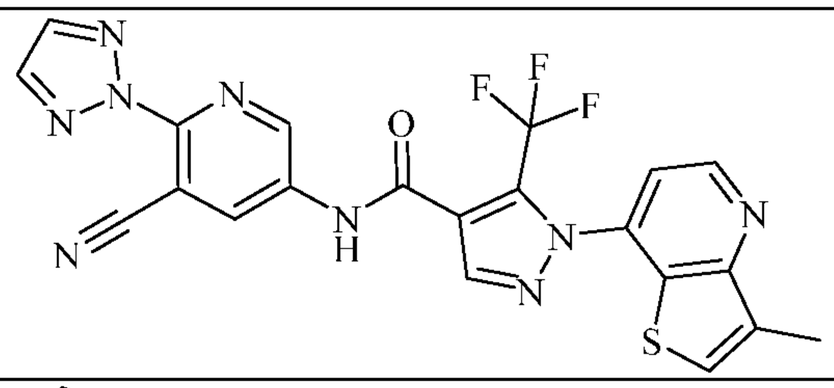
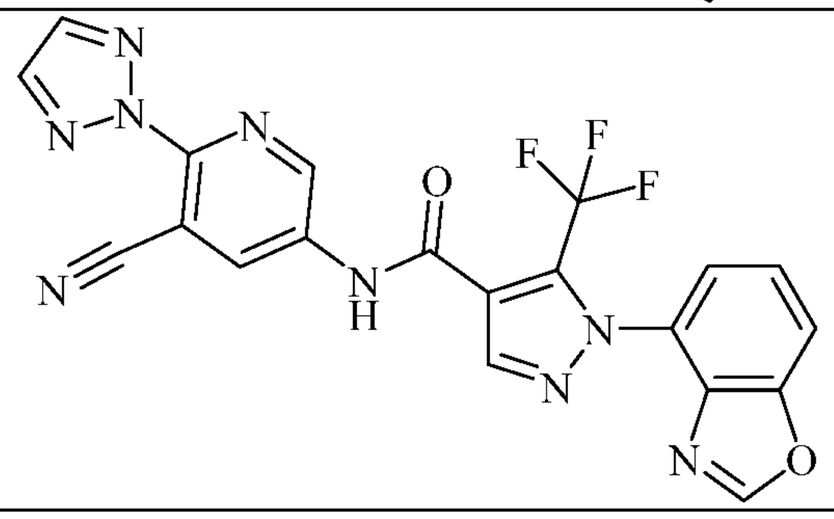
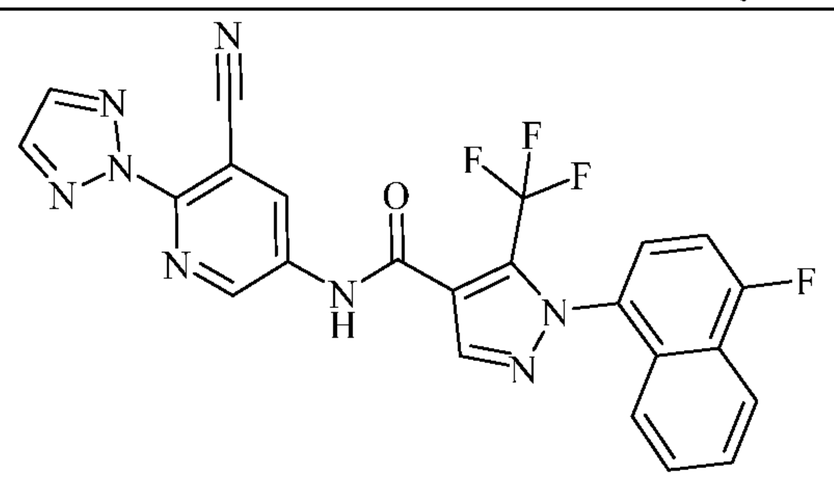
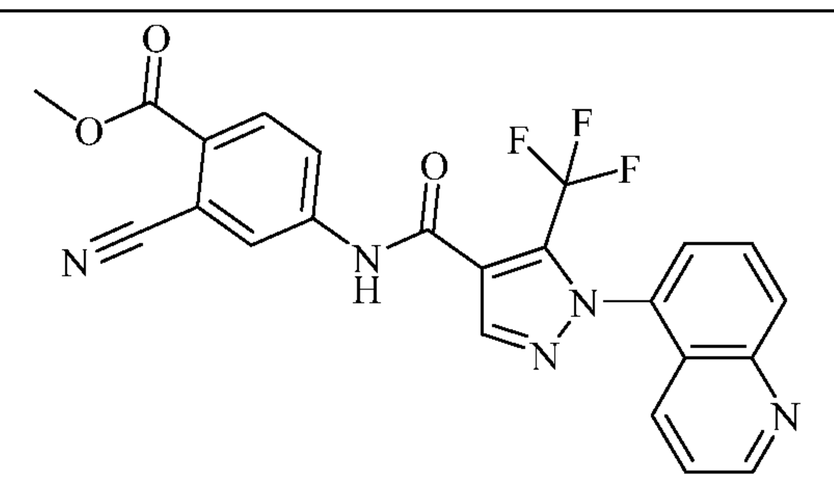
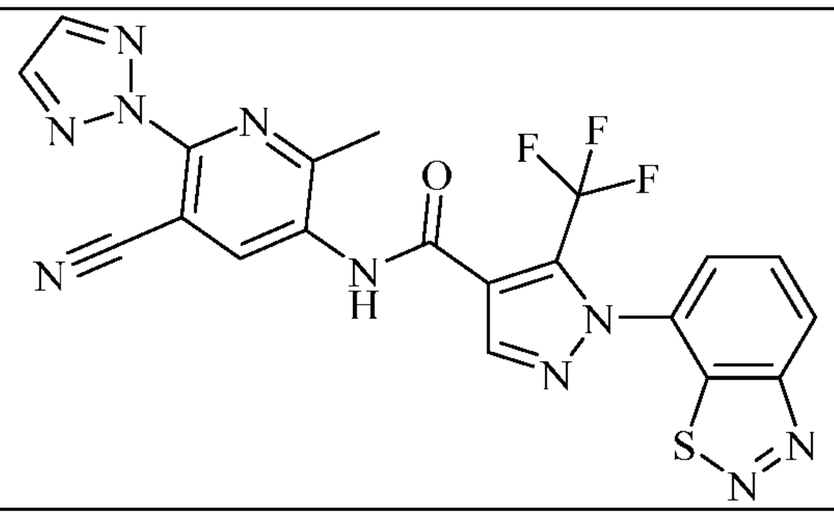
Structure	Cpd No.	Cpd Name
	**285**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-chloroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**286**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**287**	N-(5-bromo-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**288**	N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**289**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

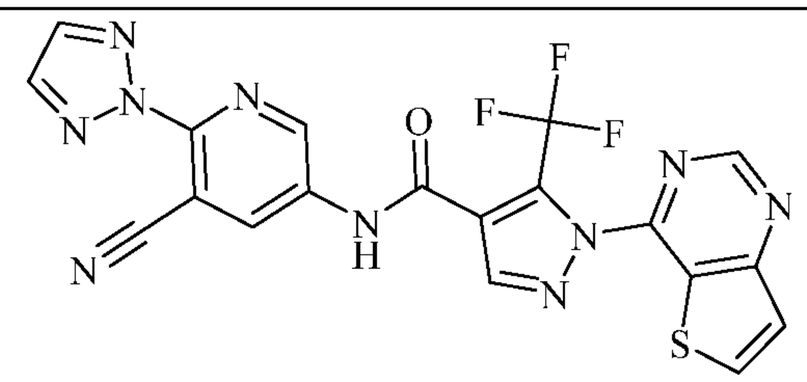
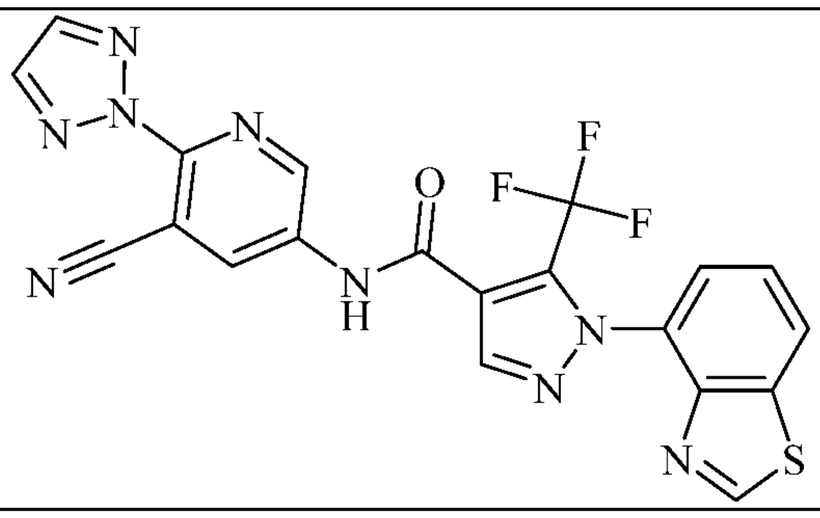
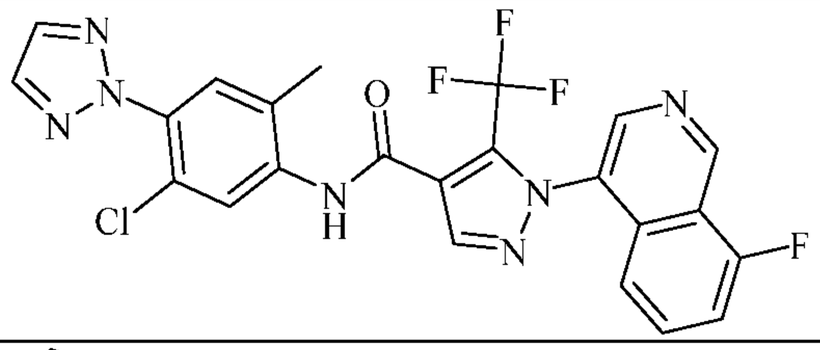
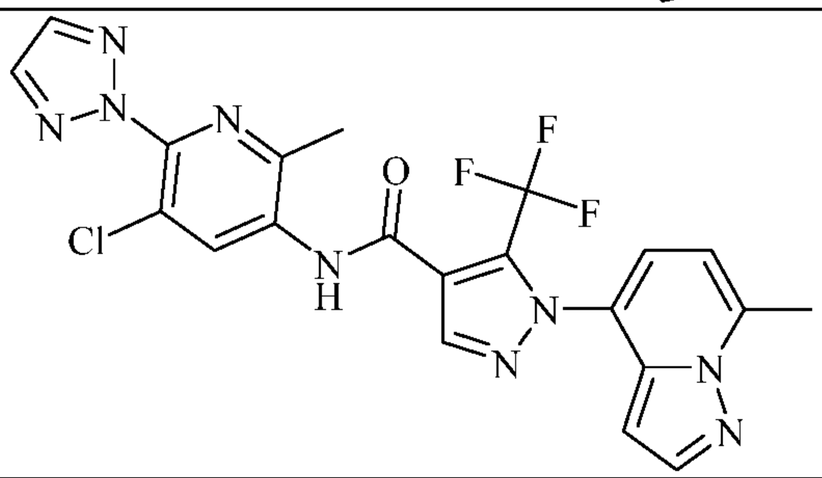
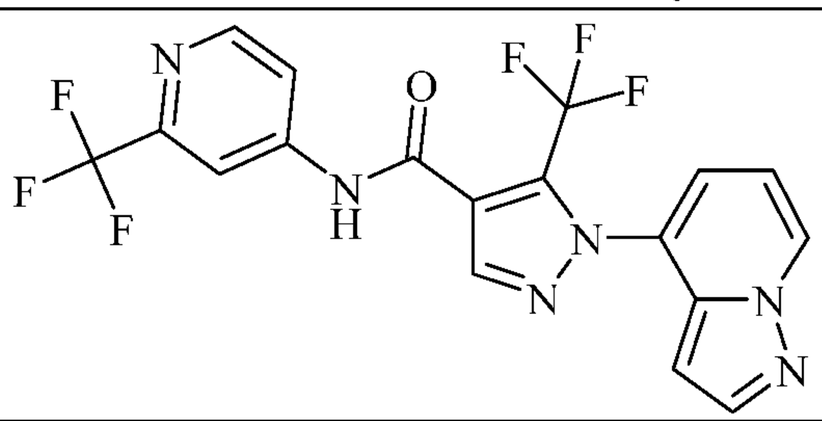
Structure	Cpd No.	Cpd Name
	**290**	1-(benzo[d]isothiazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**291**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**292**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**293**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**294**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thiazolo[5,4-d]pyrimidin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

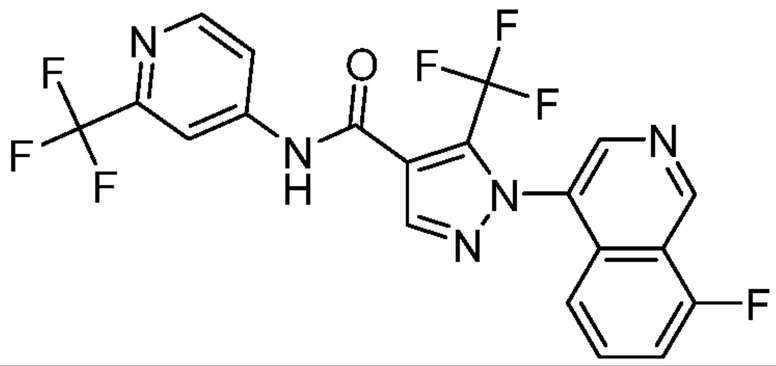
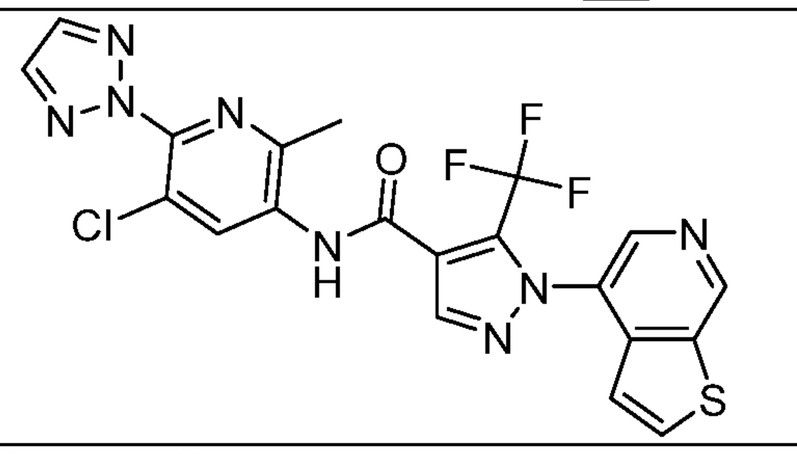
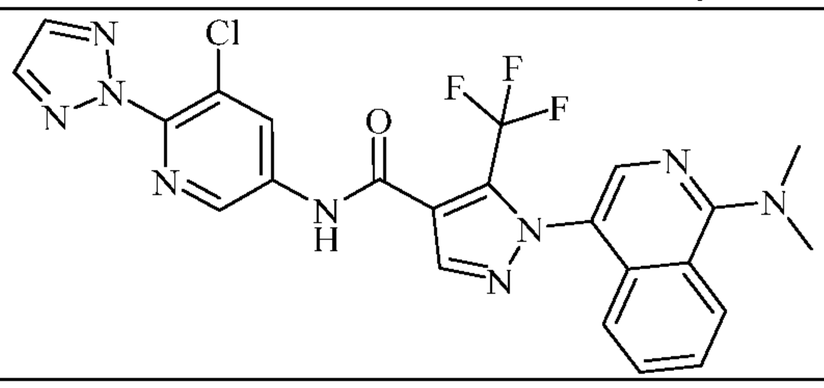
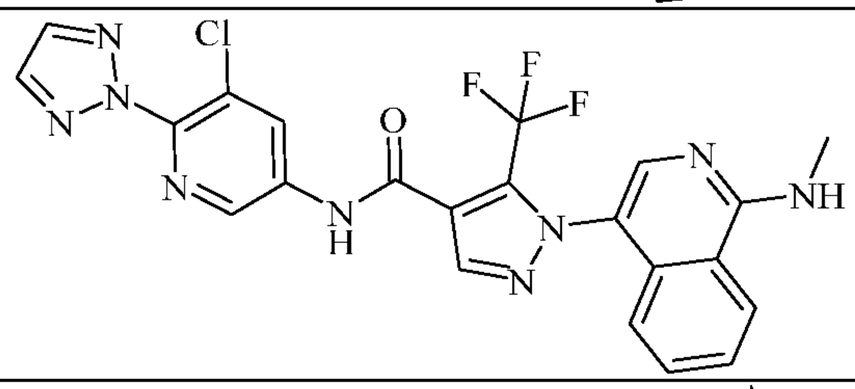
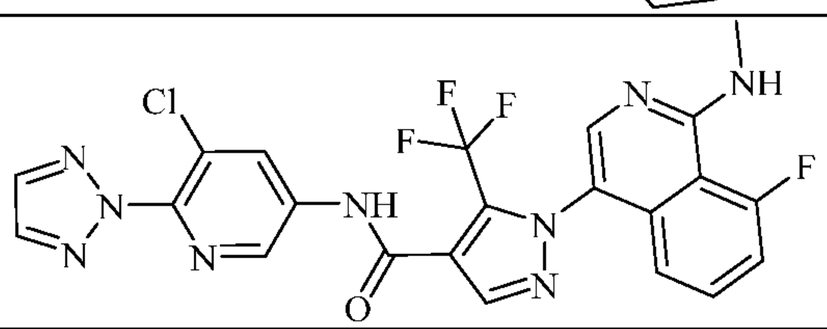
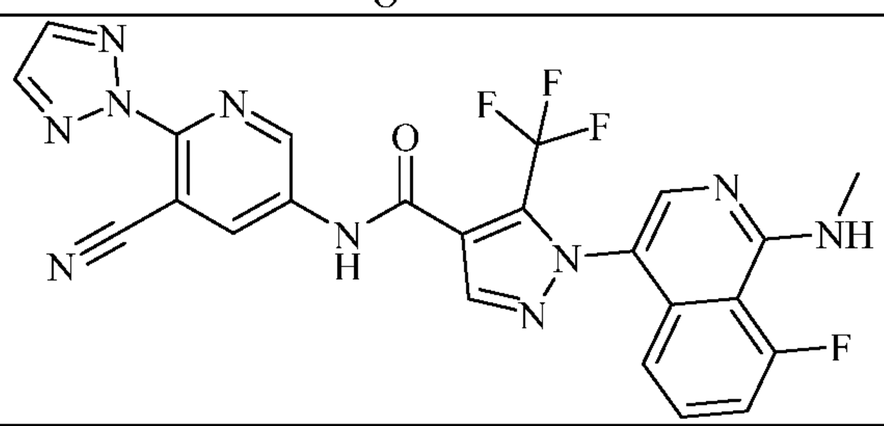
Structure	Cpd No.	Cpd Name
	**295**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**296**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinazolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**297**	1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**298**	1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**299**	N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(benzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

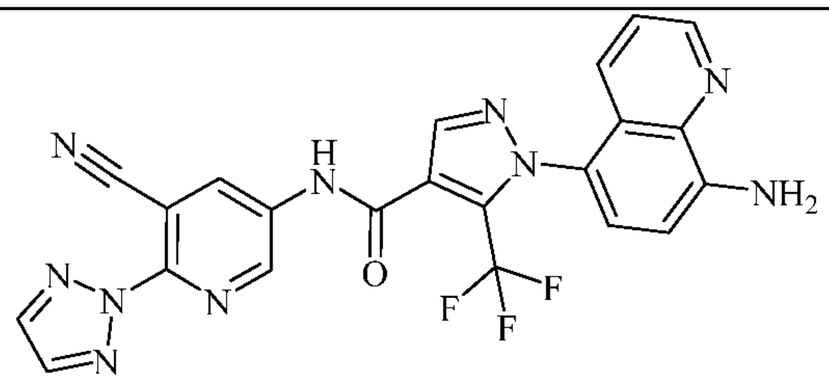
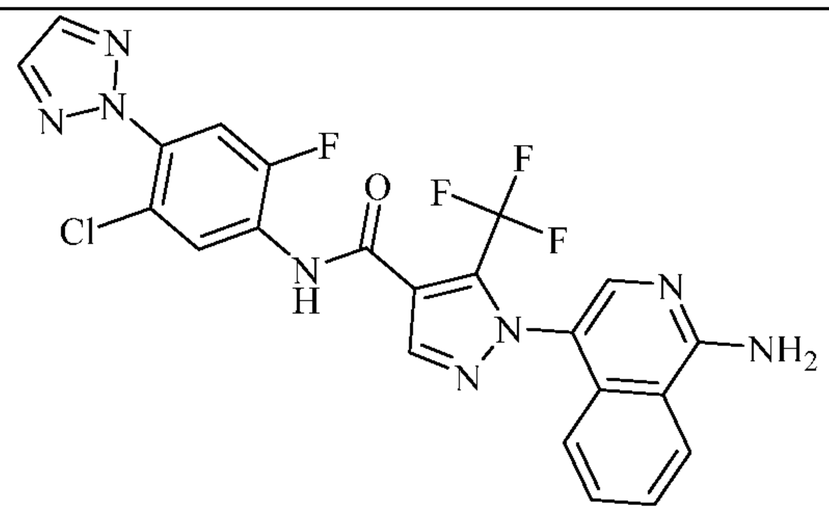
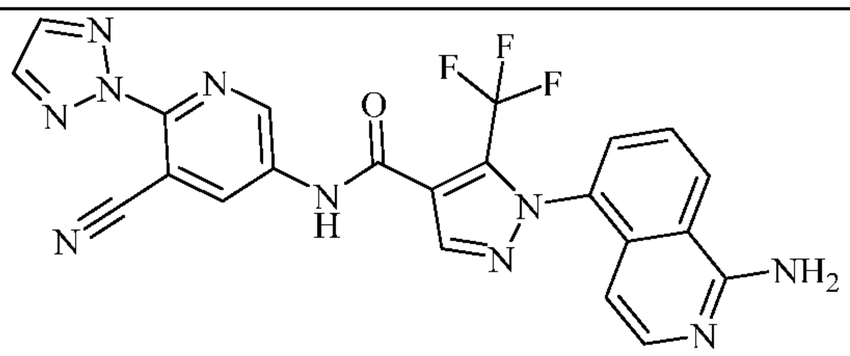
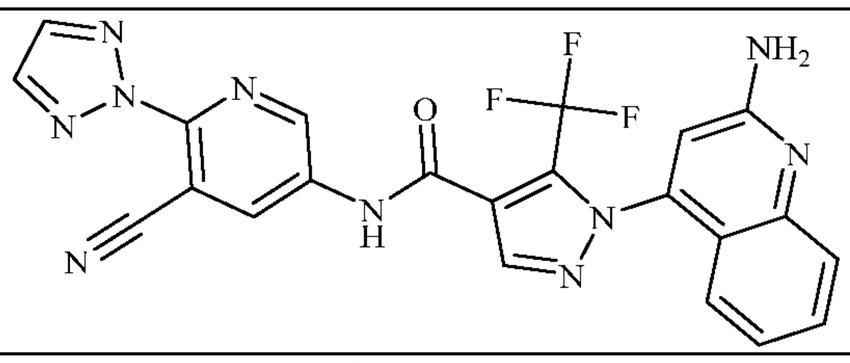
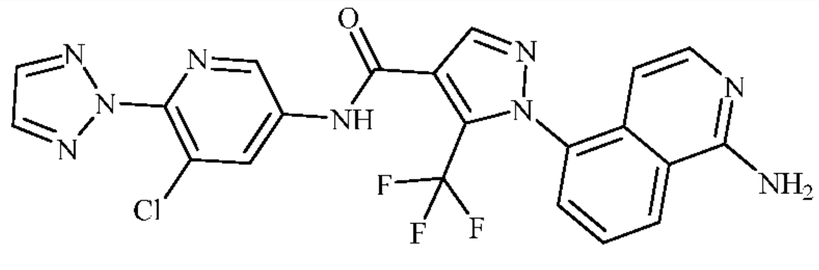
Structure	Cpd No.	Cpd Name
	**300**	1-(benzo[d]thiazol-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**301**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**302**	N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**303**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**304**	N-(5-chloro-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

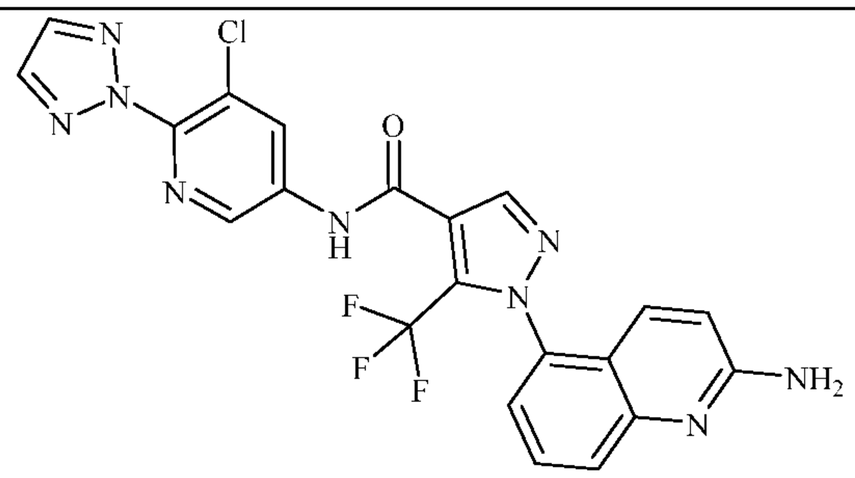
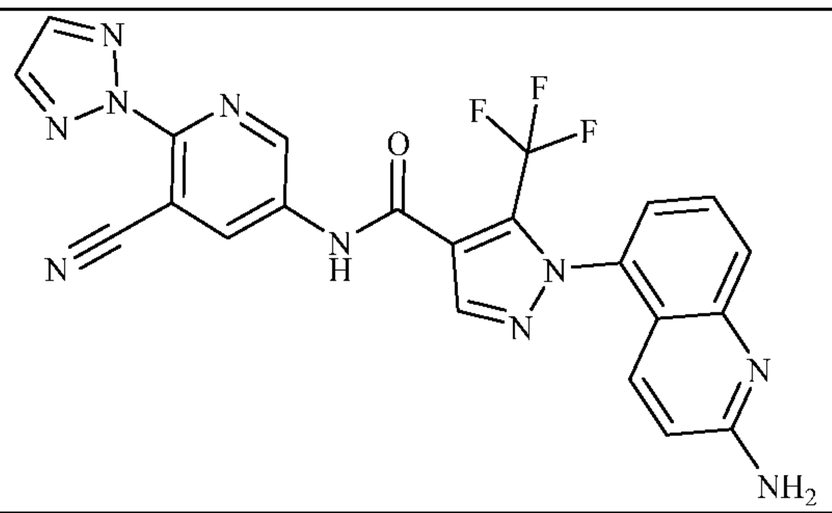
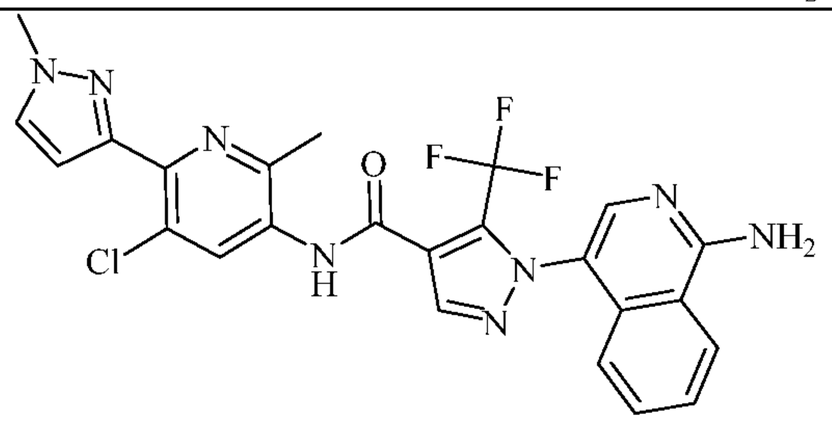
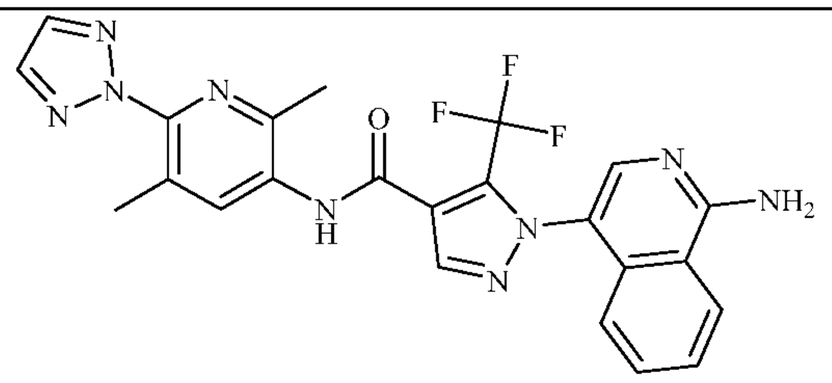
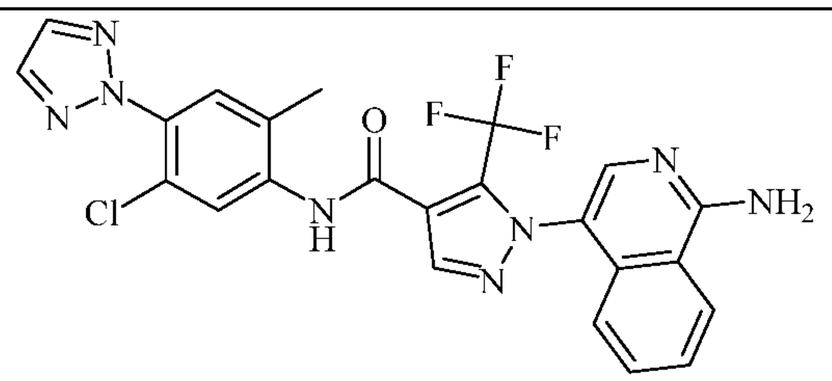
Structure	Cpd No.	Cpd Name
	**305**	N-(5-methyl-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**306**	1-(benzo[d]thiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**307**	N-(5-chloro-6-(2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**308**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**309**	N-(5-chloro-6-(2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

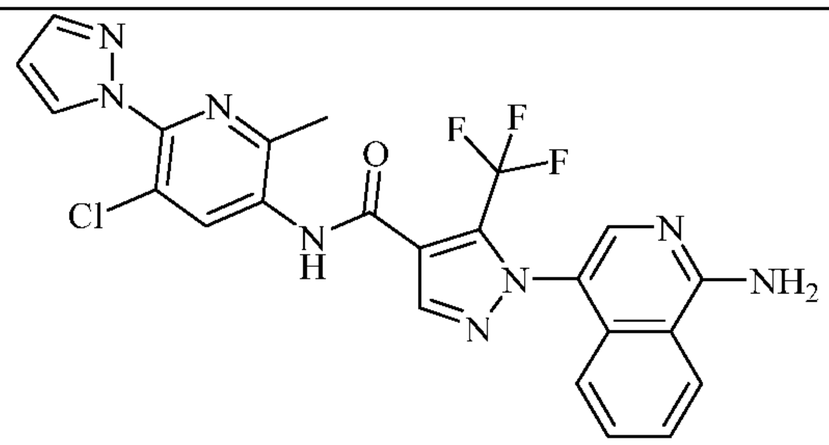
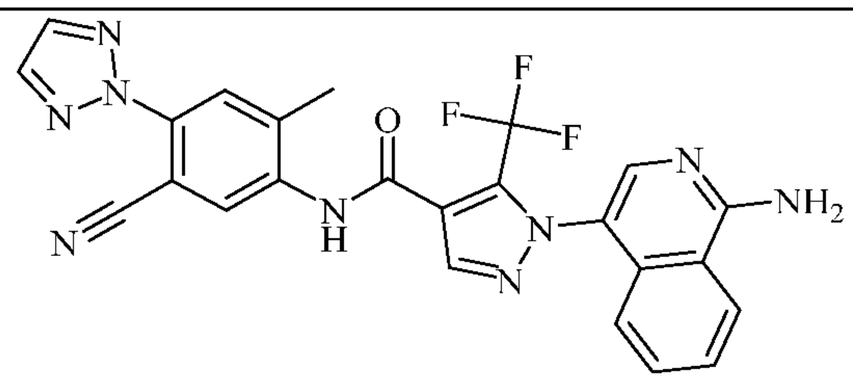
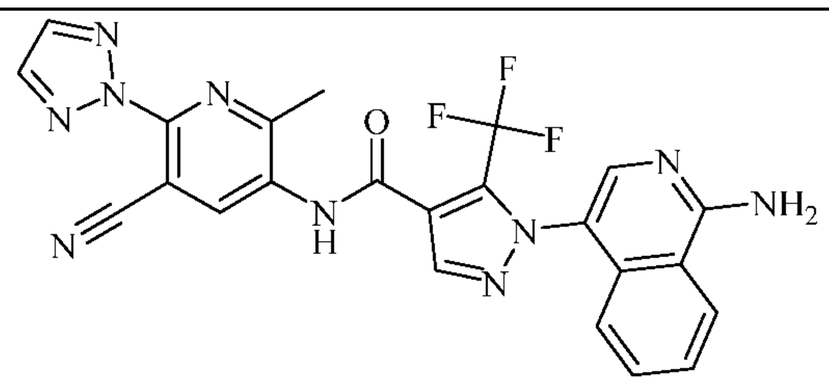
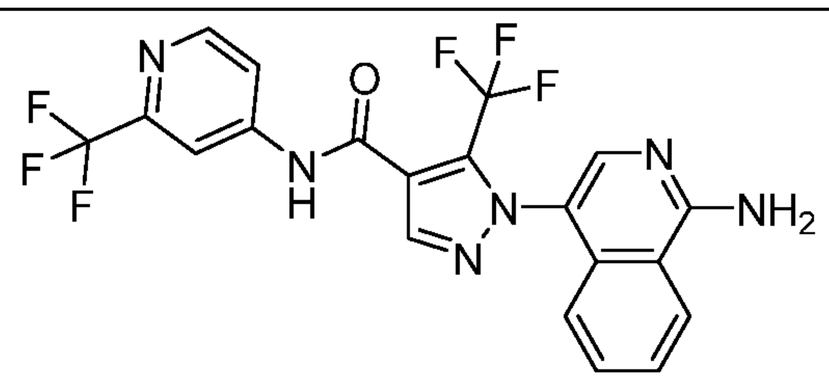
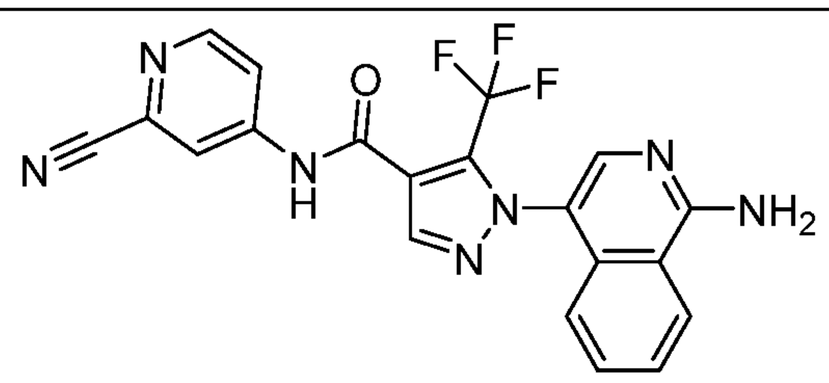
Structure	Cpd No.	Cpd Name
	**310**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**311**	1-(benzo[d]oxazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**312**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**313**	methyl 2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoate
	**314**	1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

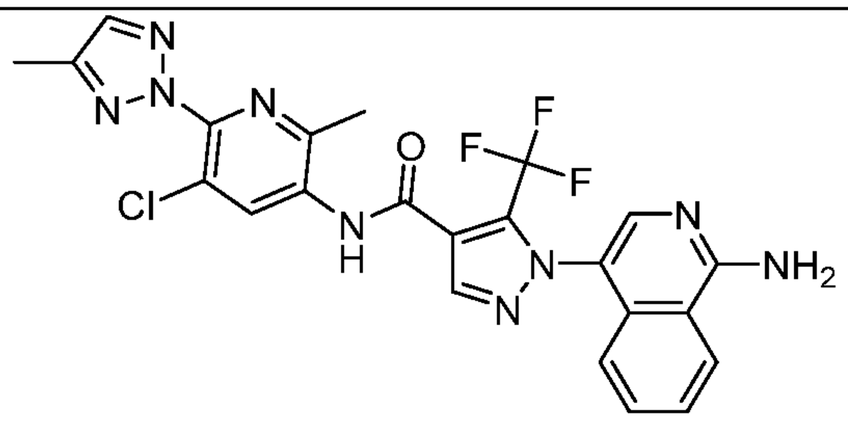
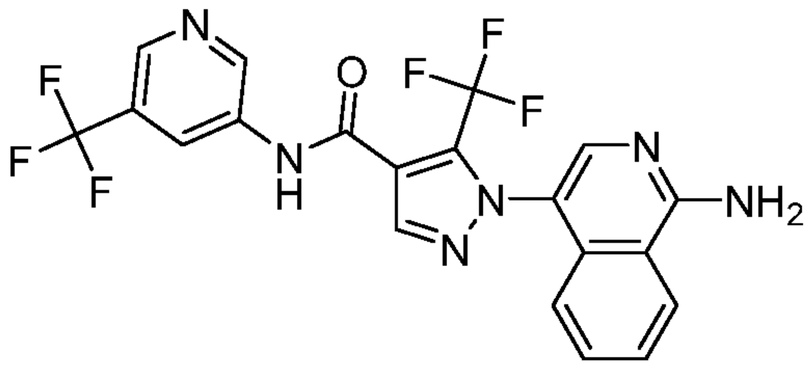
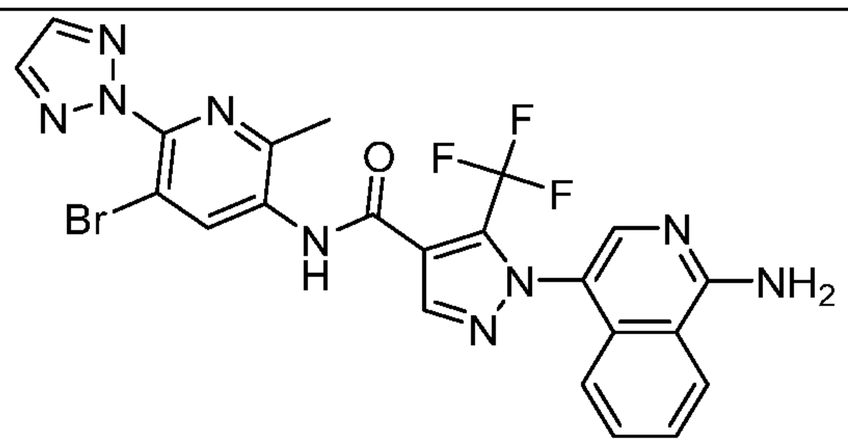
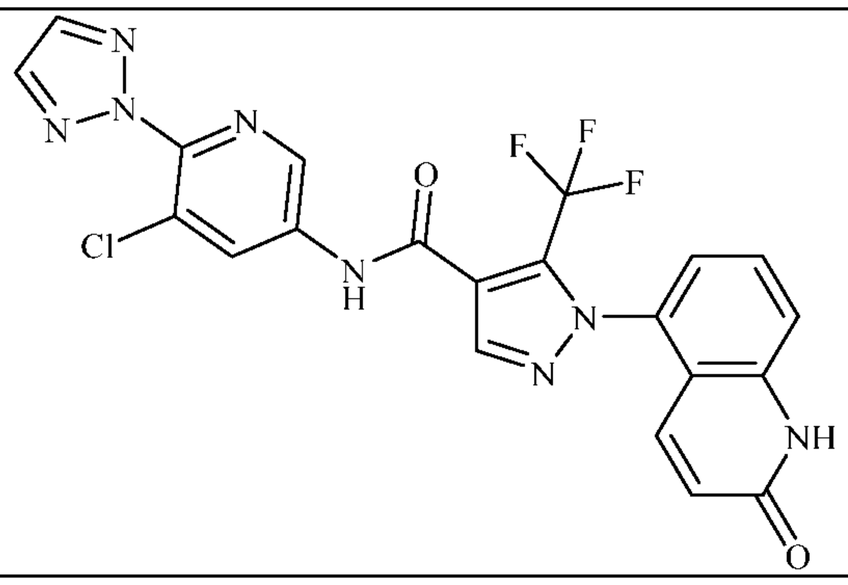
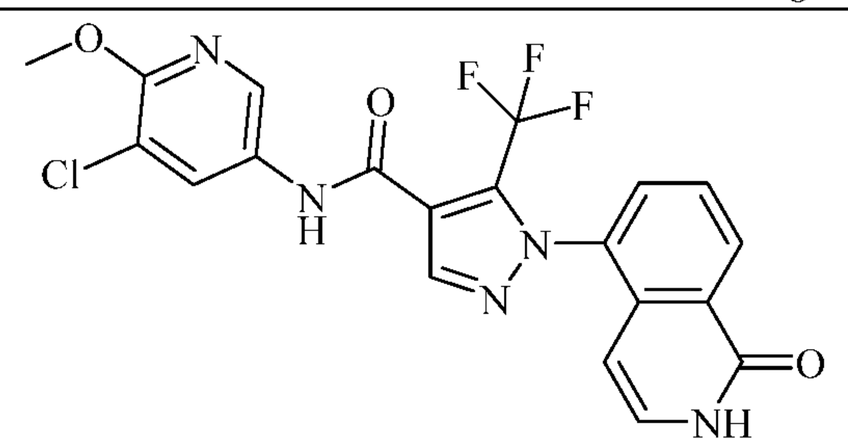
Structure	Cpd No.	Cpd Name
	**315**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**316**	1-(benzo[d]thiazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**317**	N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**318**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**319**	1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide

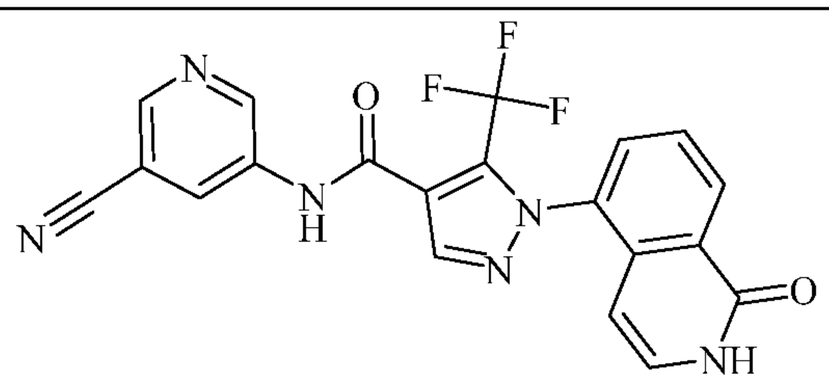
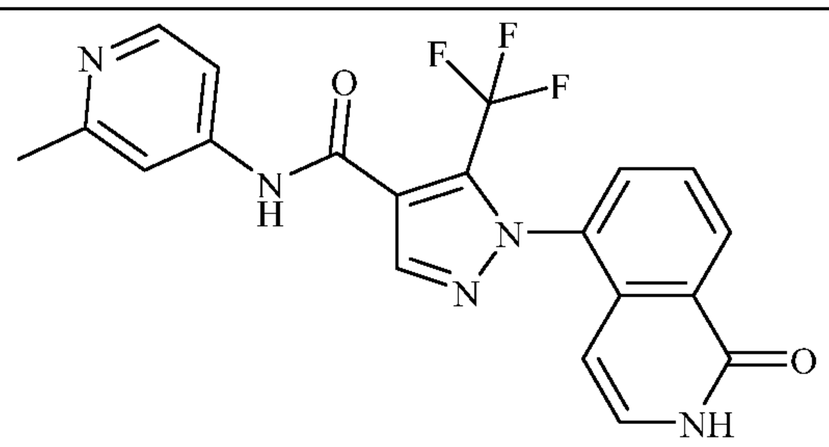
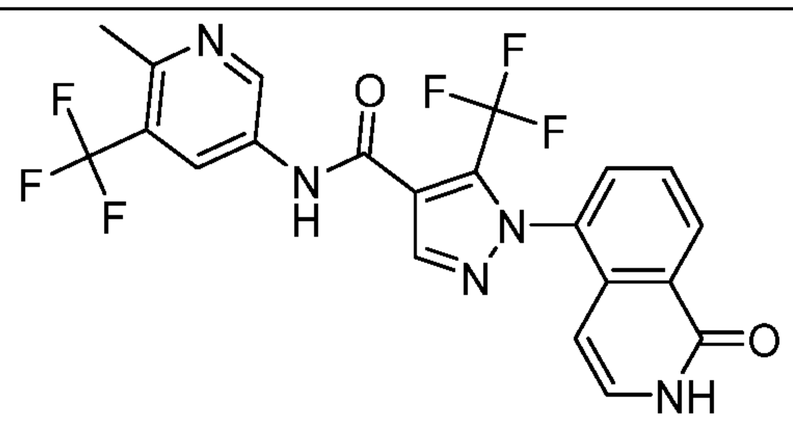
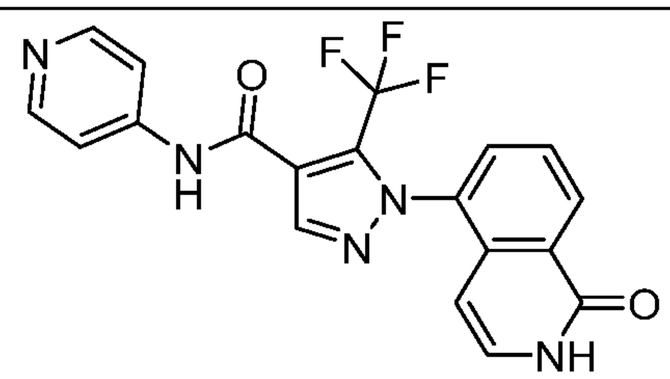
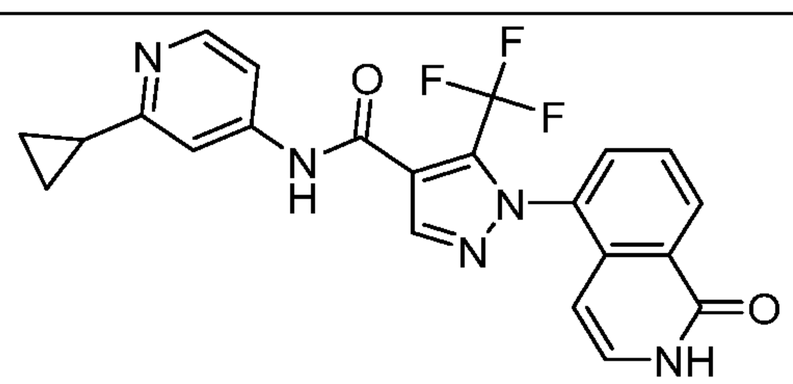
Structure	Cpd No.	Cpd Name
	**320**	1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**321**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**322**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(dimethylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**323**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**324**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**325**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

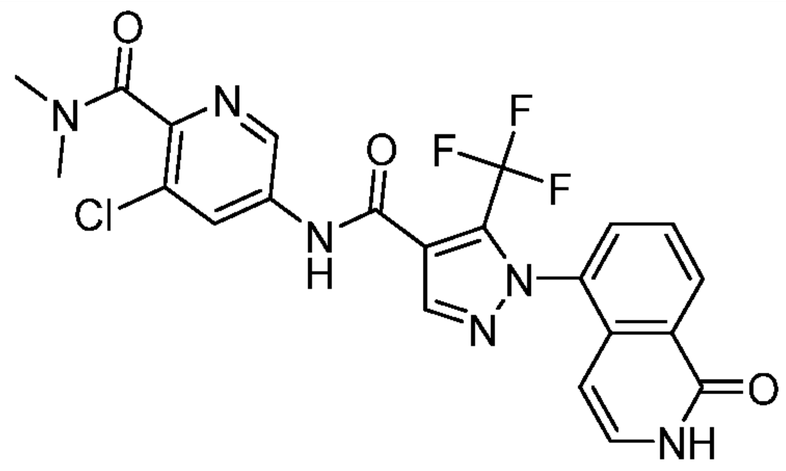
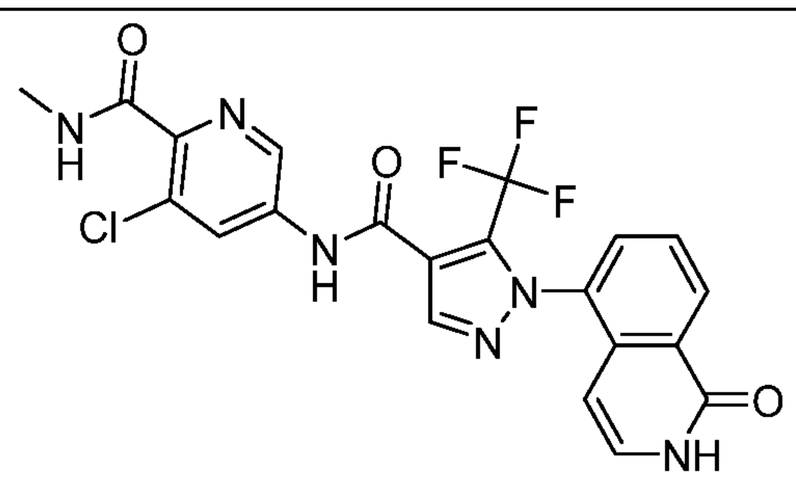
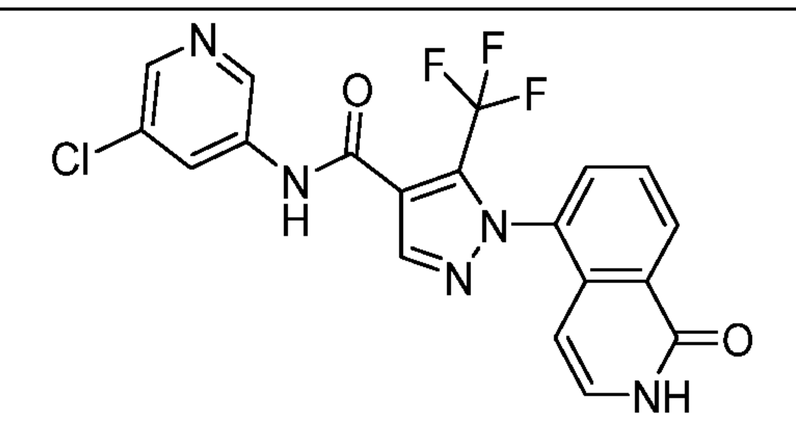
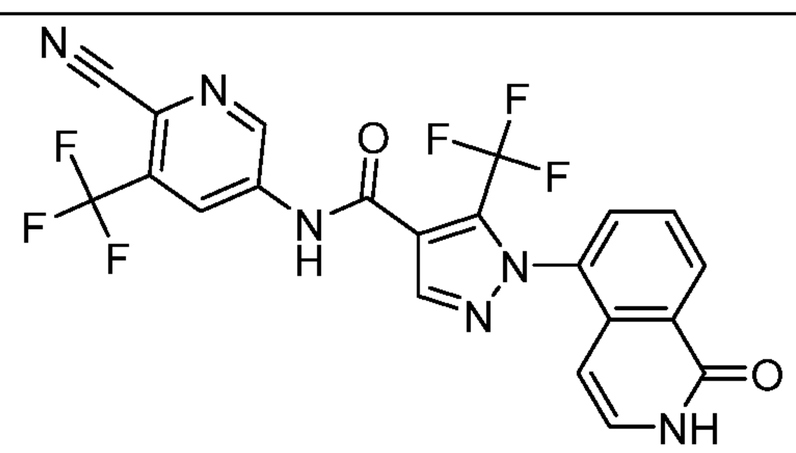
Structure	Cpd No.	Cpd Name
	**326**	1-(8-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**327**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**328**	1-(1-aminoisoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**329**	1-(2-aminoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**330**	1-(1-aminoisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

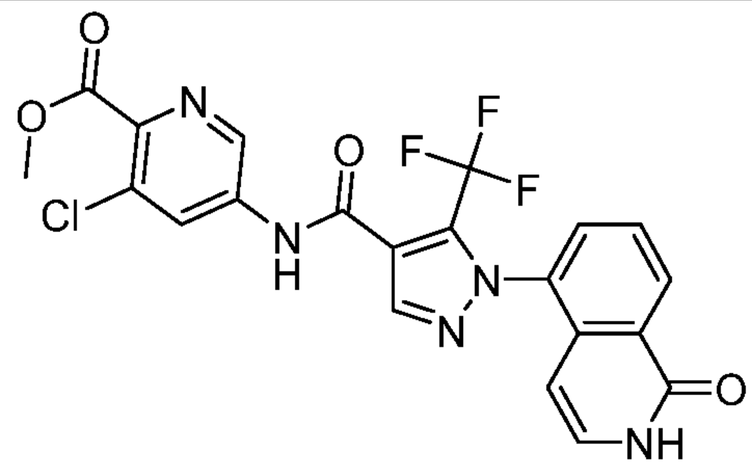
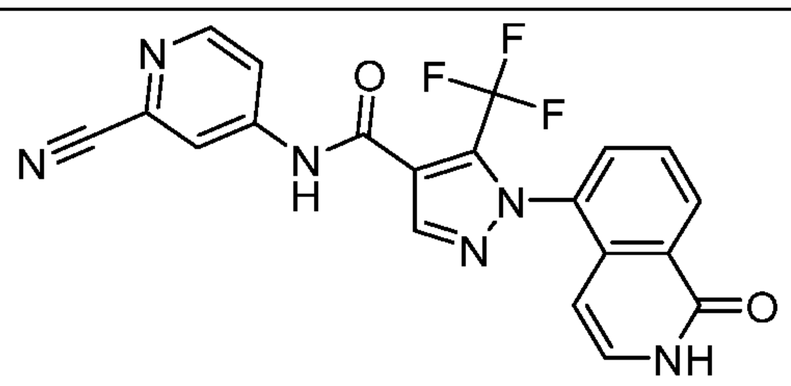
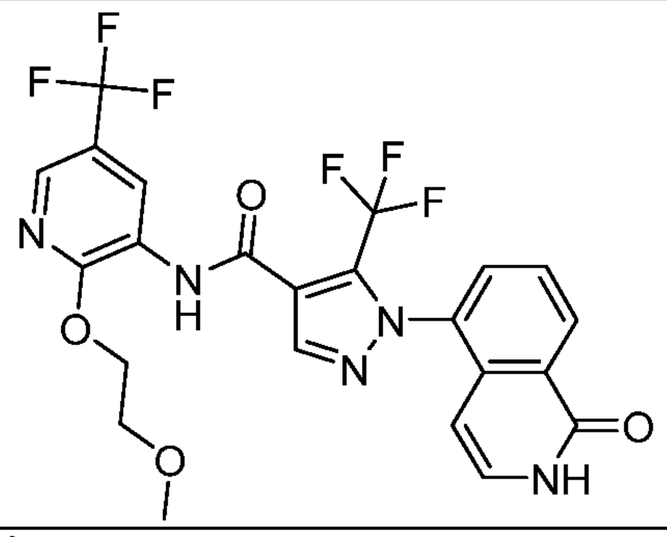
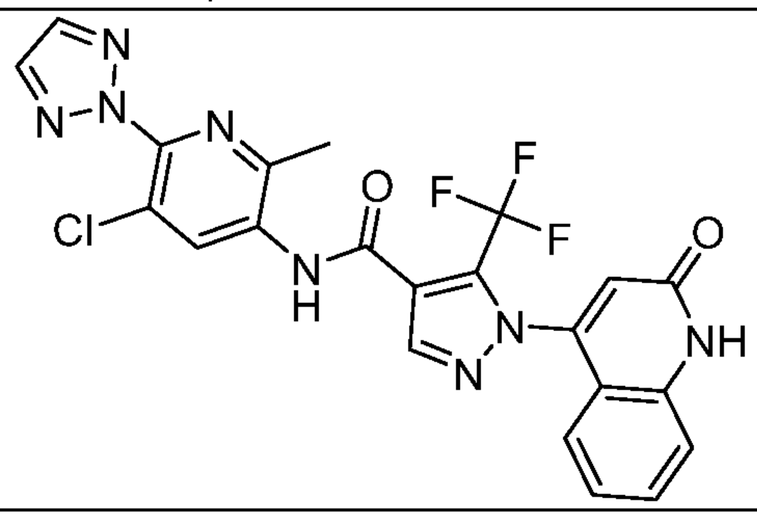
Structure	Cpd No.	Cpd Name
	**331**	1-(2-aminoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**332**	1-(2-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**333**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**334**	1-(1-aminoisoquinolin-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**335**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

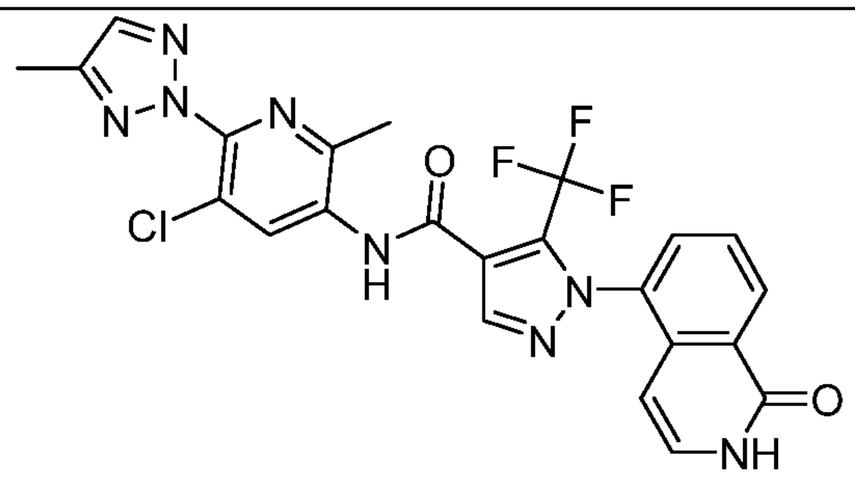
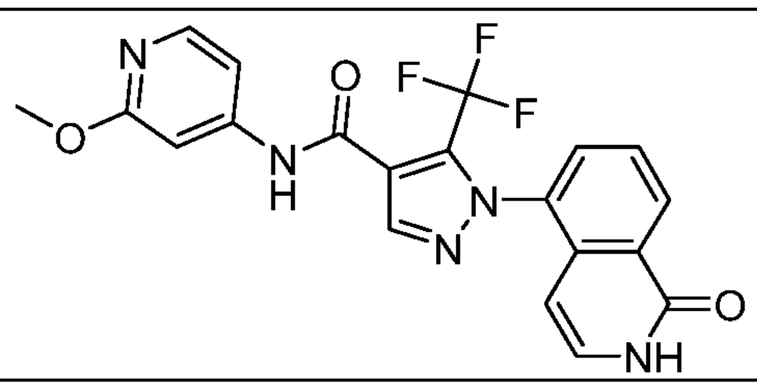
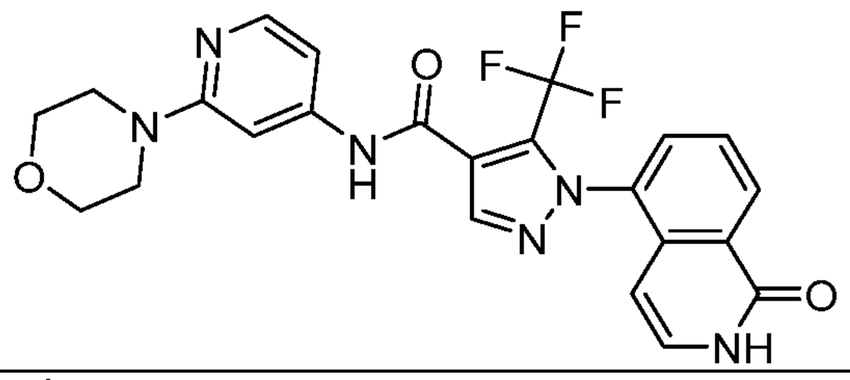
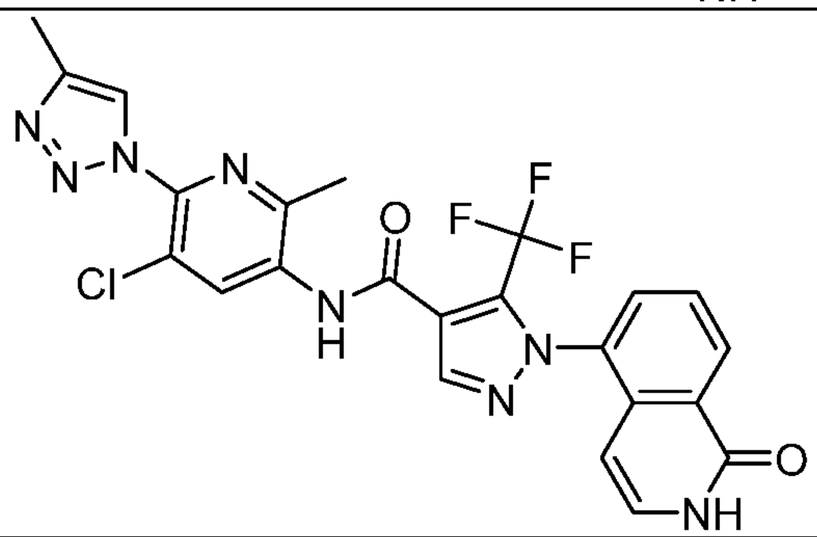
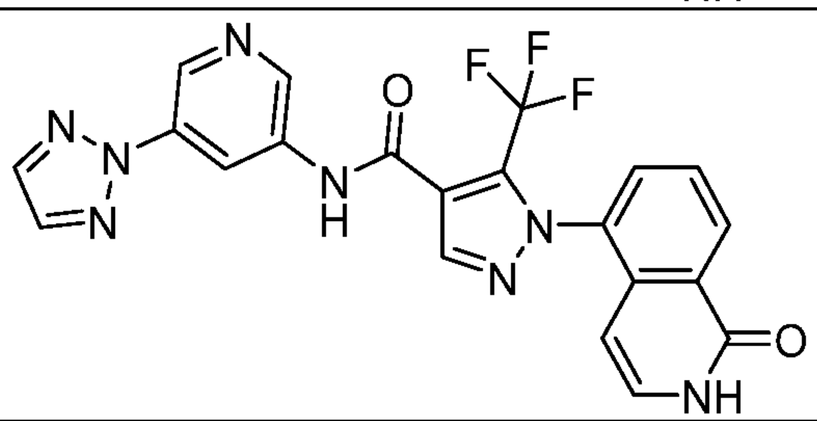
Structure	Cpd No.	Cpd Name
	**336**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**337**	1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**338**	1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**339**	1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**340**	1-(1-aminoisoquinolin-4-yl)-N-(2-cyanopyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

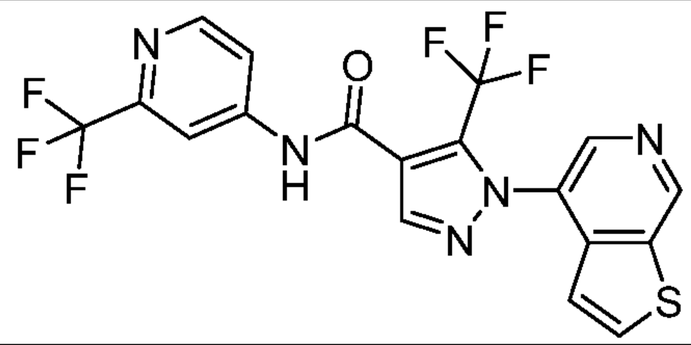
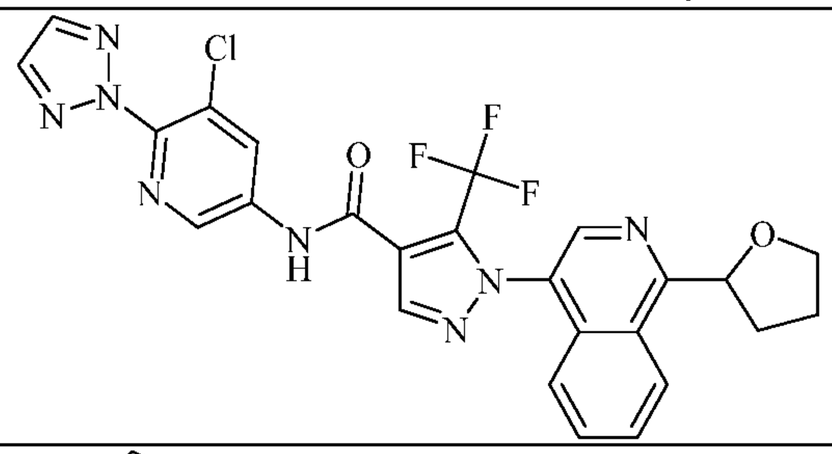
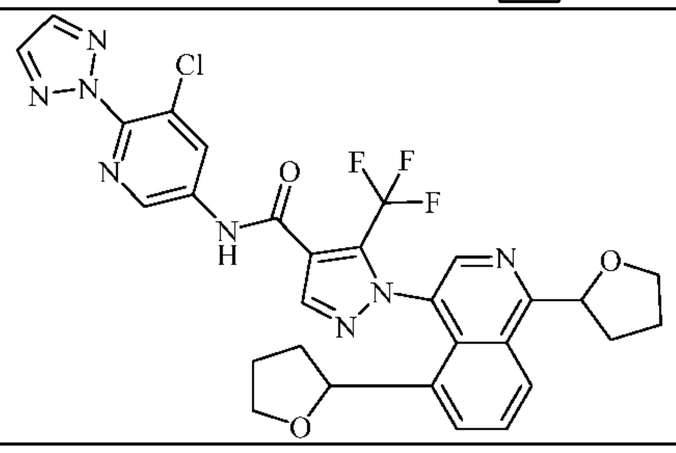
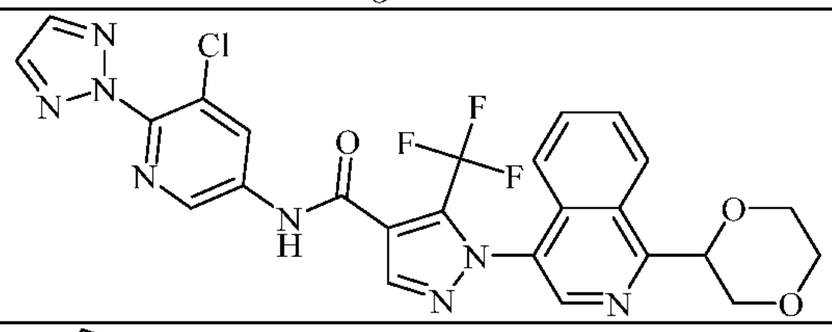
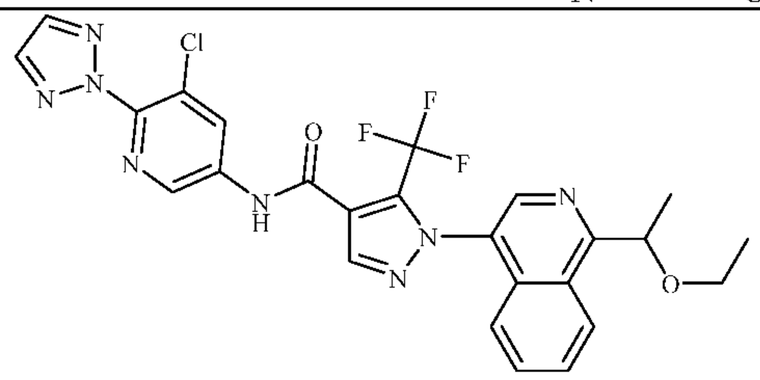
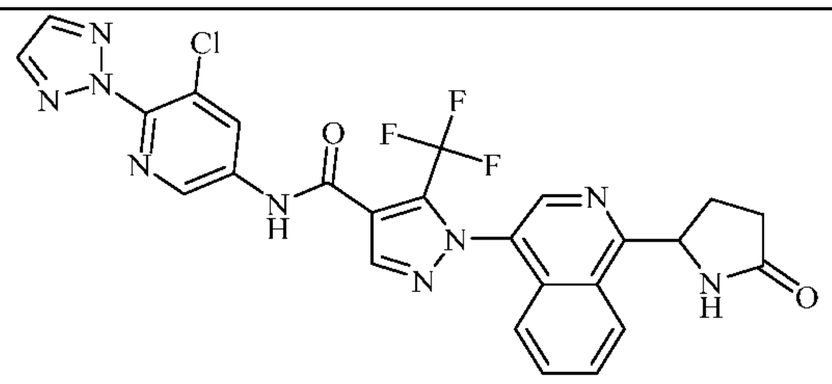
Structure	Cpd No.	Cpd Name
	**341**	1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**342**	1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide
	**343**	1-(1-aminoisoquinolin-4-yl)-N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**344**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**345**	N-(5-chloro-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

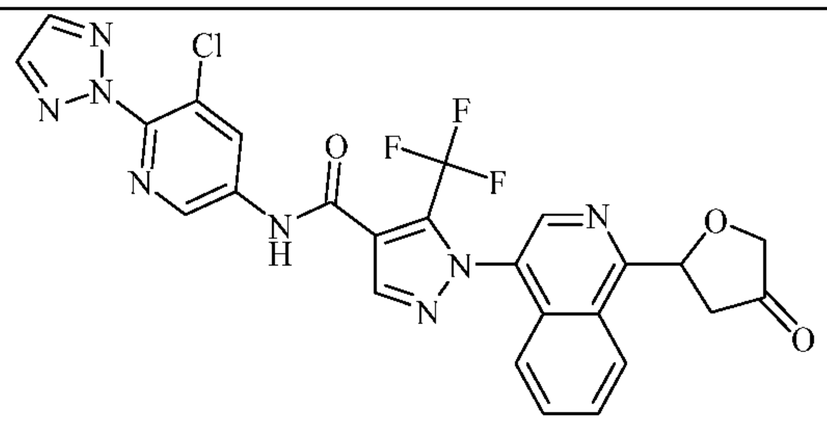
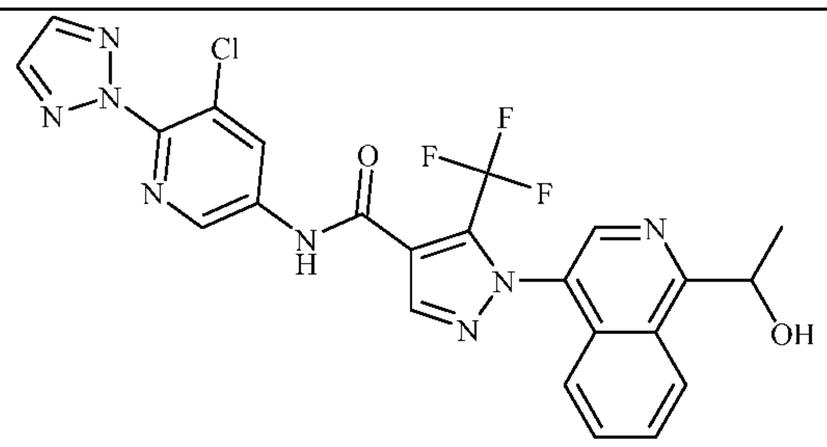
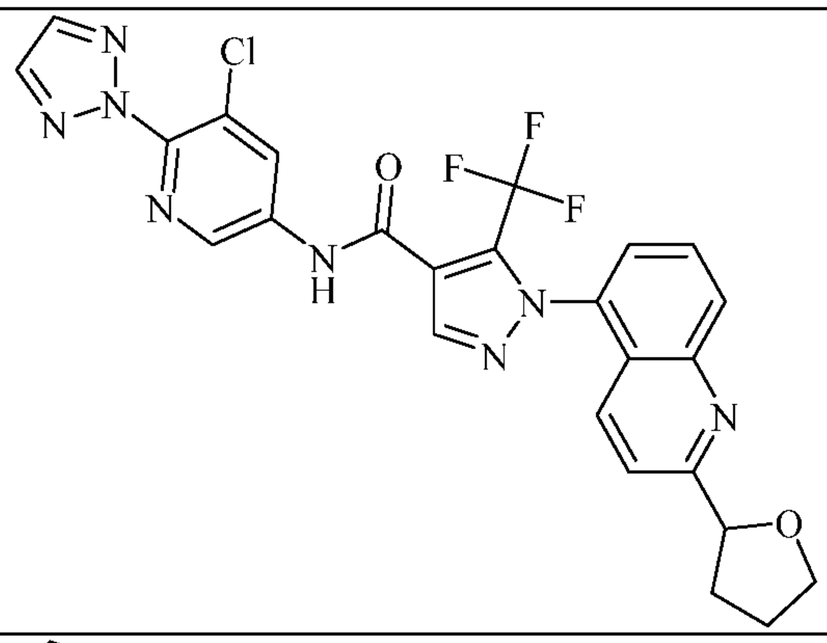
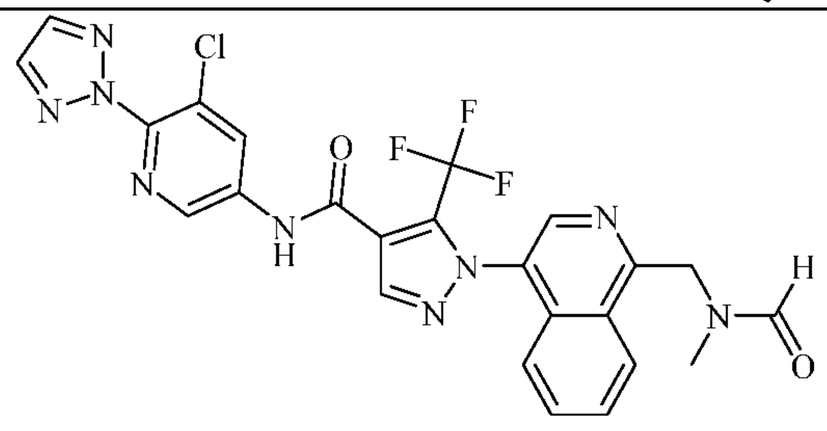
Structure	Cpd No.	Cpd Name
	**346**	N-(5-cyanopyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**347**	N-(2-methylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**348**	N-(6-methyl-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**349**	1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-N-(pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**350**	N-(2-cyclopropylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

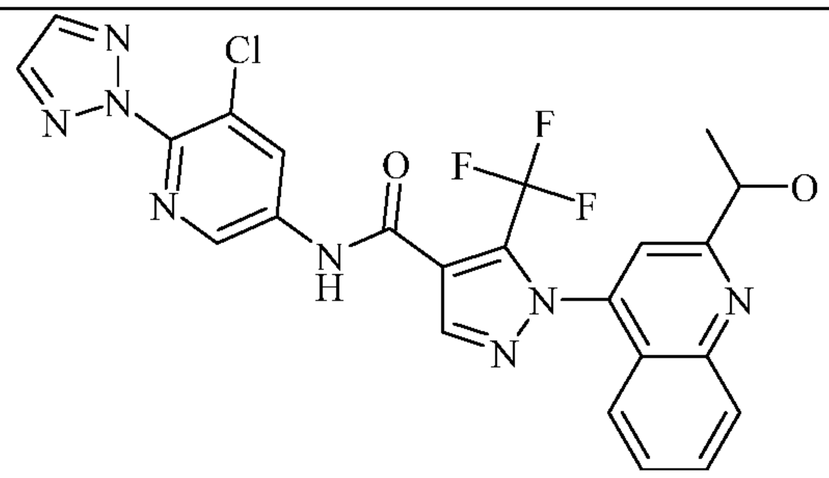
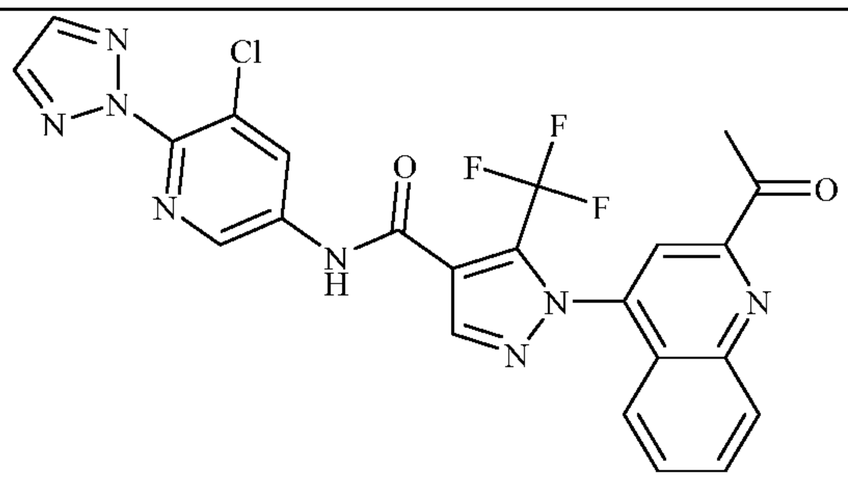
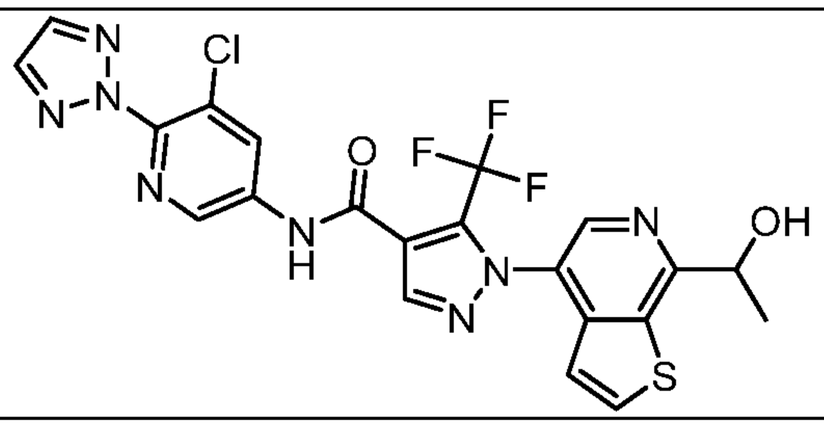
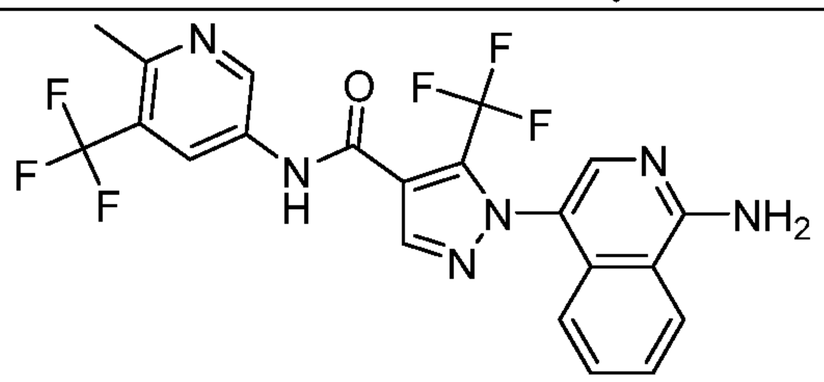
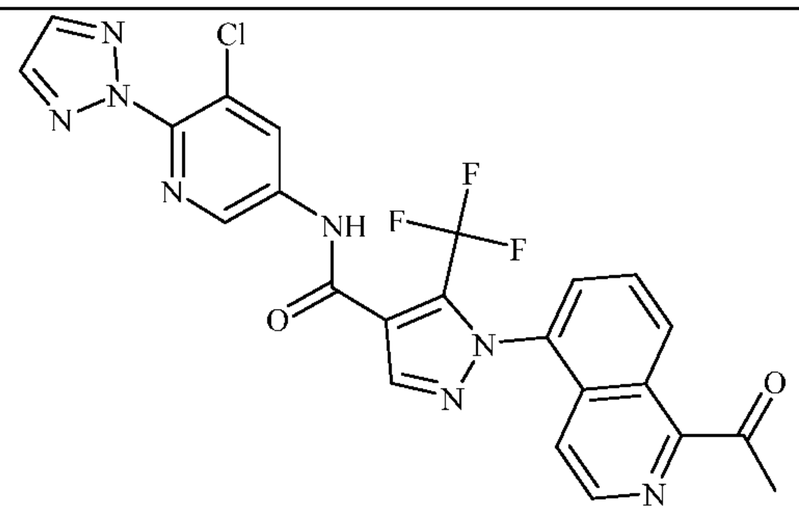
Structure	Cpd No.	Cpd Name
	**351**	3-chloro-N,N-dimethyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide
	**352**	3-chloro-N-methyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide
	**353**	N-(5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**354**	N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

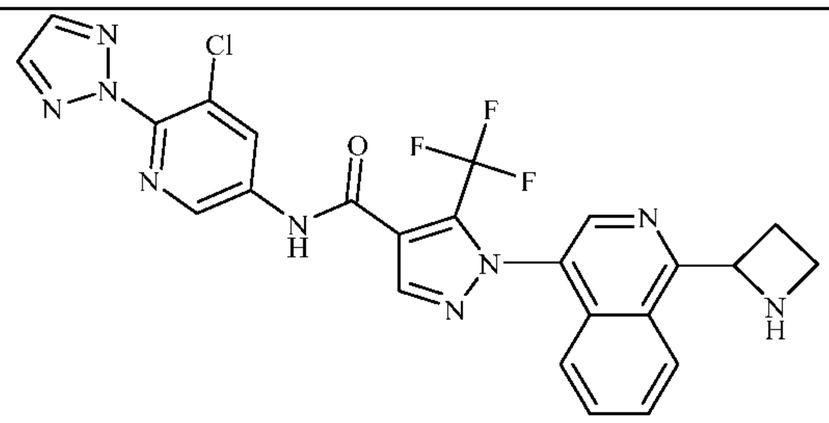
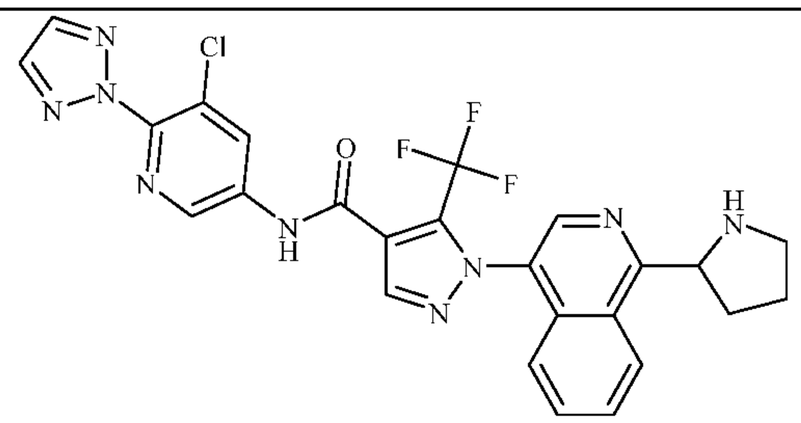
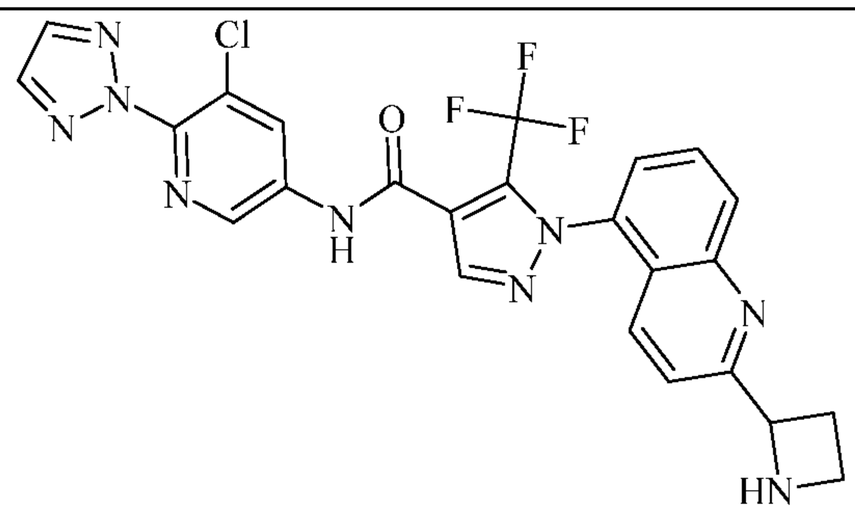
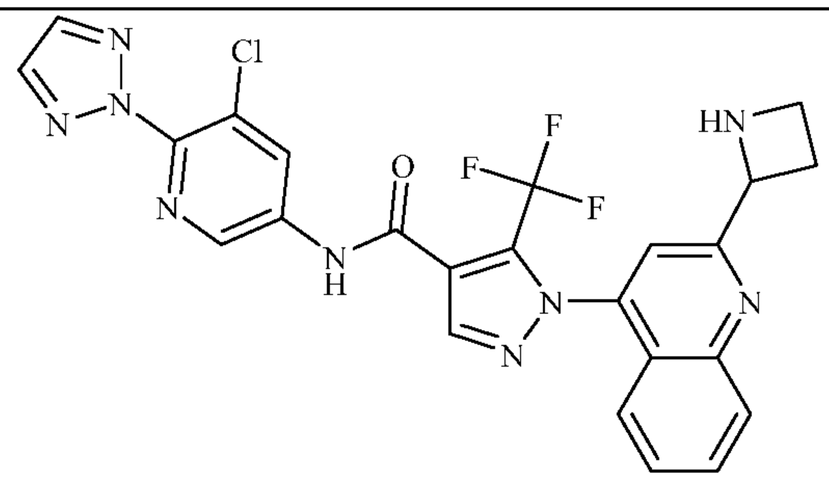
Structure	Cpd No.	Cpd Name
	**355**	methyl 3-chloro-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate
	**356**	N-(2-cyanopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**357**	N-(2-(2-methoxyethoxy)-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**358**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

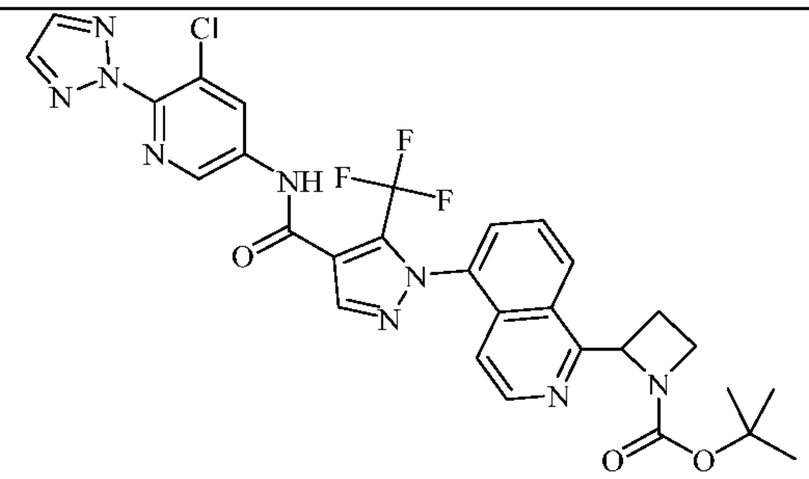
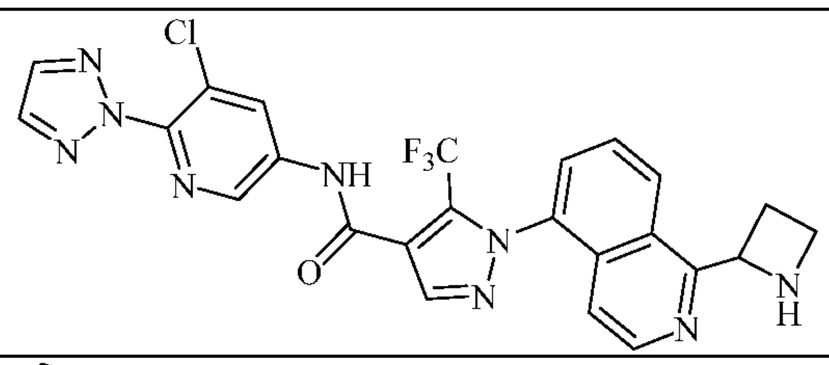
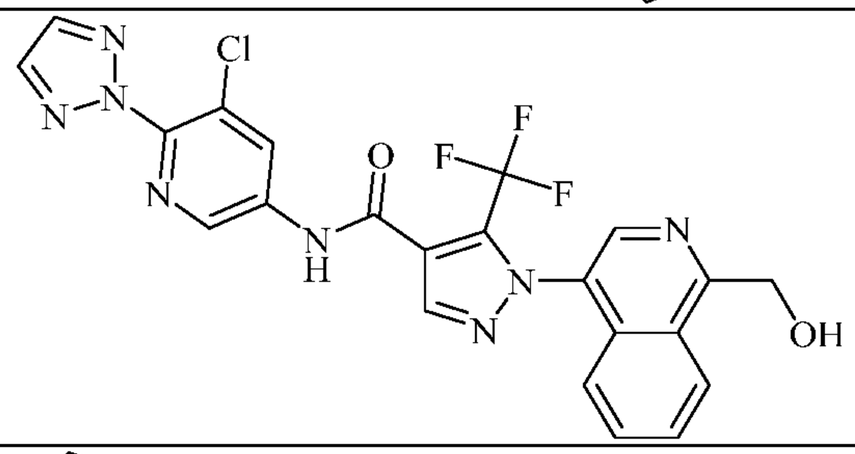
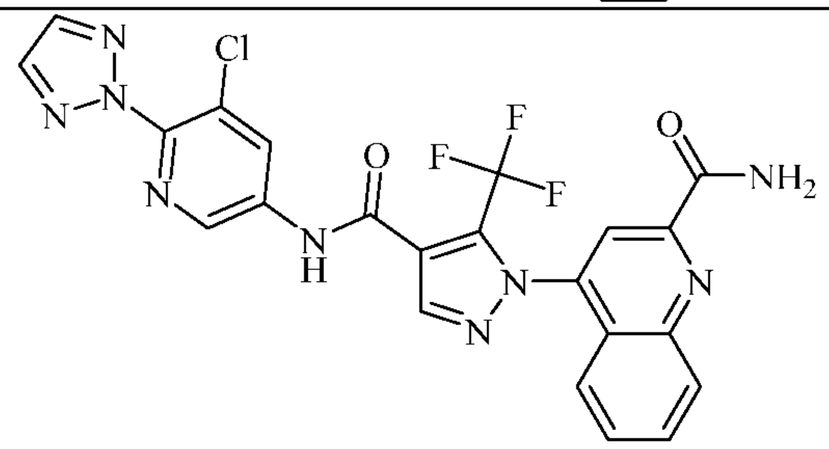
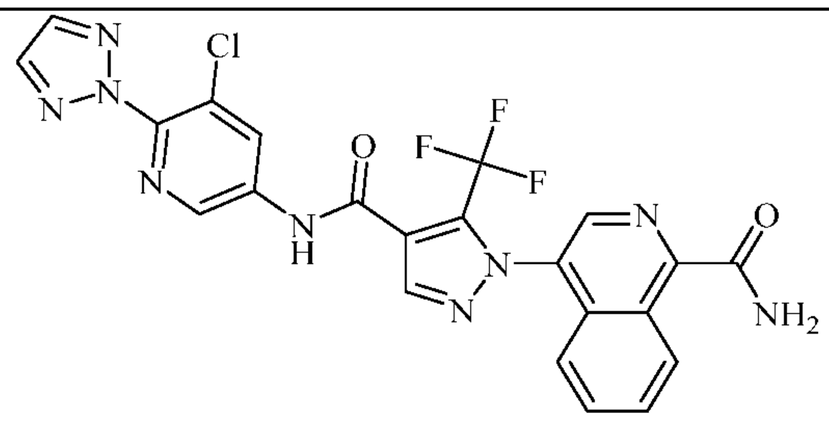
Structure	Cpd No.	Cpd Name
	**359**	N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**360**	N-(2-methoxypyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**361**	N-(2-morpholinopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**362**	N-(5-chloro-2-methyl-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**363**	N-(5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

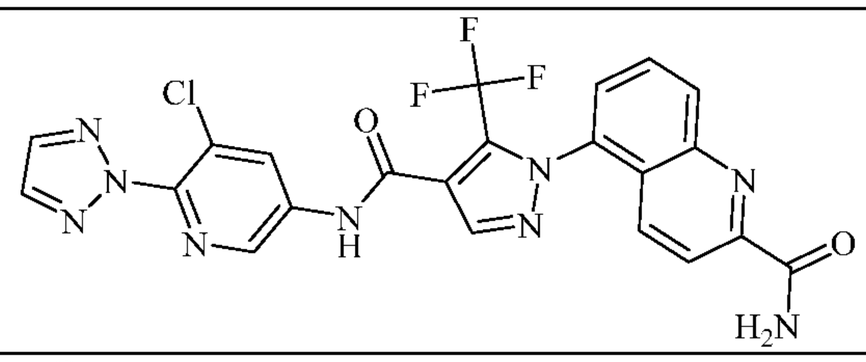
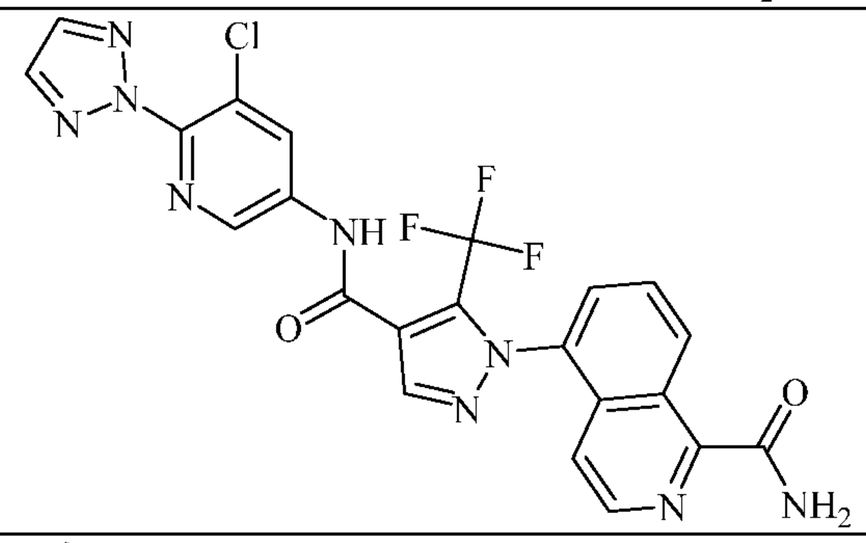
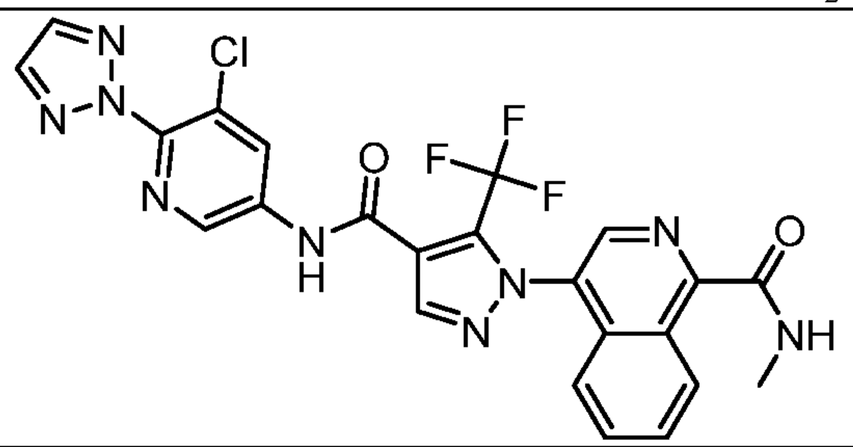
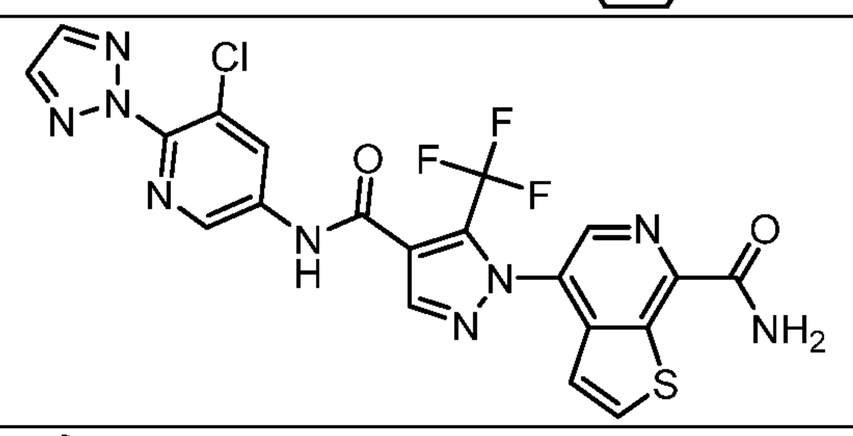
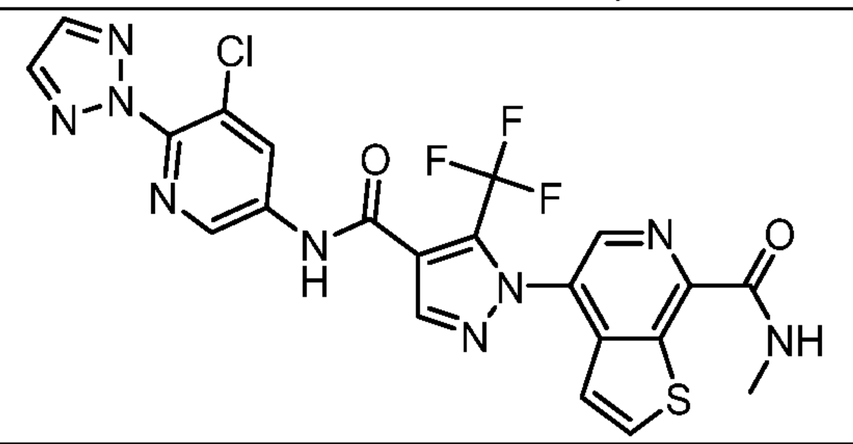
Structure	Cpd No.	Cpd Name
	**364**	1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide
	**365**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**366**	1-(1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**367**	1-(1-(1,4-dioxan-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**368**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-ethoxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**369**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(5-oxopyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

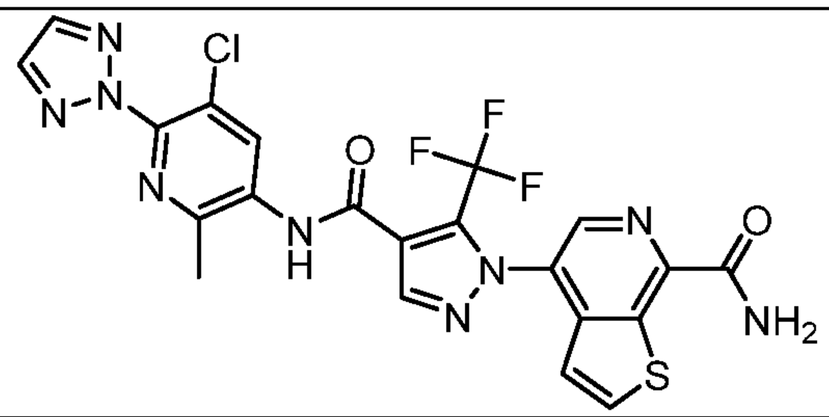
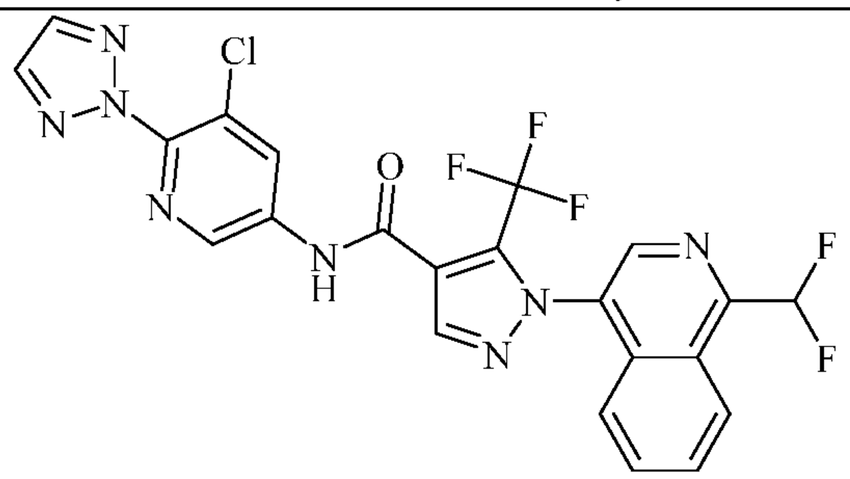
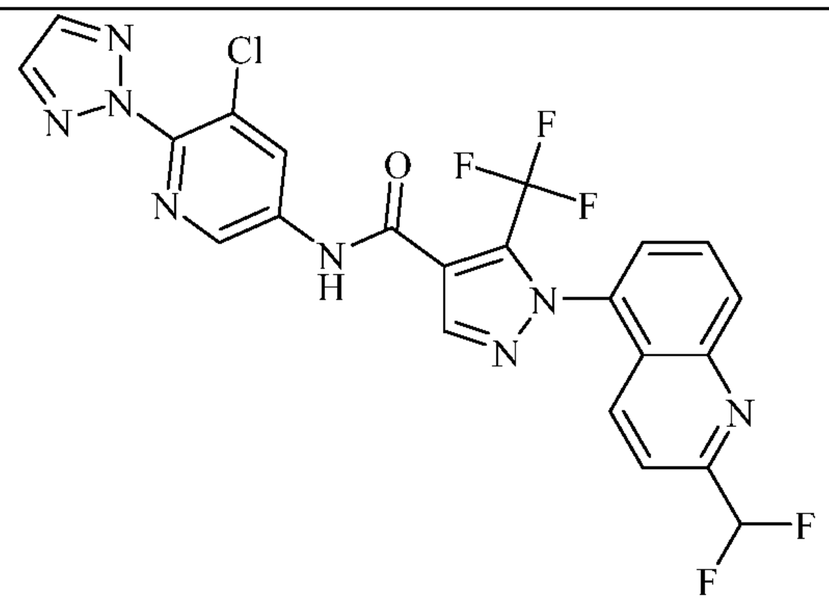
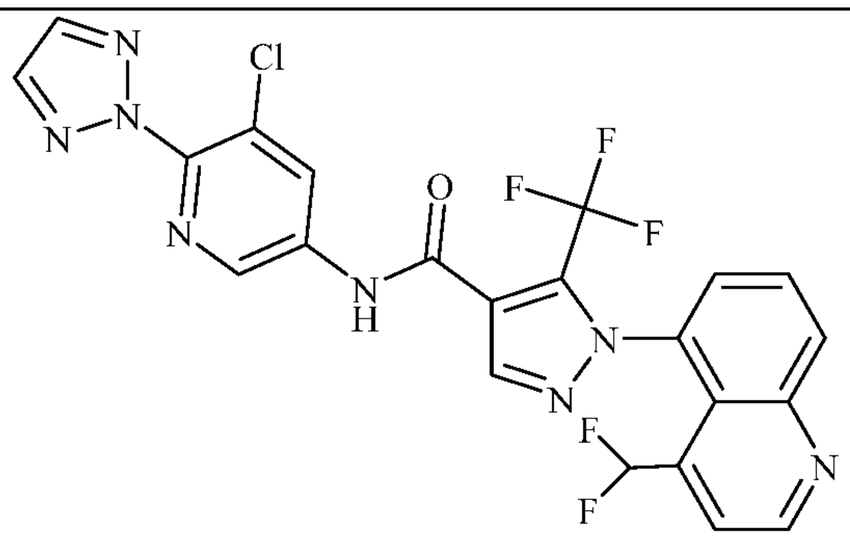
Structure	Cpd No.	Cpd Name
	**370**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**371**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**372**	*N*-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**373**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-((N-methylformamido)methyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

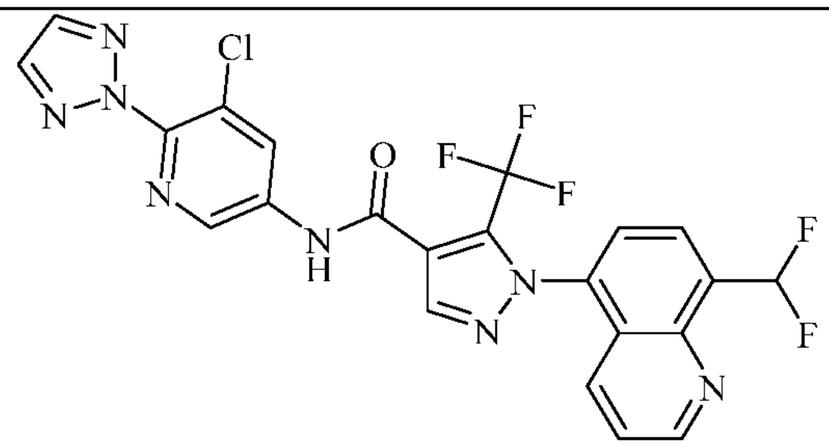
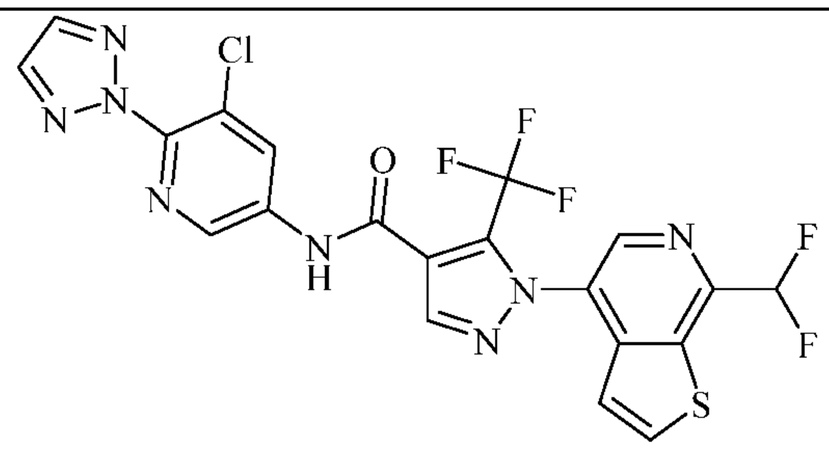
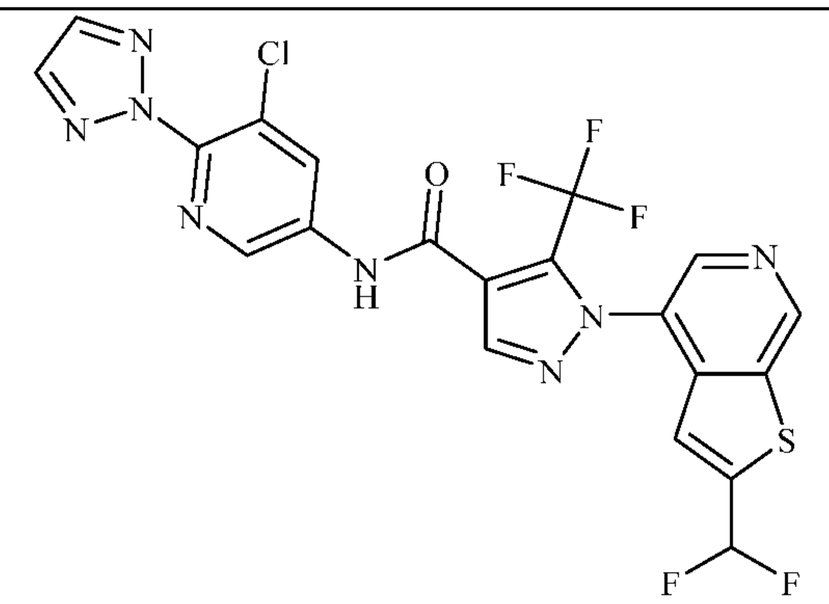
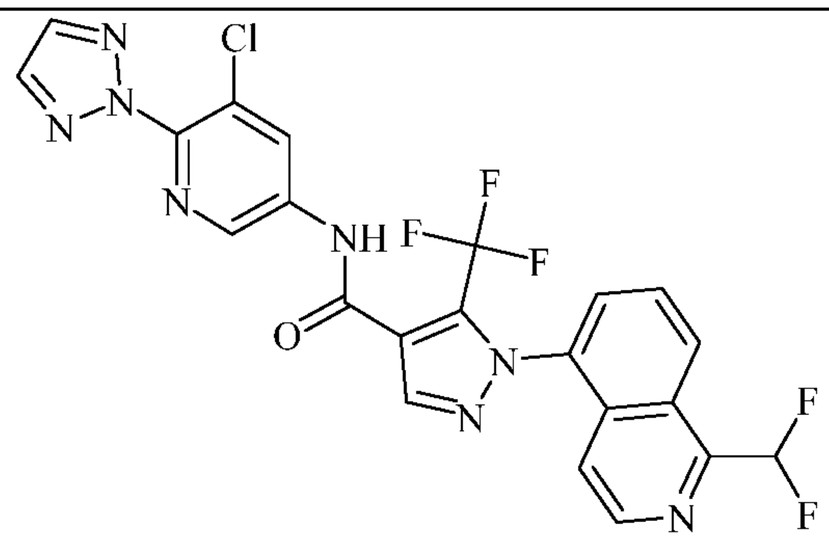
Structure	Cpd No.	Cpd Name
	**374**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(1-hydroxyethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**375**	1-(2-acetylquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**376**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**377**	1-(1-aminoisoquinolin-4-yl)-N-(6-methyl-5-(trifluoromethyl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**378**	1-(1-acetylisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

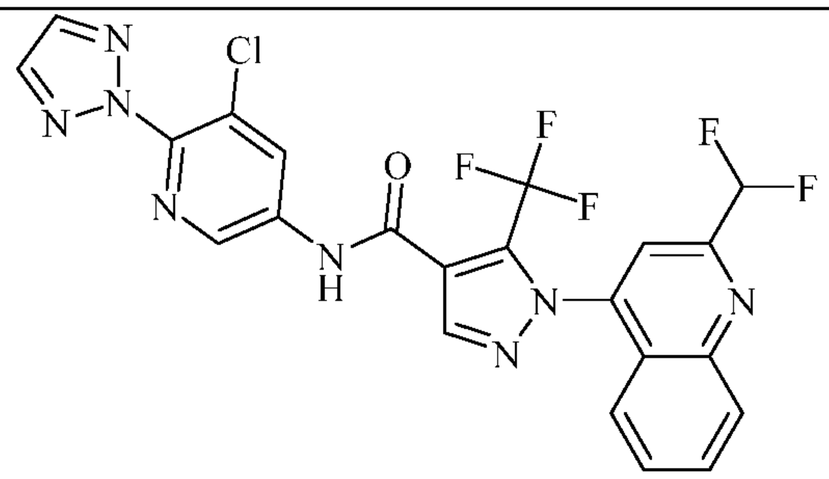
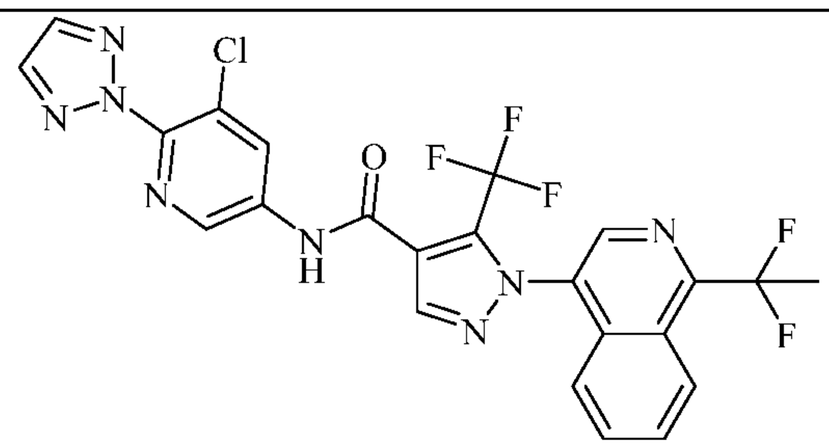
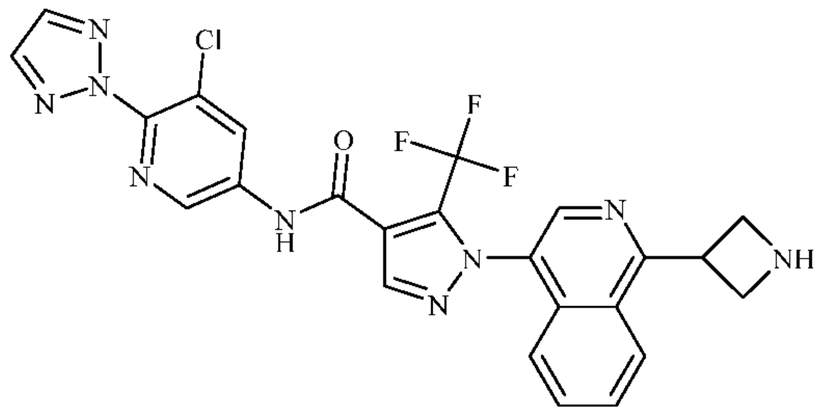
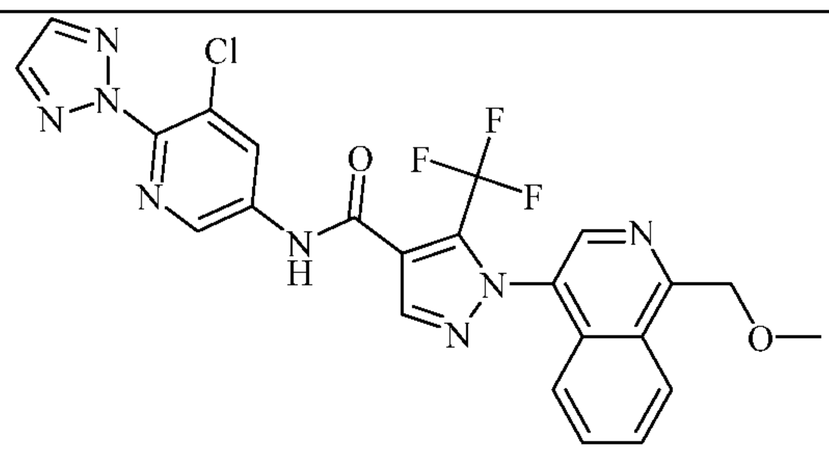
Structure	Cpd No.	Cpd Name
	**379**	1-(1-(azetidin-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**380**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(pyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**381**	1-(2-(azetidin-2-yl)quinolin-5-yl)- *N* -(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**382**	1-(2-(azetidin-2-yl)quinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

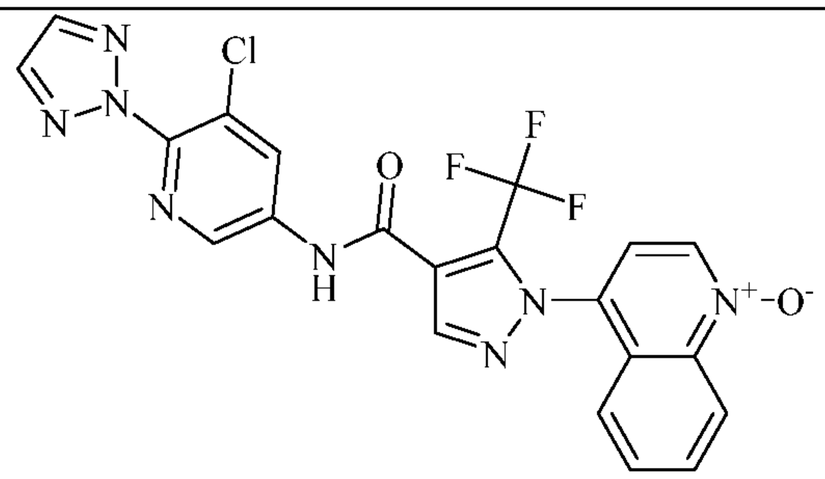
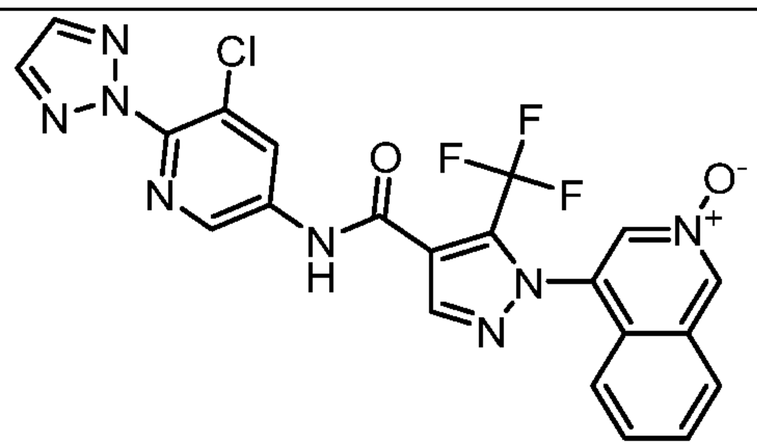
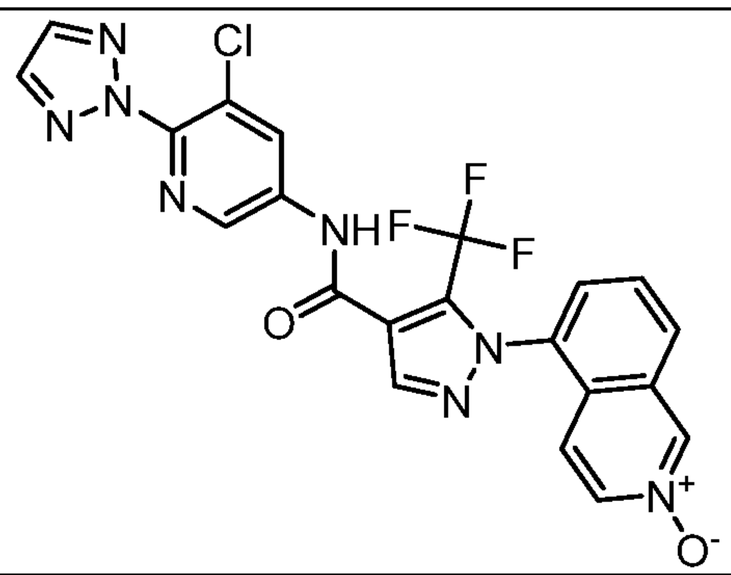
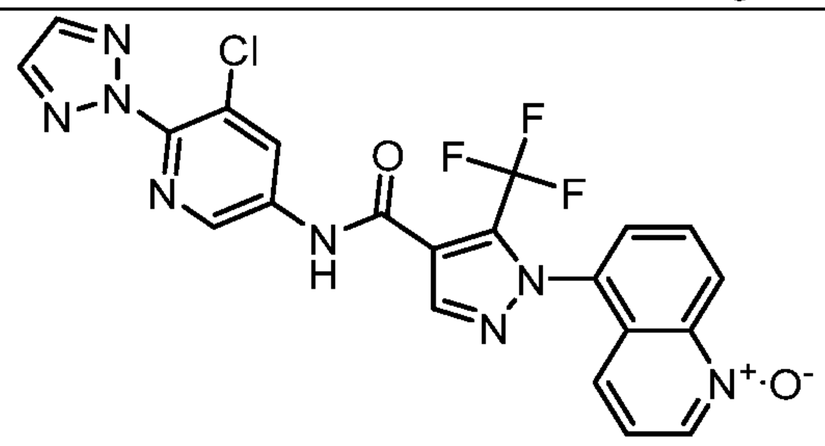
Structure	Cpd No.	Cpd Name
	**383**	*tert*-butyl 2-(5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)azetidine-1-carboxylate
	**384**	1-(1-(azetidin-2-yl)isoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**385**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(hydroxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**386**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide
	**387**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide

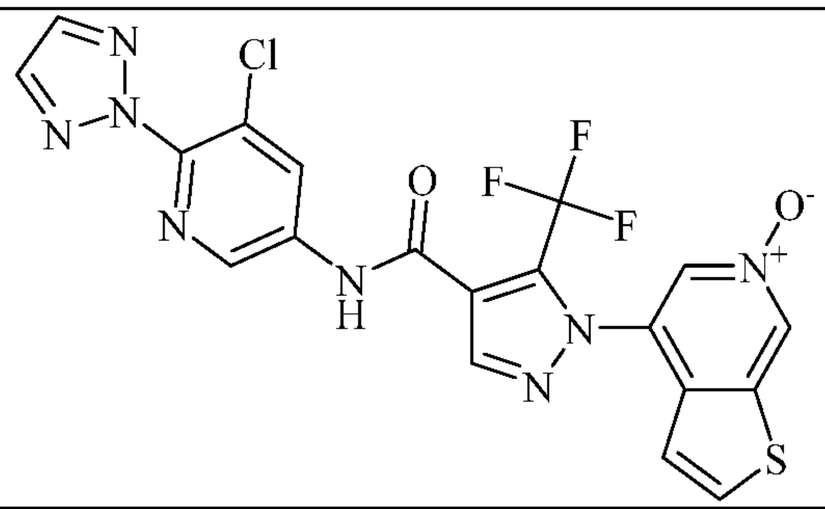
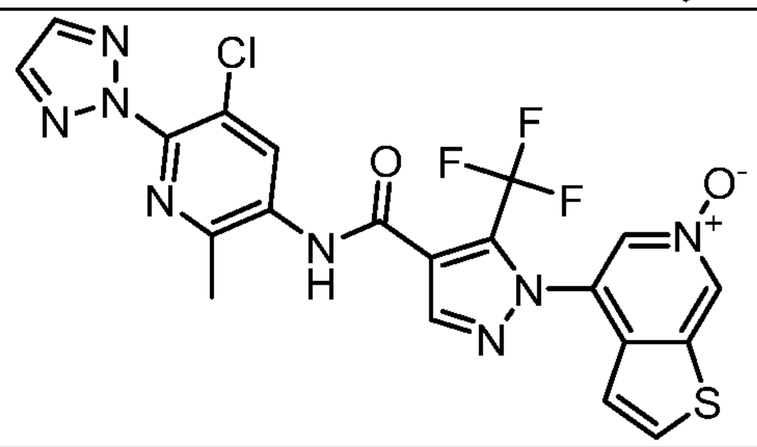
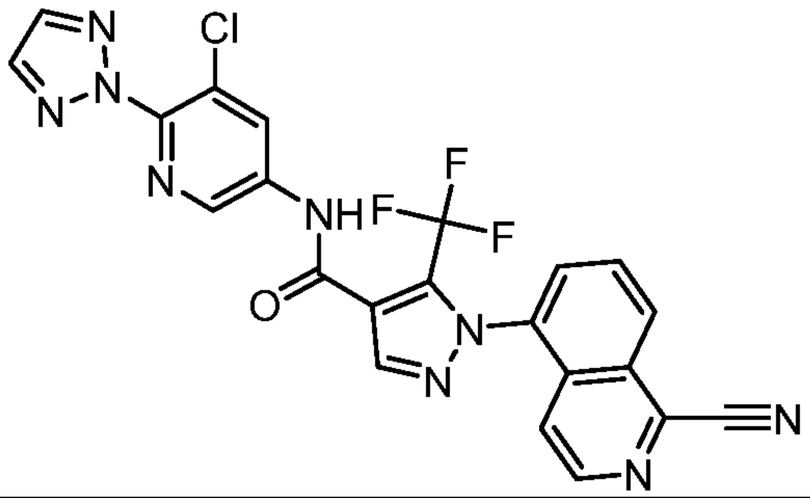
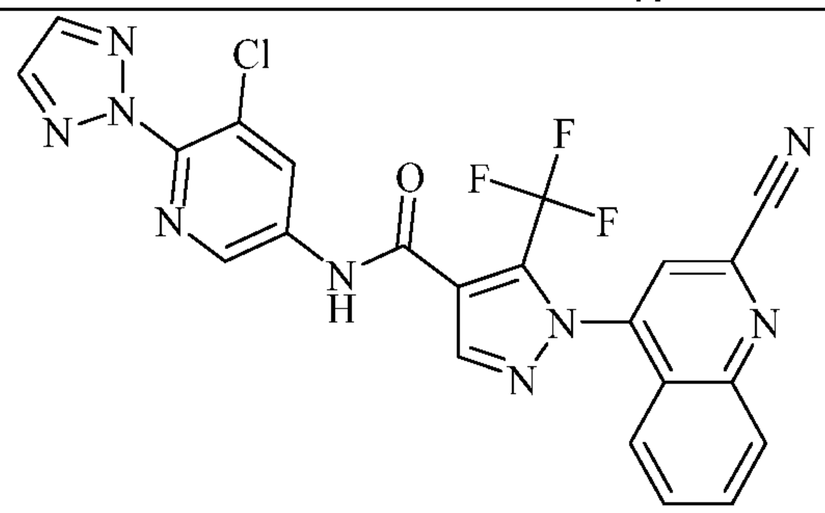
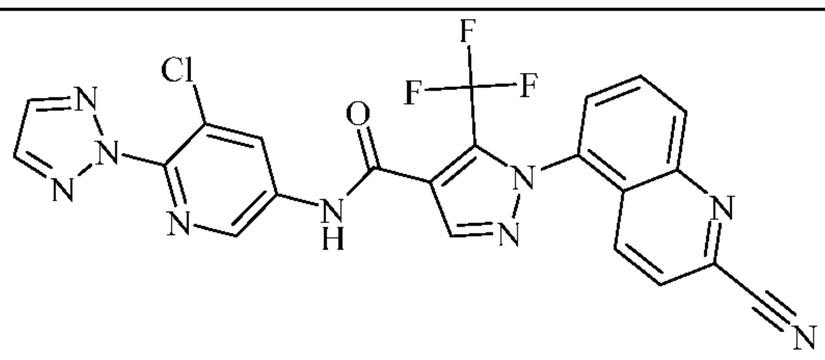
Structure	Cpd No.	Cpd Name
	**388**	5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide
	**389**	5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide
	**390**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-methylisoquinoline-1-carboxamide
	**391**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide
	**392**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-methylthieno[2,3-c]pyridine-7-carboxamide

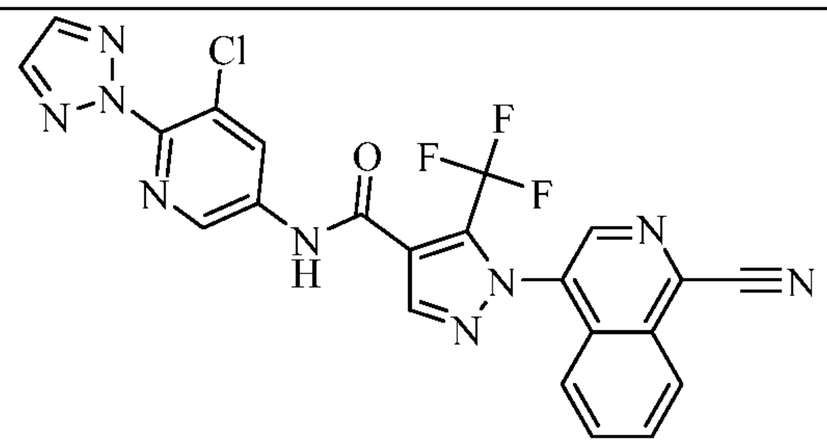
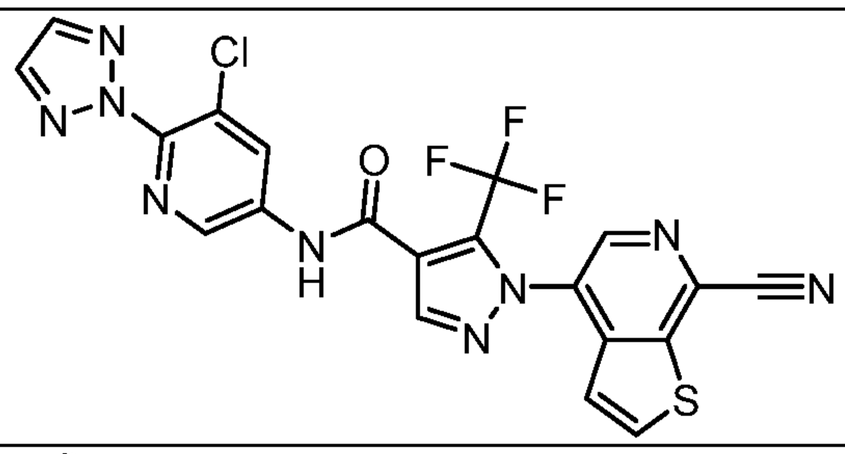
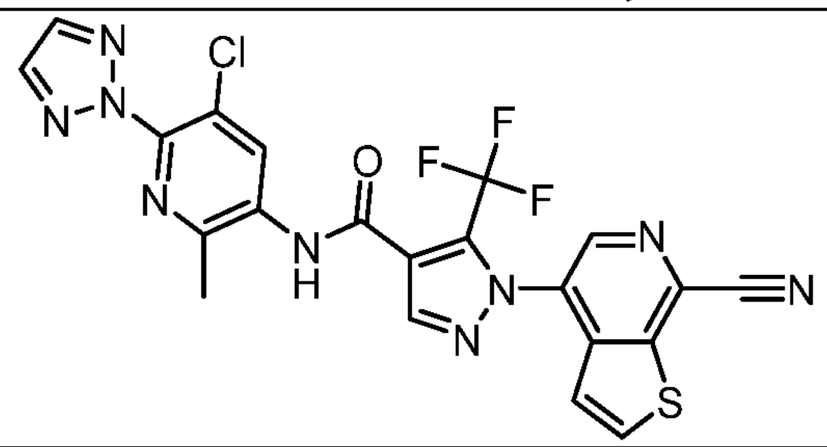
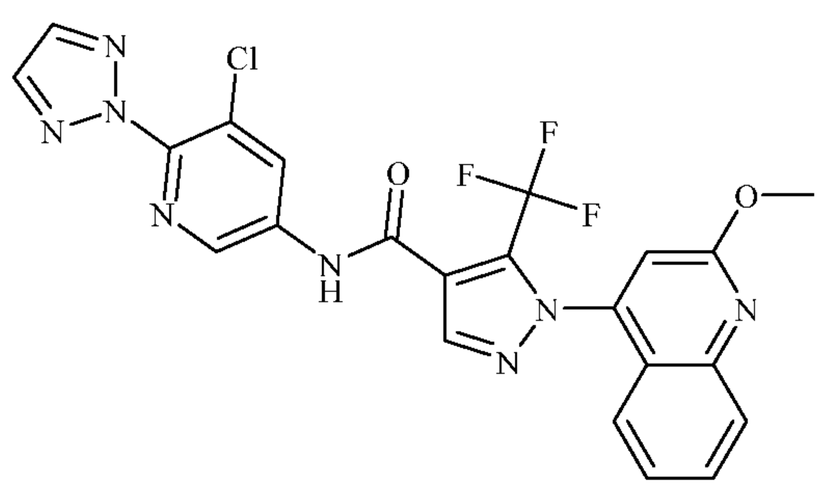
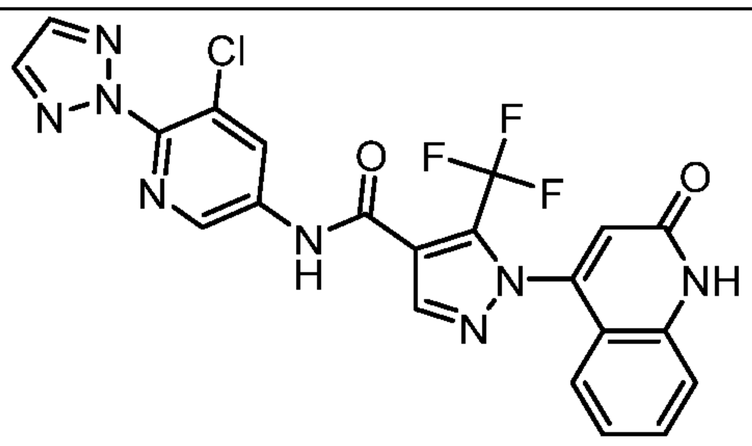
Structure	Cpd No.	Cpd Name
	**393**	4-(4-((5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide
	**394**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**395**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**396**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

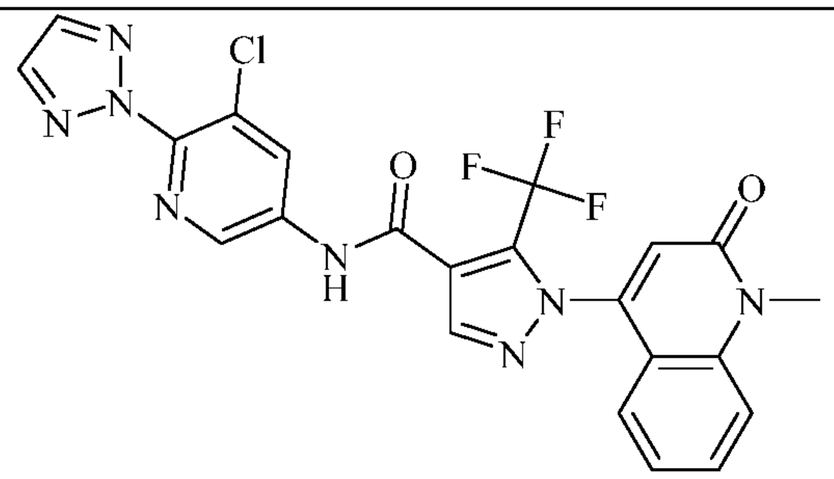
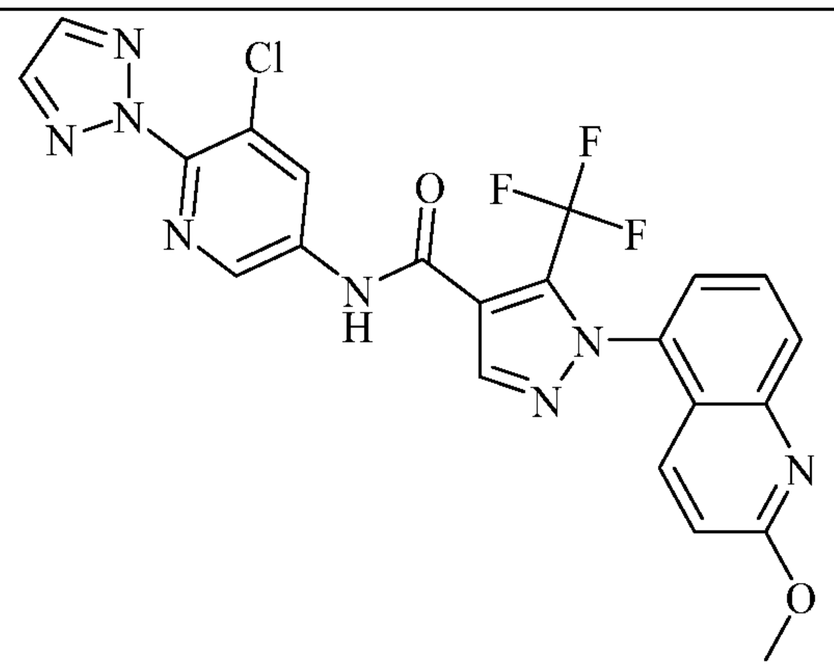
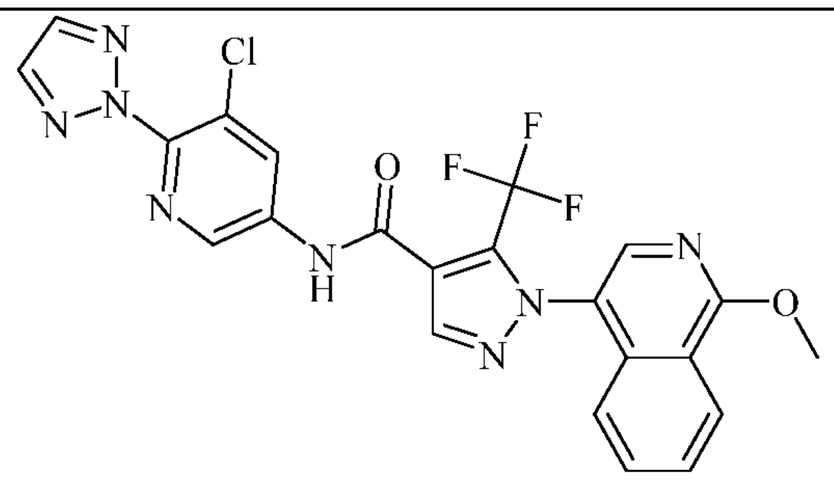
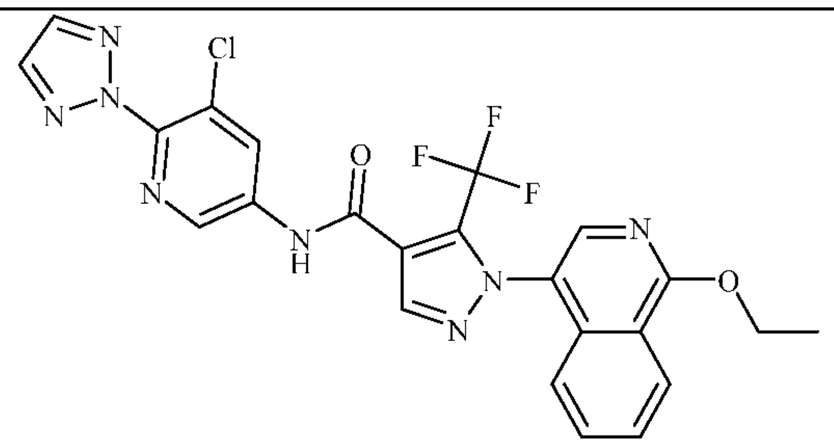
Structure	Cpd No.	Cpd Name
	**397**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**398**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**399**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**400**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamid

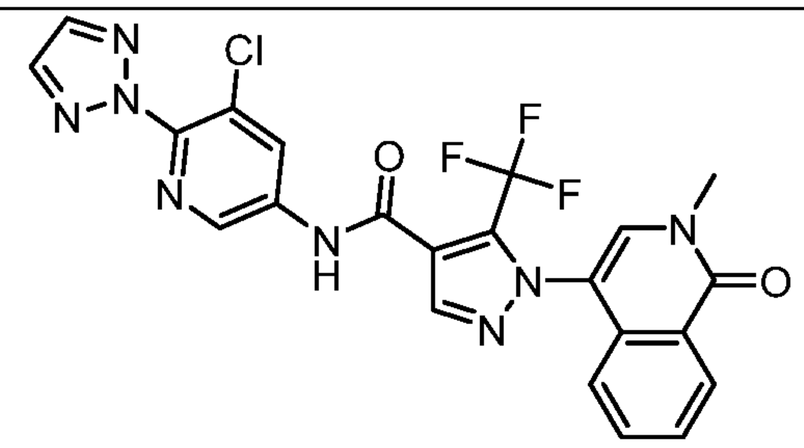
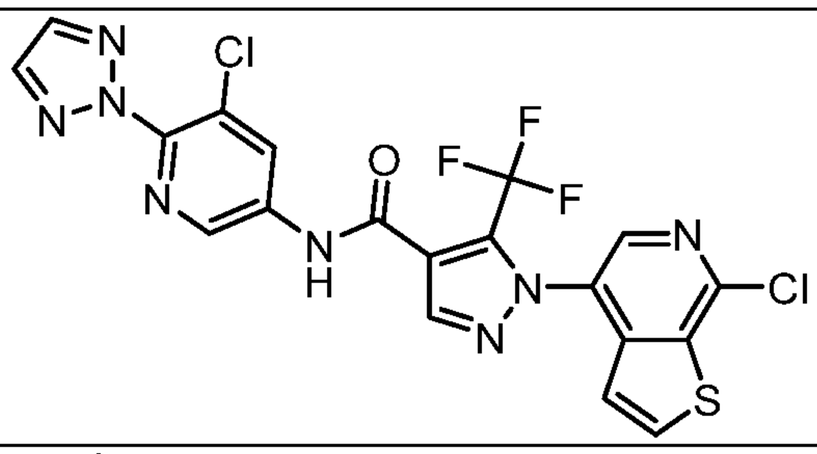
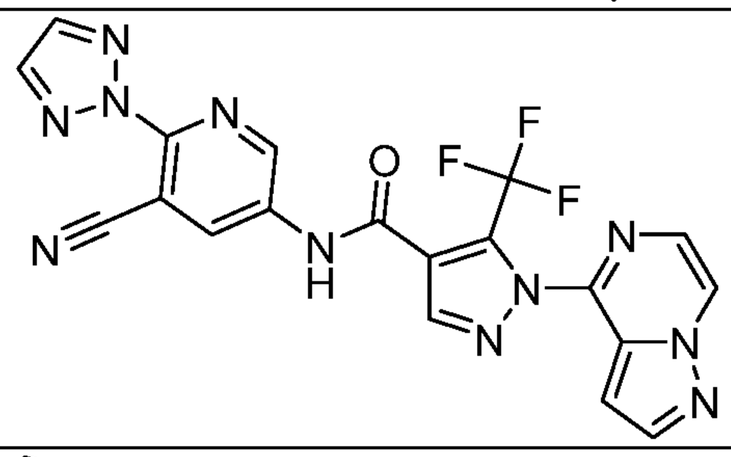
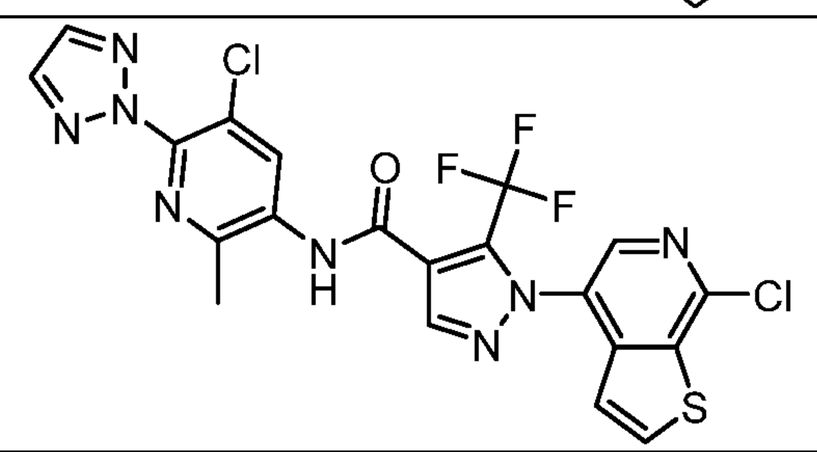
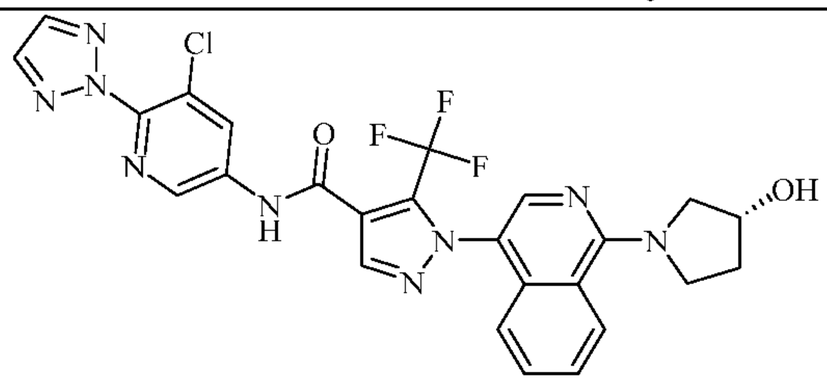
Structure	Cpd No.	Cpd Name
	**401**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**402**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1,1-difluoroethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**403**	1-(1-(azetidin-3-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**404**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methoxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

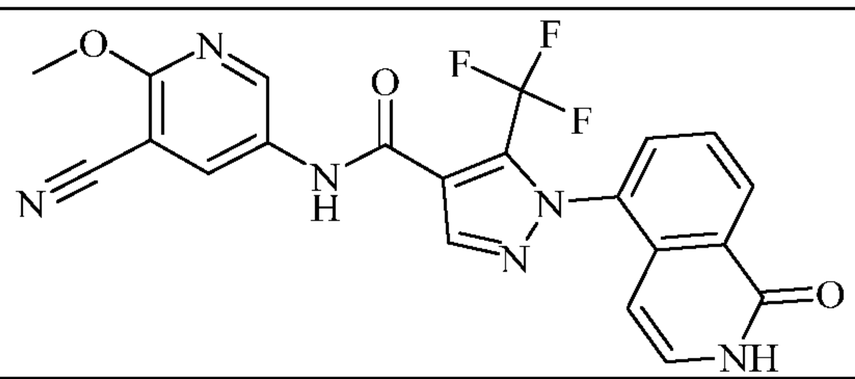
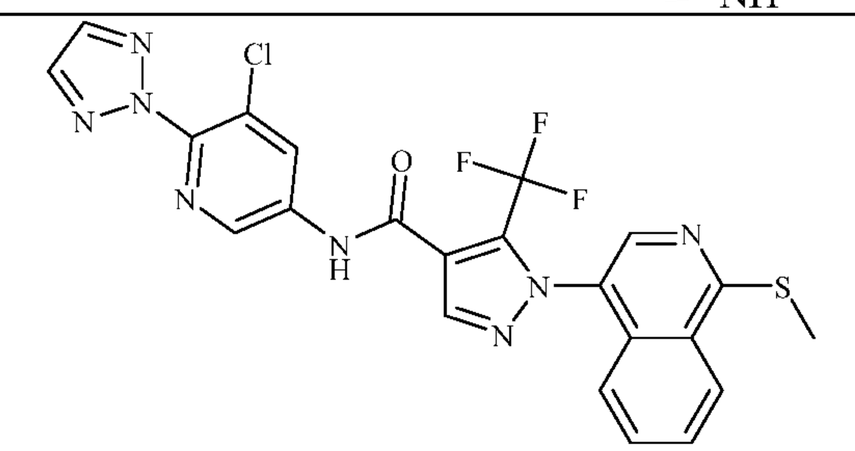
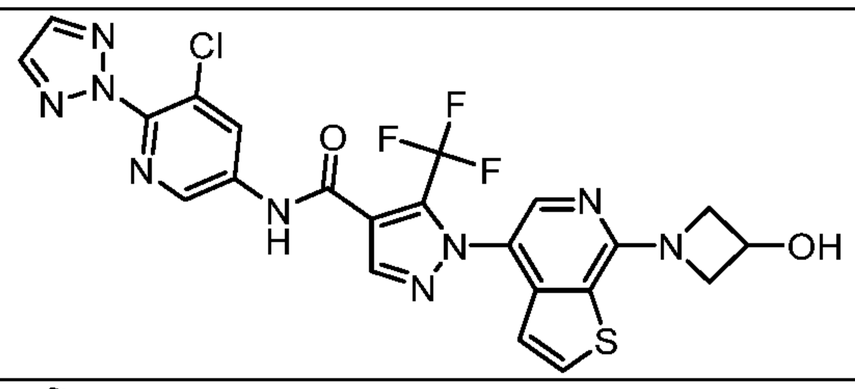
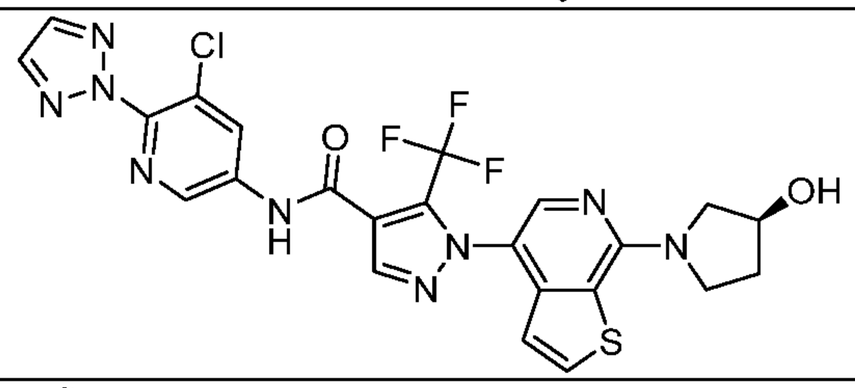
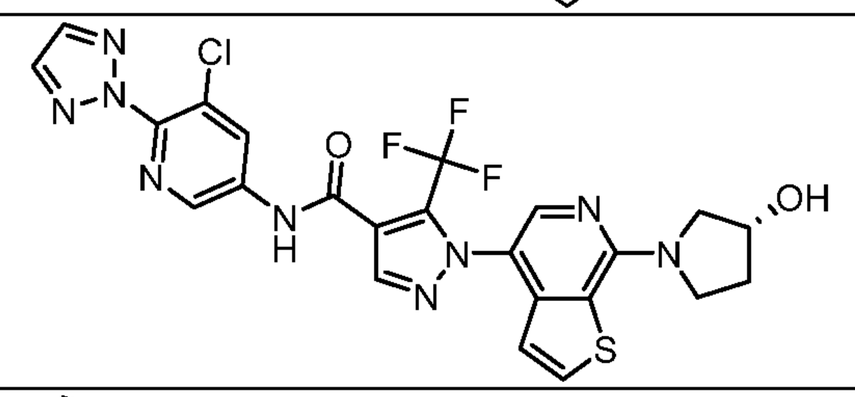
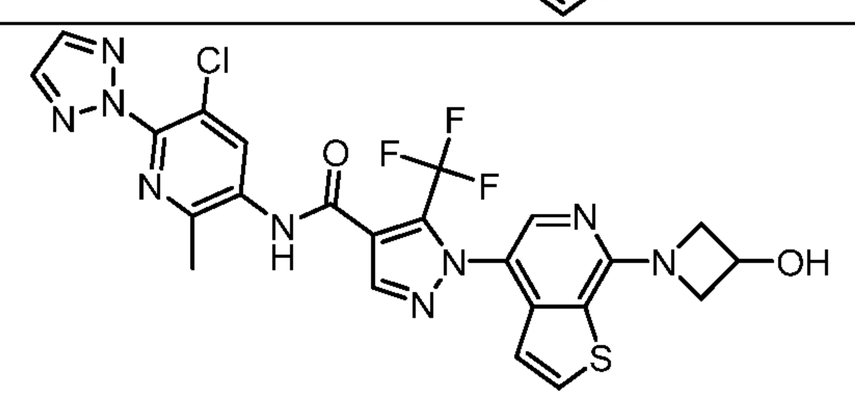
Structure	Cpd No.	Cpd Name
	**405**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline 1-oxide
	**406**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline 2-oxide
	**407**	5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline 2-oxide
	**408**	5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline 1-oxide

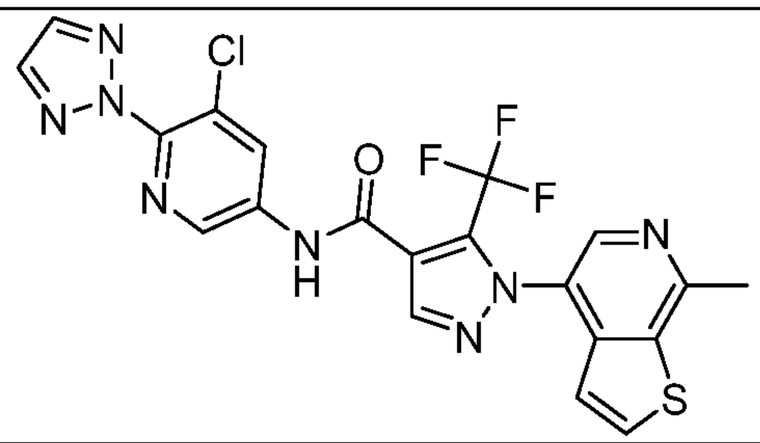
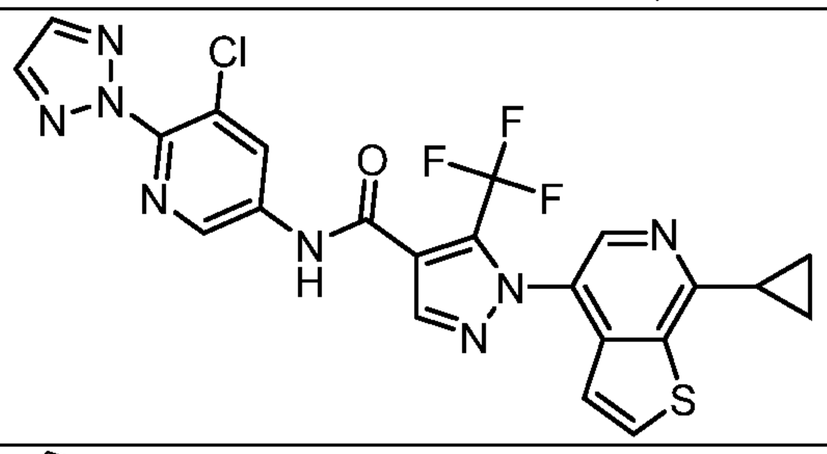
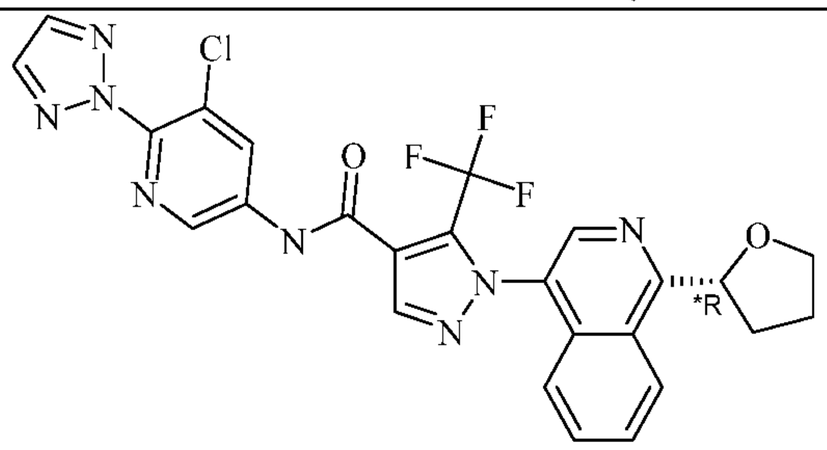
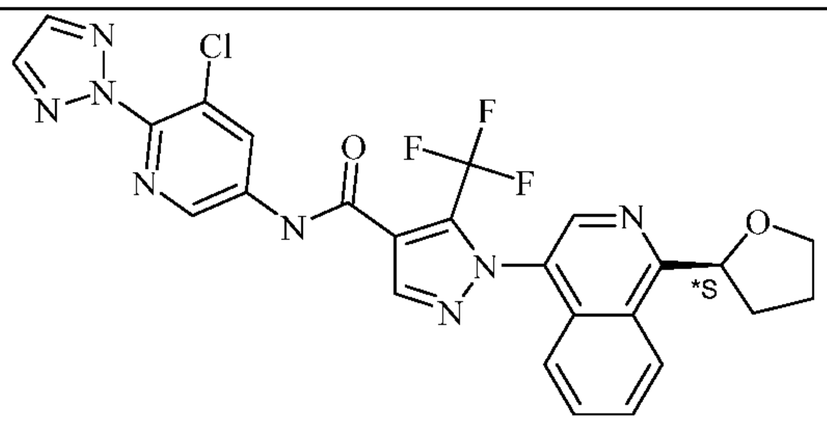
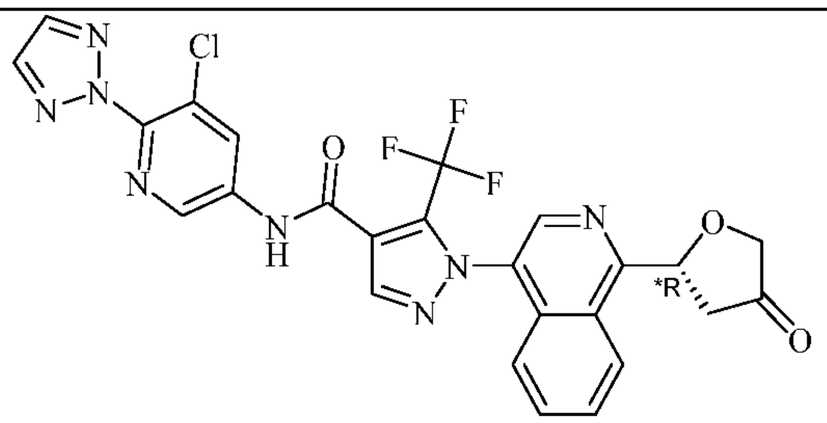
Structure	Cpd No.	Cpd Name
	**409**	4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine 6-oxide
	**410**	4-(4-((5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine 6-oxide
	**411**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**412**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**413**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

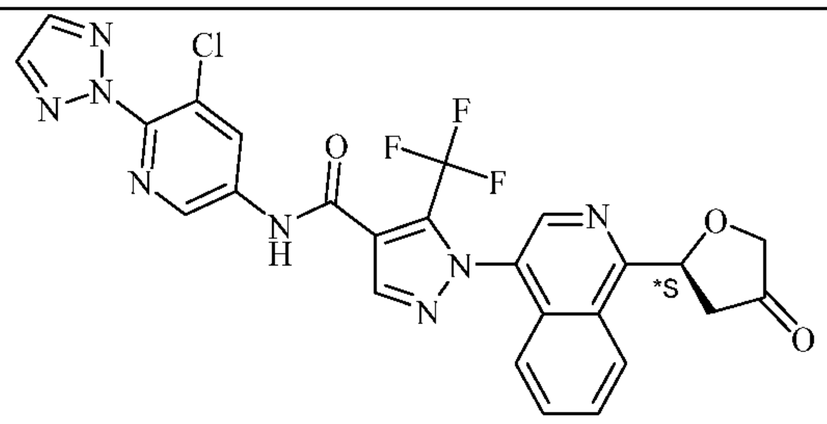
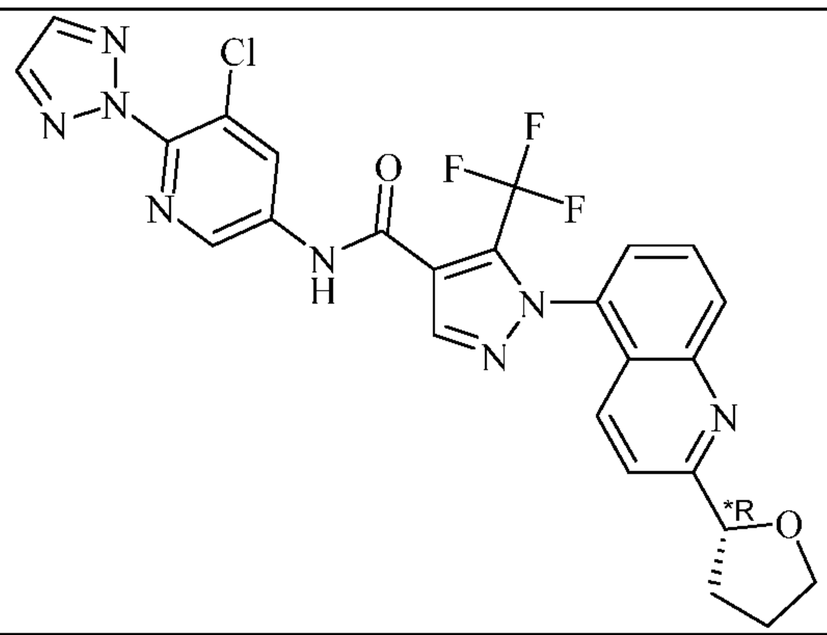
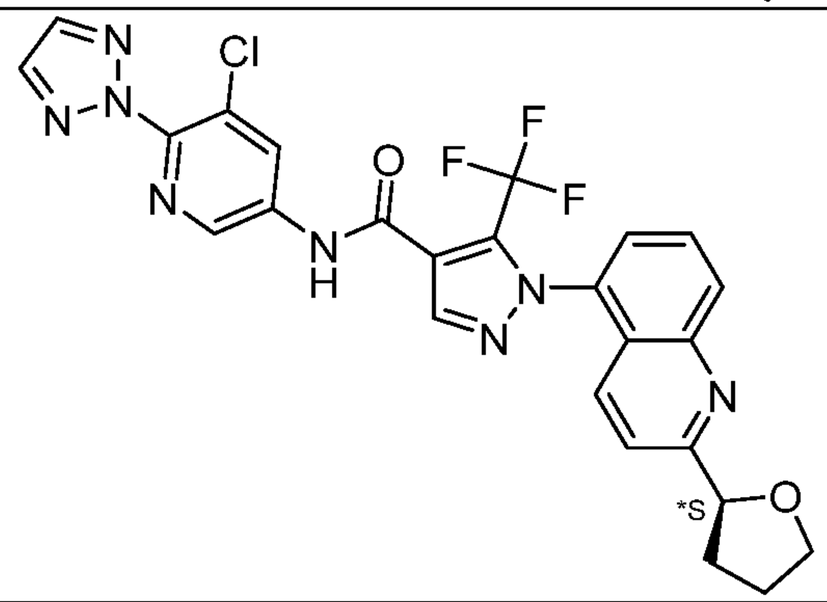
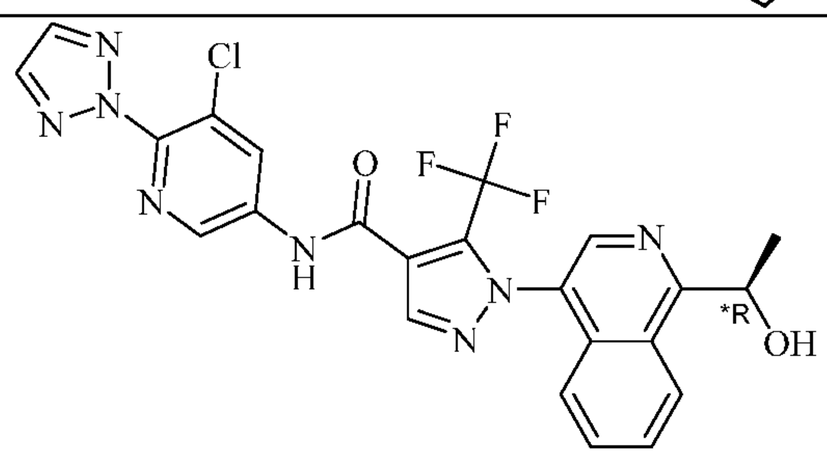
Structure	Cpd No.	Cpd Name
	**414**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**415**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**416**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**417**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**418**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

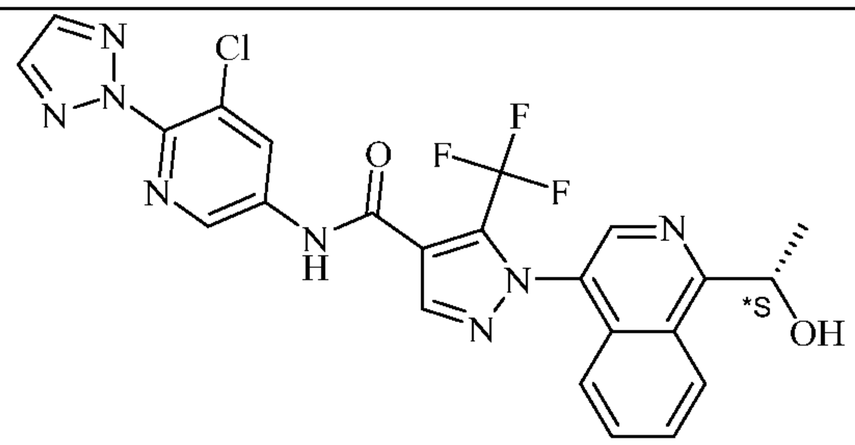
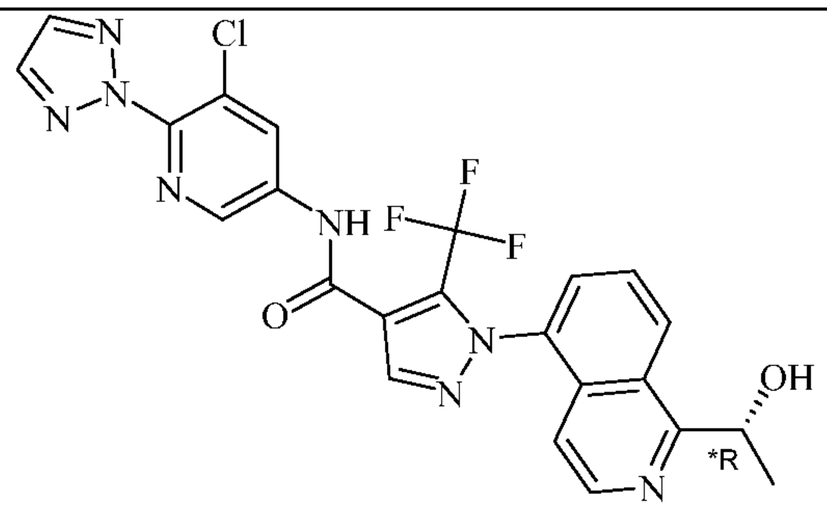
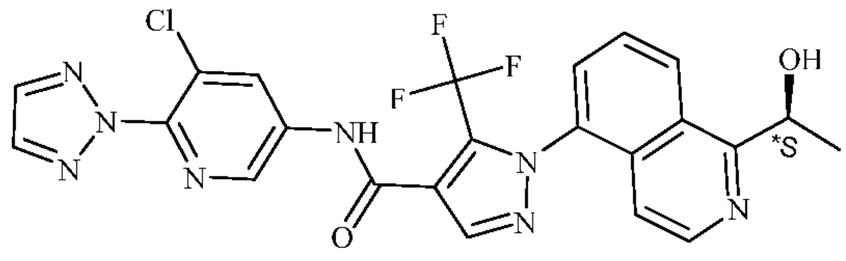
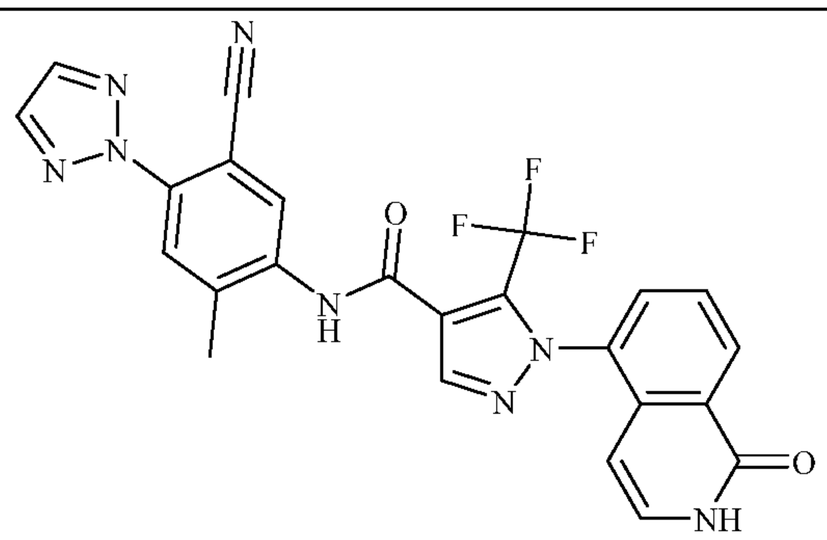
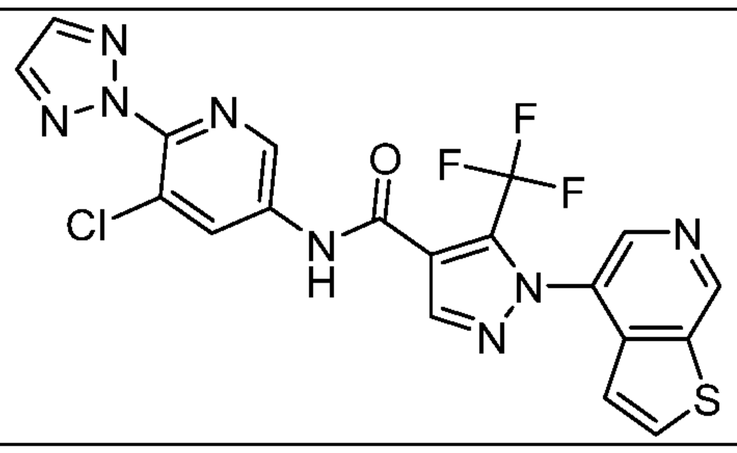
Structure	Cpd No.	Cpd Name
	**419**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**420**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**421**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**422**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-ethoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

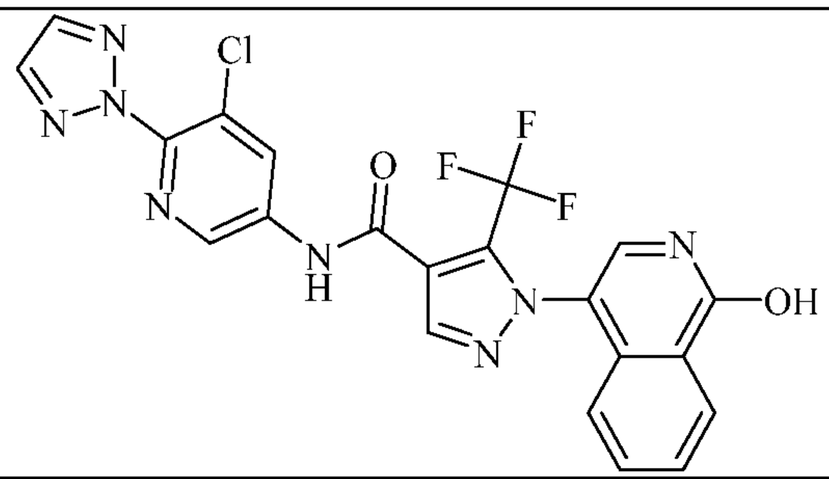
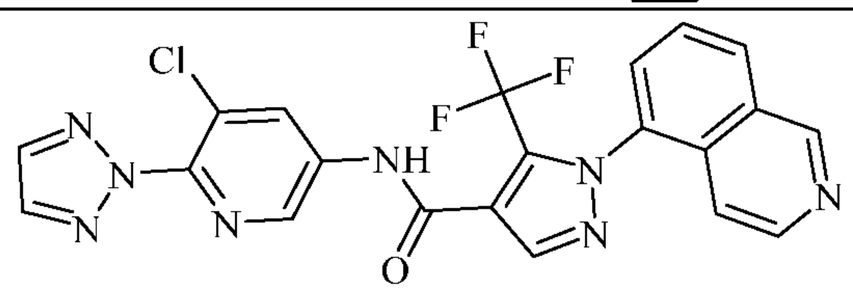
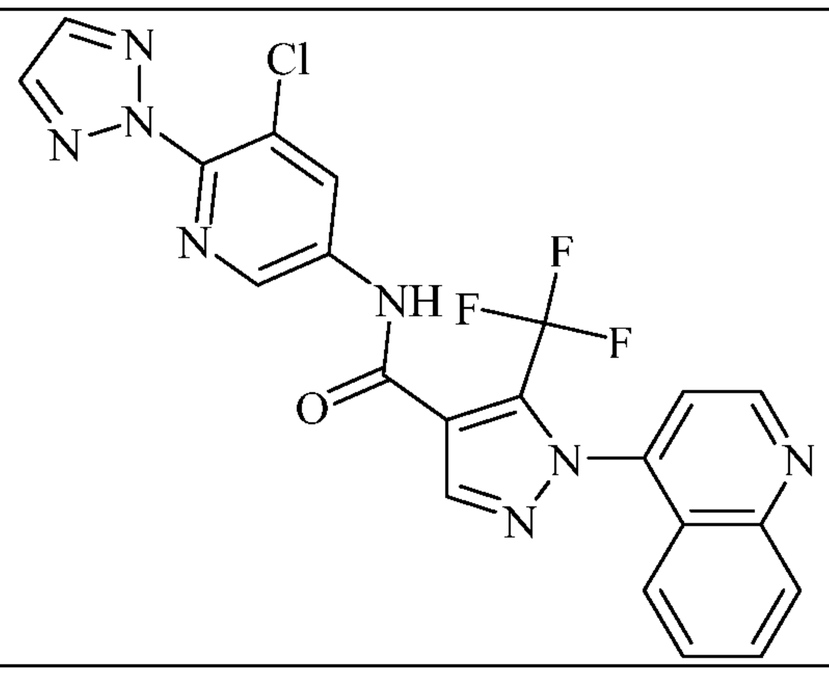
Structure	Cpd No.	Cpd Name
	**423**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**424**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**425**	N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**426**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**427**	(R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

Structure	Cpd No.	Cpd Name
	**428**	N-(5-cyano-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**429**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylthio)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**430**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**431**	(S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**432**	(R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**433**	N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

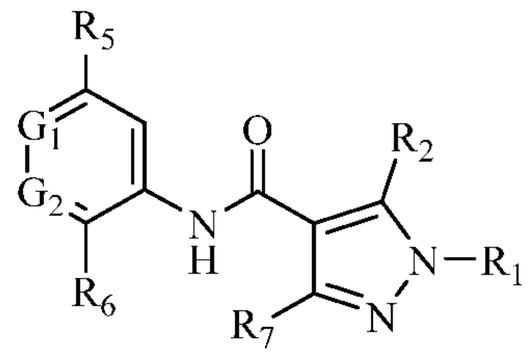
Structure	Cpd No.	Cpd Name
	**434**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**435**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyclopropylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**436**	(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**437**	(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**438**	(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

Structure	Cpd No.	Cpd Name
	**439**	(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**440**	(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**441**	(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**442**	(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

Structure	Cpd No.	Cpd Name
	**443**	(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**444**	(*R)-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide
	**445**	(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**446**	N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**447**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

Structure	Cpd No.	Cpd Name
	**448**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**449**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide
	**450**	N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide

In a further embodiment, the invention is directed to a compound of Formula (I)



Formula (I)

selected from the group consisting of

N-(2-cyanopyridin-4-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide;

1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(5-(trifluoromethyl)pyridin-3-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(quinolin-5-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-methoxyphenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-pyrazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isobutyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-ethyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isopropyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(benzofuran-4-yl)-*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(1-methoxyethyl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-fluoropyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

methyl 3-chloro-5-(3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamido)picolinate;

N-(5-chloro-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(difluoromethyl)-1-(isoquinolin-1-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-cyano-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-fluoro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-cyano-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(thiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(*1H*-indazol-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-imidazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-aminobutyl)-3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamide;

1-(isoquinolin-4-yl)-*N*-(2-methyl-6-(trifluoromethyl)pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

methyl 6-chloro-4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate;

methyl 4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(2-cyanopyridin-4-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-ethoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(4-aminobutoxy)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(cinnolin-4-yl)-*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(4-(4-aminobutyl)piperazine-1-carbonyl)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(phthalazin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinoxalin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

tert-butyl 2-(5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)azetidine-1-carboxylate;

N -(3-(methylsulfonyl)-4-(1H-1,2,3-triazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-2-yl)isoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(3-(methylsulfonyl)-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-(azetidin-2-yl)quinolin-5-yl)- *N* -(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(2,5-diethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

1-(2-chloroquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-chloroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

(**R*)-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(**R*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-cyano-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylic acid;

N-(1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-methylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-3-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylic acid;

N-(5-methoxy-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-aminobutyl)-3-cyano-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide;

2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoic acid

N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-methylphenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methyl-6-(1-methyl-1H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-ethoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-acetylisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(pyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(difluoromethoxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-b]pyridazin-6-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylthio)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-cyano-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-acetylquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-(aminomethyl)-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-(azetidin-2-yl)quinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-ethoxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate

1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-ethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrimidin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methoxy-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-(methoxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

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

N-(6-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylate;

N-(5-cyano-6-(2-methyl-2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate;

N-(6-(1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

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

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(dimethylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoroquinolin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[4,3-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoroisoquinolin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1,1-difluoroethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(5-oxopyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylate;

N-(5-cyano-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,5-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-((dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-(aminomethyl)-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-([1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-((N-methylformamido)methyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isothiazolo[5,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(1H-pyrrol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(1H-1,2,3-triazol-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]isoxazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-bromo-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-chloroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide;

1-(1-(1,4-dioxan-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide;

N-(5-chloro-6-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(benzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methoxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(1-hydroxyethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]isothiazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine 6-oxide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thiazolo[5,4-d]pyrimidin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinazolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methyl-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(methoxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-chlorophenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(hydroxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]oxazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(8-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline 1-oxide;

N-(5-cyano-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoate;

N-(6-(5-amino-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-cyano-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-cyanopyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate;

N-(5-chloro-6-(4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(4-aminonaphthalen-1-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoro-2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-Dquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide;

1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-morpholinopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-methoxypyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-ethynyl-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyclopropylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-methylthieno[2,3-c]pyridine-7-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-methyl-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-N-(pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-cyclopropylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N,N-dimethyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide

1-(1-aminoisoquinolin-4-yl)-N-(2-cyanopyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-methyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide;

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

N-(5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-chloro-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate;

1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(2-cyanopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-(2-methoxyethoxy)-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

or a pharmaceutically acceptable salt form thereof.

For use in medicine, salts of compounds of Formula (I) refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of compounds of Formula (I) or of their pharmaceutically acceptable salt forms thereof. Suitable pharmaceutically acceptable salts of compounds of Formula (I) include acid addition salts that can, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as, hydrochloric acid, sulfuric

acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of Formula (I) carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts such as, sodium or potassium salts; alkaline earth metal salts such as, calcium or magnesium salts; and salts formed with suitable organic ligands such as, quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, *N*-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Representative acids and bases that may be used in the preparation of pharmaceutically acceptable salts include acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucoronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid,

L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, *N*-methyl-glucamine, hydrabamine, *1H*-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine, tromethamine, and zinc hydroxide.

Embodiments of the present invention include prodrugs of compounds of Formula (I). In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treating or preventing embodiments of the present invention, the term "administering" encompasses the treatment or prevention of the various diseases, conditions, syndromes and disorders described with the compound specifically disclosed or with a compound that may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to a patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to embodiments of this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorph and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention. The skilled artisan will understand that the term compound as used herein, is meant to include solvated compounds of Formula (I).

Where the processes for the preparation of the compounds according to certain embodiments of the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as, preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as, the formation of diastereomeric pairs by salt formation with an optically active acid such as, (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chomatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

One embodiment of the present invention is directed to a composition, including a pharmaceutical composition, comprising, consisting of, and/or consisting essentially of the (+)-enantiomer of a compound of Formula (I) wherein said composition is substantially free from the (-)-isomer of said compound. In the present context, substantially free means less than about 25 %, preferably less than about 10 %, more preferably less than about 5 %, even more preferably less than about 2 % and even more preferably less than about 1 % of the (-)-isomer calculated as

$$\%(+)\text{-enantiomer} = \frac{(mass\,(+)\text{-enantiomer})}{(mass\,(+)\text{-enantiomer}) + (mass(-)\text{-enantiomer})} \times 100$$

Another embodiment of the present invention is a composition, including a pharmaceutical composition, comprising, consisting of, and consisting essentially of the (-)-enantiomer of a compound of Formula (I) wherein said composition is substantially free from the (+)-isomer of said compound. In the present context, substantially free from means less than about 25 %, preferably less than about 10 %, more preferably less than about 5 %, even more preferably less than about 2 % and even more preferably less than

about 1 % of the (+)-isomer calculated as

$$\%(-)\text{-enantiomer} = \frac{(mass\,(-)\text{-enantiomer})}{(mass\,(+)\text{-enantiomer}) + (mass(-)\text{-enantiomer})} \times 100$$

It is intended that within the scope of the present invention, any one or more element(s), in particular when mentioned in relation to a compound of Formula (I), shall comprise all isotopes and isotopic mixtures of said element(s), either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{16}O and ^{18}O. The isotopes may be radioactive or non-radioactive. Radiolabelled compounds of formula (I) may comprise one or more radioactive isotope(s) selected from the group of ^{3}H, ^{11}C, ^{18}F, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. Preferably, the radioactive isotope is selected from the group of ^{2}H, ^{3}H, ^{11}C and ^{18}F.

During any of the processes for preparation of the compounds of the various embodiments of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups such as those described in *Protective Groups in Organic Chemistry*, *Second Edition*, J.F.W. McOmie, Plenum Press, 1973; T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, *Third Edition,* John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Even though the compounds of embodiments of the present invention (including their pharmaceutically acceptable salts and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a

pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent selected with regard to the intended route of administration and standard pharmaceutical or veterinary practice. Thus, particular embodiments of the present invention are directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and at least one pharmaceutically acceptable carrier, pharmaceutically acceptable excipient, and/or pharmaceutically acceptable diluent.

By way of example, in the pharmaceutical compositions of embodiments of the present invention, the compounds of Formula (I) may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilizing agent(s), and combinations thereof.

Solid oral dosage forms such as, tablets or capsules, containing the compounds of the present invention may be administered in at least one dosage form at a time, as appropriate. It is also possible to administer the compounds in sustained release formulations.

Additional oral forms in which the present inventive compounds may be administered include elixirs, solutions, syrups, and suspensions; each optionally containing flavoring agents and coloring agents.

Alternatively, compounds of Formula (I) can be administered by inhalation (intratracheal or intranasal) or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream comprising, consisting of, and/or consisting essentially of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between about 1 % and about 10 % by weight of the cream, into an ointment comprising, consisting of, and/or consisting essentially of a wax or soft paraffin base together with any stabilizers and preservatives as may be required. An alternative means of administration includes transdermal administration by using a skin or transdermal patch.

The pharmaceutical compositions of the present invention (as well as the

compounds of the present invention alone) can also be injected parenterally, for example, intracavernosally, intravenously, intramuscularly, subcutaneously, intradermally, or intrathecally. In this case, the compositions will also include at least one of a suitable carrier, a suitable excipient, and a suitable diluent.

For parenteral administration, the pharmaceutical compositions of the present invention are best used in the form of a sterile aqueous solution that may contain other substances, for example, enough salts and monosaccharides to make the solution isotonic with blood.

For buccal or sublingual administration, the pharmaceutical compositions of the present invention may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

By way of further example, pharmaceutical compositions containing at least one of the compounds of Formula (I) as the active ingredient can be prepared by mixing the compound(s) with a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, and/or a pharmaceutically acceptable excipient according to conventional pharmaceutical compounding techniques. The carrier, excipient, and diluent may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral, etc.). Thus, for liquid oral preparations such as, suspensions, syrups, elixirs and solutions, suitable carriers, excipients and diluents include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations such as, powders, capsules, and tablets, suitable carriers, excipients and diluents include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations also may be optionally coated with substances such as, sugars, or be enterically coated so as to modulate the major site of absorption and disintegration. For parenteral administration, the carrier, excipient and diluent will usually include sterile water, and other ingredients may be added to increase solubility and preservation of the composition. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives such as, solubilizers and preservatives.

A therapeutically effective amount of a compound of Formula (I) or a pharmaceutical composition thereof includes a dose range from about 0.1 mg to about 3000 mg, or any particular amount or range therein, in particular from about 1 mg to about 1000 mg, or any particular amount or range therein, or, more particularly, from about 10 mg to about 500 mg, or any particular amount or range therein, of active ingredient in a regimen of about 1 to about (4x) per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for a compound of Formula (I) will vary as will the diseases, syndromes, conditions, and disorders being treated.

For oral administration, a pharmaceutical composition is preferably provided in the form of tablets containing about 1.0, about 10, about 50, about 100, about 150, about 200, about 250, and about 500 milligrams of a compound of Formula (I).

An embodiment of the present invention is directed to a pharmaceutical composition for oral administration, comprising a compound of Formula (I) in an amount of from about 25 mg to about 500 mg.

Advantageously, a compound of Formula (I) may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, thee and (4x) daily.

Optimal dosages of a compound of Formula (I) to be administered may be readily determined and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease, syndrome, condition or disorder. In addition, factors associated with the particular subject being treated, including subject gender, age, weight, diet and time of administration, will result in the need to adjust the dose to achieve an appropriate therapeutic level and desired therapeutic effect. The above dosages are thus exemplary of the average case. There can be, of course, individual instances wherein higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of Formula (I) may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever use of a compound of Formula (I) is required for

a subject in need thereof.

In an embodiment, cancers that may benefit from a treatment with MALT1 inhibitors of the present invention include, but are not limited to, lymphomas, leukemias, carcinomas, and sarcomas, e.g. non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), mucosa-associated lymphoid tissue (MALT) lymphoma, marginal zone lymphoma, T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, chonic lymphocytic leukemia (CLL), lymphoblastic T cell leukemia, chonic myelogenous leukemia (CML), hairy-cell leukemia, acute lymphoblastic T cell leukemia, plasmacytoma, immunoblastic large cell leukemia, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, erytholeukemia, brain (gliomas), glioblastomas, breast cancer, colorectal/colon cancer, prostate cancer, lung cancer including non-small-cell, gastric cancer, endometrial cancer, melanoma, pancreatic cancer, liver cancer, kidney cancer, squamous cell carcinoma, ovarian cancer, sarcoma, osteosarcoma, thyroid cancer, bladder cancer, head&neck cancer, testicular cancer, Ewing's sarcoma, rhabdomyosarcoma, medulloblastoma, neuroblastoma, cervical cancer, renal cancer, urothelial cancer, vulval cancer, esophageal cancer, salivary gland cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, and GIST (gastrointestinal stromal tumor).

In another embodiment, MALT1 inhibitors of the present invention may be used for the treatment of immunological diseases including, but not limited to, autoimmune and inflammatory disorders, e.g. arthitis, inflammatory bowel disease, gastritis, ankylosing spondylitis, ulcerative colitis, pancreatits, Crohn's disease, celiac disease, multiple sclerosis, systemic lupus erythematosus, lupus nephitis, rheumatic fever, gout, organ or transplact rejection, chonic allograft rejection, acute or chonic graft-versus-host disease, dermatitis including atopic, dermatomyositis, psoriasis, Behcet's diseases, uveitis, myasthenia gravis, Grave's disease, Hashimoto thyroiditis, Sjoergen's syndrome, blistering disorders, antibody-mediated vasculitis syndromes, immune-complex vasculitides, allergic disorders, asthma, bronchitis, chonic obstructive pulmonary disease (COPD), cystic fibrosis, pneumonia, pulmonary diseases including oedema, embolism, fibrosis,

sarcoidosis, hypertension and emphysema, silicosis, respiratory failure, acute respiratory distress syndrome, BENTA disease, berylliosis, and polymyositis.

In another embodiment of the present invention, the compounds of the present invention may be employed in combination with one or more other medicinal agents, more particularly with other anti-cancer agents, e.g. chemotherapeutic, anti-proliferative or immunomodulating agents, or with adjuvants in cancer therapy, e.g. immunosuppressive or anti-inflammatory agents.

Possible combinations of the compounds of the present invention may include, but are not limited to, BTK (Bruton's tyrosine kinase) inhibitors such as ibrutinib, SYK inhibitors, PKC inhibitors, PI3K pathway inhibitors, BCL family inhibitors, JAK inhibitors, PIM kinase inhibitors, rituximab or other B cell antigen-binding antibodies, as well as immune cell redirection agents (e.g. blinatumomab or CAR T-cells) and immunomodulatory agents such as daratumumab, anti-PD1 antibodies, and anti-PD-L1 antibodies.

GENERAL SYNTHETIC METHODS

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the schemes and examples that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions described in the schemes and examples. Compounds analogous to the target compounds of these examples can be made according to similar routes. The disclosed compounds are useful as pharmaceutical agents as described herein. The various starting materials used in the schemes and examples are commercially available or may be prepared by methods well within the skill of persons versed in the art.

Abbreviations used in the instant specification, particularly the schemes and examples, are as follows:

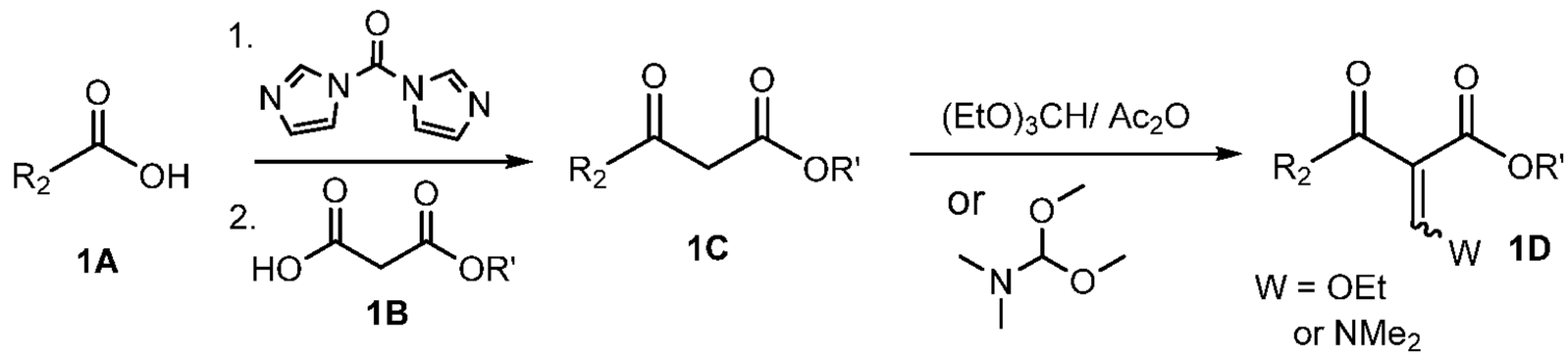
ACN	acetonitrile

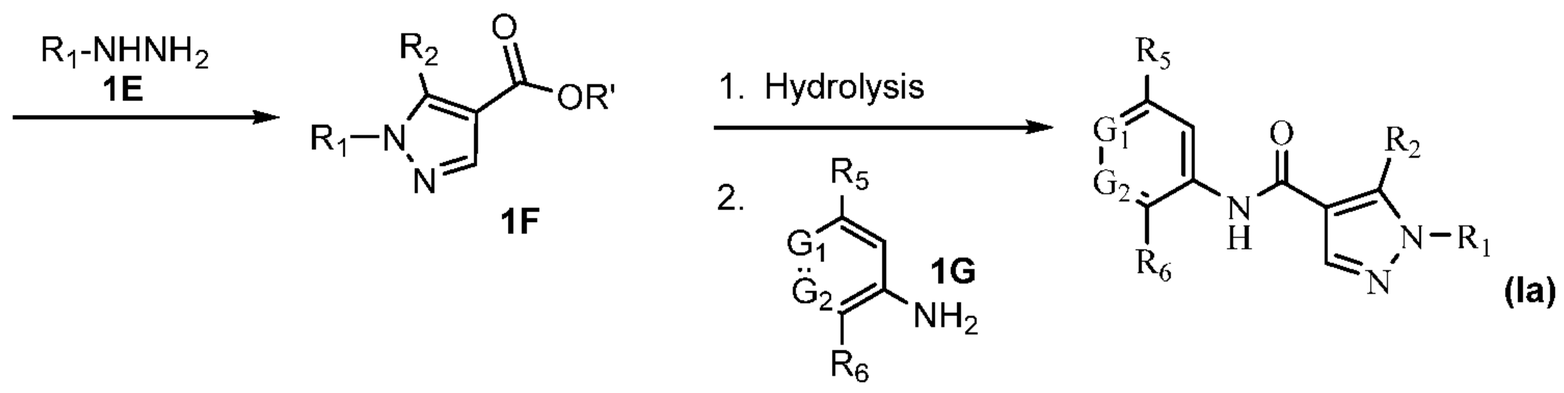
AcOH	acetic acid
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Boc	*tert*-butyl carbamate
BuLi	butyllithium
Cbz	benzyl carbamate
DCM	dichloromethane
DMA	dimethylacetamide
DME	ethylene glycol dimethyl ether
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EA	ethyl acetate
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethyl alcohol
FCC	flash column chromatography
h	hour(s)
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HCHO	formaldehyde
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
KCN	potassium cyanide
LCMS	high pressure liquid choatography with mass spectrometer
LDA	lithium diisopropylamide
LiOH	lithium hydroxyde
Me	methyl
MeCN	acetonitrile
MeOH	methyl alcohol

mg	milligram
min	minute
NaCN	sodium cyanide
NaOH	sodium hydroxide
NaOtBu	sodium tert-butoxide
NH_4Cl	ammonium chloride
Pd/C	palladium on charcoal
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium
$Pd(OAc)_2$	palladium diacetate
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium
PPh_3	triphenyl phosphine
p-TsOH	para-toluenesulfonic acid
rt or RT	room temperature
TBAF	tetrabutyl ammonium fluoride
TMSI	iodotrimethylsilane
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Compounds of Formula (Ia) wherein R_7 is hydrogen, may be prepared according to the process outlined in Scheme 1.

Scheme 1





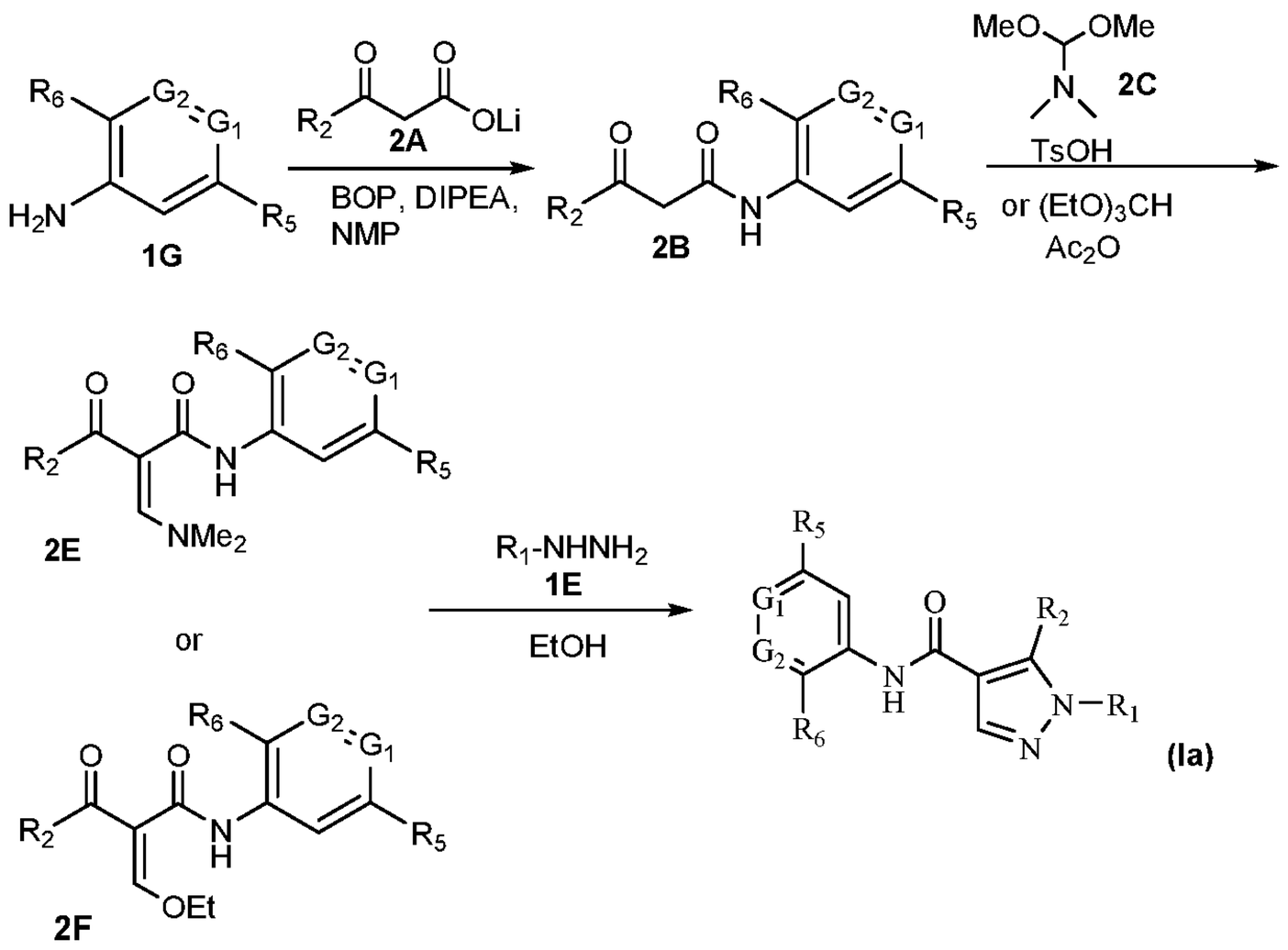
A carboxylic acid of formula (**1A**) may be treated with carbonyldiimidazole followed by addition of a mono-ester of malonic acid of formula (**1B**), wherein R′ is C_{1-4}alkyl, and a base, such as isopropylmagesium chloride, to yield a ketoester of formula (**1C**).

Condensation with triethyl orthoformate in acetic anhydride or with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine may yield a 2-ethoxymethylidene-3-oxo ester (or 2-((dimethylamino)methylidene-3-oxo ester) of formula (**1D**). A compound of formula (**1D**) may be reacted with a hydrazine of formula (**1E**) to provide a pyrazole of formula (**1F**). Hydrolysis of the ester group may be effected via by treatment with aqueous sodium hydroxide in the presence of an alcohol co-solvent, to provide the corresponding carboxylic acid intermediate, which, subsequently, may be converted to a compound of Formula (**I**) upon amide coupling with a compound of formula (**1G**). The amide coupling may be carried out, for example, in the presence of phosphorus oxychloride in pyridine to afford the corresponding acid chloride, followed by treatment with a compound of formula (**1G**), in the presence of a base. In one embodiment, the amide coupling reaction is carried out in the presence of a suitable amide coupling reagent such as HATU, in the presence of a base such as, but not limited to, diisopropylethyl amine.

Alternatively, the pyrazole ester of formula (**1F**) may be directly converted to a compound of Formula (**I**) via treatment with a compound of formula (**1G**) and a base, such as potassium *tert*-butoxide.

An alternate route to compounds of Formula (Ia) wherein R_7 is hydrogen, is illustrated in Scheme 2.

Scheme 2

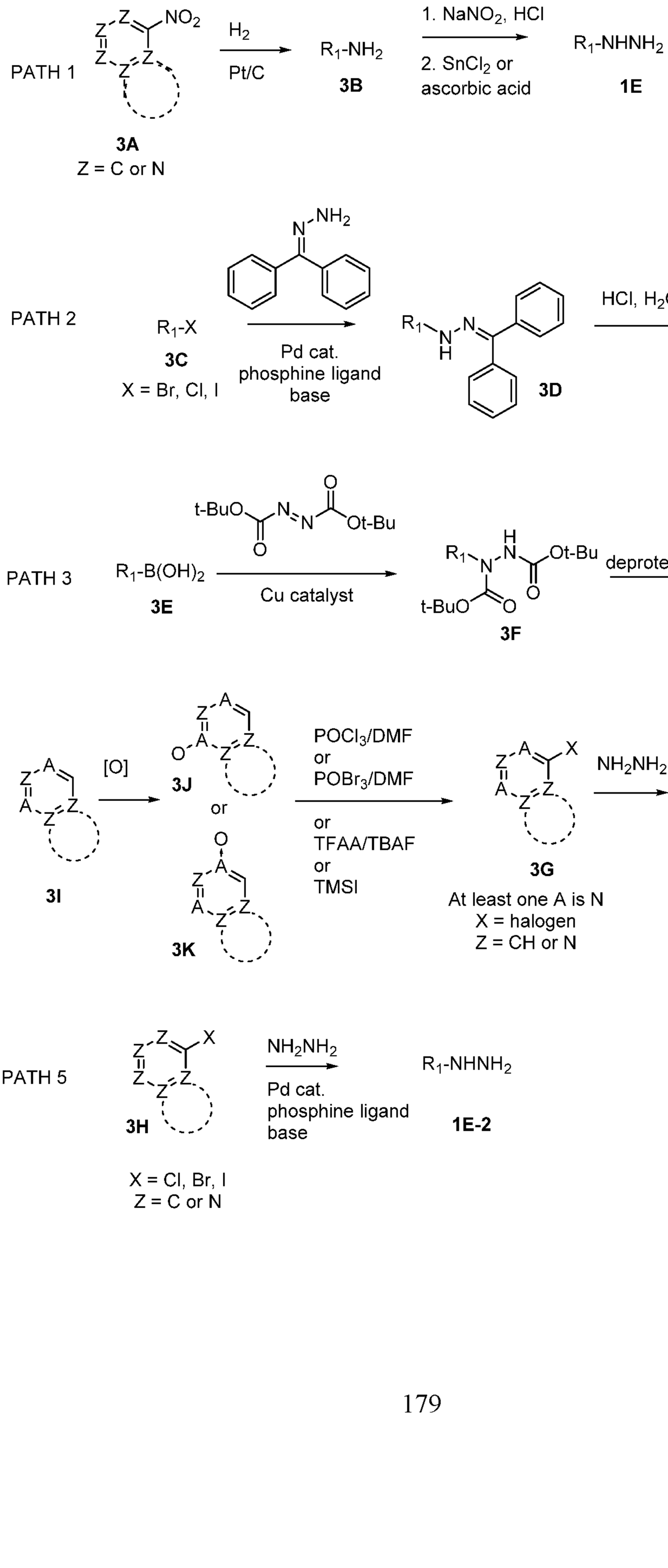


Aniline (**1G**) may be coupled with a lithium acetoacetate of formula (**2A**) in the presence of coupling reagent such as BOP, a base such as DIPEA, and a solvent such as NMP, to provide a compound of formula (**2B**). A compound of formula (**2B**) may then be reacted with DMF-DMA (**2C**) in the presence of an acid, such as TsOH, or reacted with triethoxymethane (**2D**) in AcOH to afford a compound of formula (**2E**) or (**2F**), respectively. A compound of formula (**2E**) or (**2F**) may then be treated with a hydrazine of formula (**1E**) to afford a compound of Formula (I).

Scheme 3 illustrates the preparation of certain hydrazine intermediates of formula

(**1E**), useful for the preparation of compounds of Formula (I) of the present invention.

Scheme 3



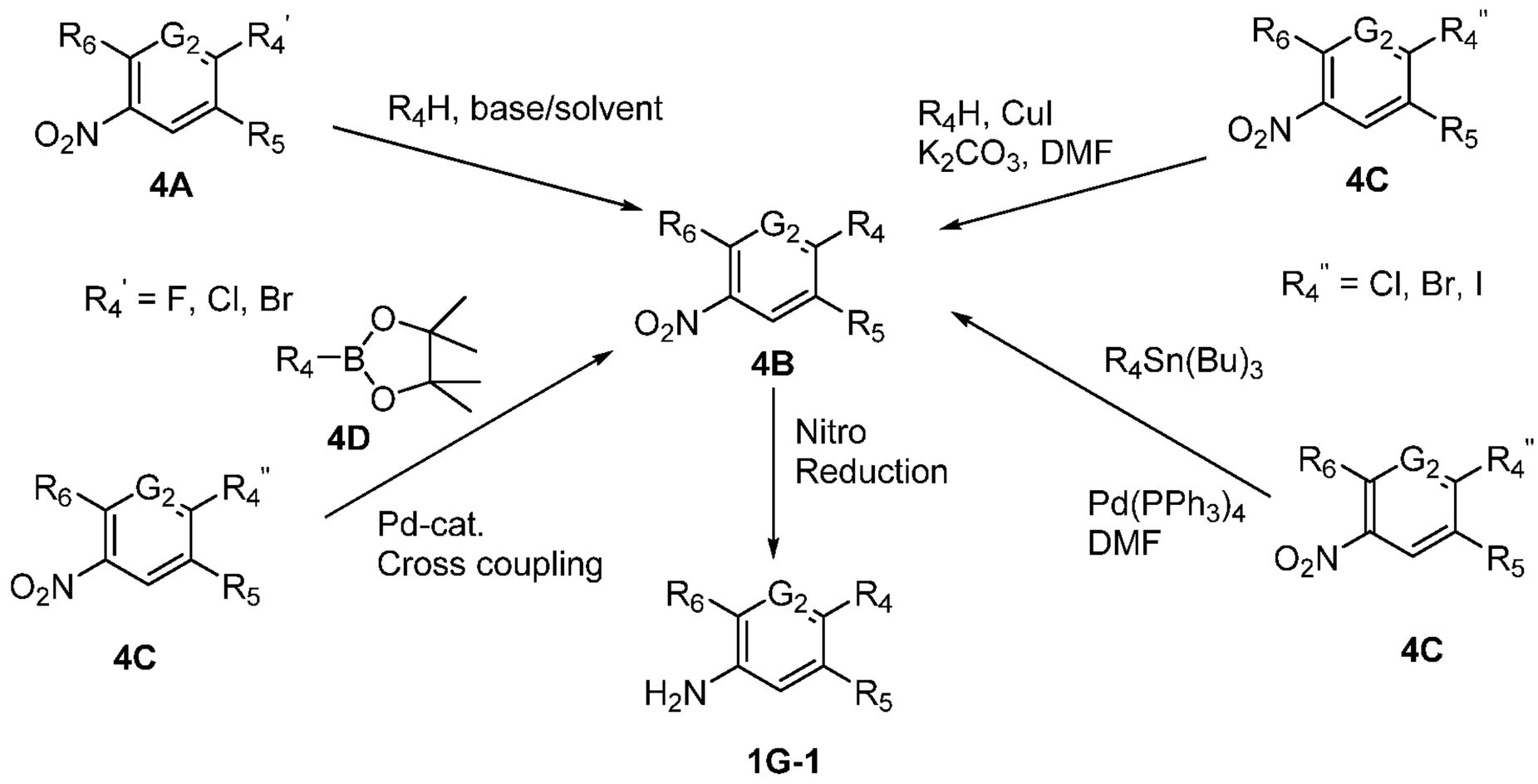
A heteroaryl amine of formula (**3B)** may be converted to a heteroaryl diazonium salt via treatment with sodium nitrite under acidic conditions. This intermediate may be reduced, using a reductant such as tin (II) chloride or ascorbic acid, to form the hydrazine of formula (**1E**). For heteroaryl amines of formula (**3B**) that are not commercially available, they may be accessed by reduction of the heteronitroarene (**3A**) using hydrogen and Pt/C or other conventional nitro-reducing conditions (path one).

R_1-substituted chlorides, bromides, and iodides may undergo a palladium catalyzed Buchwald Hartwig coupling with benzophenone hydrazine, in the presence of a ligand, such as Xantphos, and a base, such as sodium *tert*-butoxide, to form a hydrazine of formula (**3D**). Acidic hydrolysis may afford the hydrazine of formula (**1E**) (path two).

R_1-substituted boronic acids may also serve as a precursor to compounds of formula (**1E**) by the route shown in path three. A boronic acid of formula (**3E**) may undergo a Cu^{2+}-catalyzed (such as $Cu(OAc)_2$, TEA in CH_2Cl_2) addition to di-*tert*-butylazodicarboxylate to afford an intermediate of formula (**3F**), which may be deprotected under acidic conditions to yield the compound of formula (**1E**). Heteroaryl hydrazines of formula (**1E-1**), having a nitrogen atom in the *ortho*- or *para*- position with respect to the hydrazine functionality, may be prepared via direct displacement of a halogen with hydrazine or hydrazine hydrate. (Hetero) haloarenes of formula (**3G**) that are not commercially available may be prepared from their corresponding (hetero)arenes (**3I**), with an oxidant such as mCPBA, to form the N-oxide (**3J**) (or (**3K**)) that may then be converted to (hetero) haloarene **3G** via treatment with $POCl_3$ and DMF, $POBr_3$/DMF, TFAA/TBAF, or TMSI (path four). Alternatively, halogenated (hetero)arenes of formula (**3H**) may undergo palladium-catalyzed cross-coupling with hydrazine to directly furnish intermediate (**1E-2**) (path five).

Scheme 4 illustrates multiple pathways available for the synthesis of intermediate (**1G-1**), wherein G_1 is $C(R_4)$.

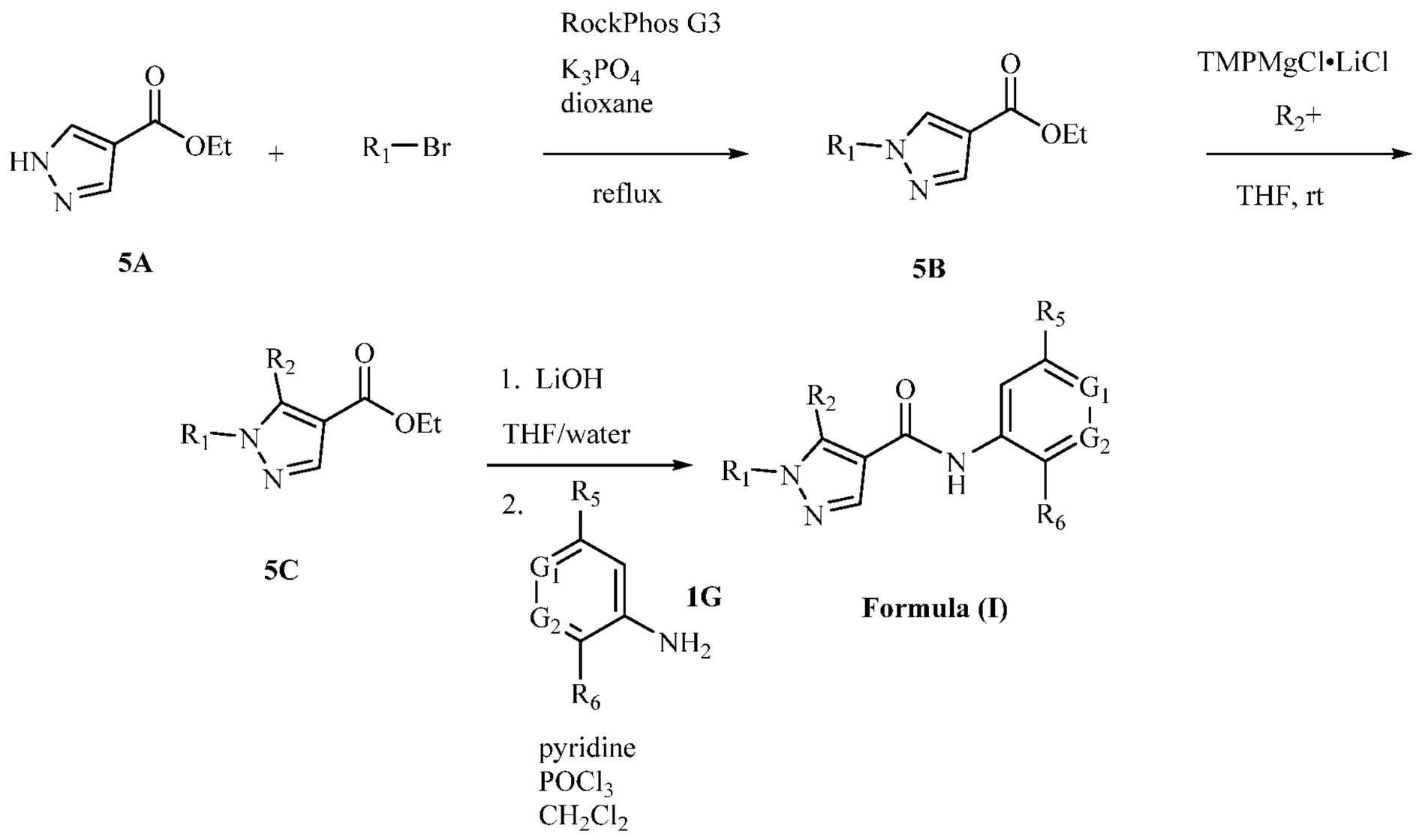
Scheme 4



Compound (**B-1**) may be reacted with a compound of formula R_4H in the presence of a base, such as Cs_2CO_3, in a solvent, such as DMF, to yield a compound of formula (**4B**). Alternatively, a compound of formula (**4C**) may be treated with a crossing coupling reagent, such as a boron reagent of formula (**4D**) or a tin reagent of formula $R_4Sn(Bu)_3$; in the presence of a palladium catalyst, including but not limited to, $Pd(dppf)Cl_2$ or $Pd(PPh_3)_4$; in a suitable solvent or solvent system such as DMF, dioxane/water, or the like; to produce a compound of formula (**4B**). Another suitable pathway includes the reaction of a compound of formula (**4C**) with a compound of formula R_4H, in the presence of a coupling reagent such as CuI, with a base such as Cs_2CO_3, and in a solvent such as DMF, to afford a compound of formula (**4B**). A compound of formula (**4B**) may be reduced to a compound of formula (**1G-1**) using a reducing agent such as Zn or Fe in the presence of NH_4Cl, in a solvent such as MeOH.

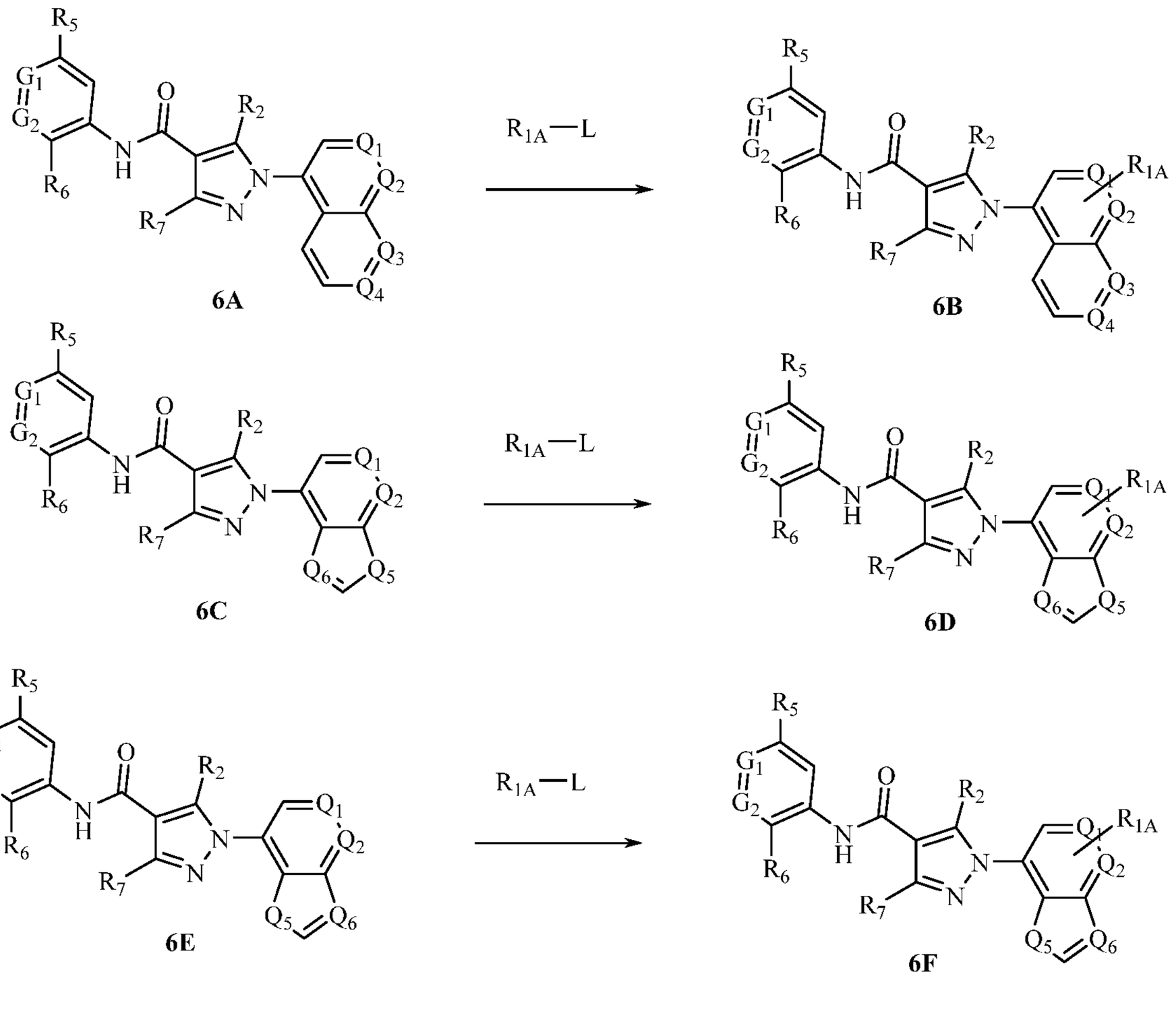
Scheme 5 illustrates the preparation of certain compounds of Formula (I) wherein R_6 is other than hydrogen.

Scheme 5



Scheme 6 illustrates the preparation of certain compounds of Formula (I) of the present invention.

Scheme 6



In the instance when L is H, alkylation of compounds of formulae **6A**, **6C** and **6E** may occur via formation of a radical from R_{1A}-L, generated by treatment with ammonium persulfate and $(IR[DF(CF_3)PPY]_2(DTBPY))PF_6$, in a mixture of water and CH_3CN or DMSO and TFA, under irradiation with blue LED.

Alternatively, in the instance when L is H, alkylation of compounds of formulae **6A**, **6C** and **6E** may occur via formation of a radical from R_{1A}-L, generated by treatment with BPO and $(IR[DF(CF_3)PPY]_2(DTBPY))PF_6$ in MEOH and TFA, under irradiation with blue LED.

When L is H, alkylation of compounds of formulae **6A**, **6C** and **6E** may occur via formation of a radical from R_{1A}-L, generated by treatment with iron(II)sulfate heptahydrate and hydrogen peroxide, in a mixture of water and CH_3CN or DMSO and H_2SO_4.

When L is a zinc sulfonate, alkylation of compounds of formulae **6A**, **6C** and **6E** may occur via formation of a radical from R_{1A}-L, generated by treatment with tert-butyl hydroperoxide, in a mixture of water and DCM and TFA.

Likewise, when L is -COOH or a BF_3-salt, alkylation of compounds of formulae **6A**, **6C** and **6E** may occur via formation of a radical from R_{1A}-L, generated by treatment with ammonium persulfate and silver nitrate, in a mixture of water and DCM or CH_3CN or DMSO or dioxane and TFA.

Compounds of formulae **6A**, **6C** and **6E** may also be converted to their corresponding N-oxides via treatment with an oxidizing agent such as m-CPBA in DCM or THF. Said N-oxides by optionally be converted to their corresponding ortho -CN derivatives using trimethylsilyl cyanide and DBU, in a solvent such as THF. Said N-oxides may also be converted to their alkoxy or cycloalkoxy derivatives by the action of tosylanhydride, Na_2CO_3 and an appropriately substituted alkyl-OH or cycloalkyl-OH reagent.

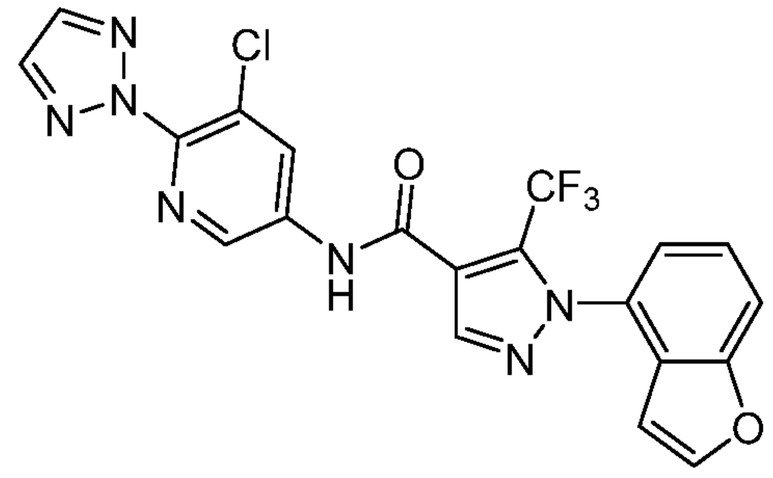
Alternatively, the N-oxides of compounds of formulae **6A**, **6C** and **6E** may be converted to their corresponding ortho-chloro derivatives by the action of $POCl_3$, optionally in a solvent such as $CHCl_3$, which may be used as an intermediate for the preparation of $C_{1\text{-}6}$alkylthio, $C_{1\text{-}6}$cycloalkylthio, and sulfur-linked heterocyclic rings of the present invention. Similarly, the ortho-chloro derivatives may be reacted with appropriately substituted amines to afford $C_{1\text{-}6}$alkylamino, $C_{1\text{-}6}$cycloalkylamino, or N-linked heterocyclic rings of the present invention. Or, the ortho-chloro derivatives may undergo a Suzuki-type reaction in a subsequent step, with an appropriately substituted corresponding alkyl- or cycloalkyl-boronic acid to form a compound of Formula (I).

Specific Examples

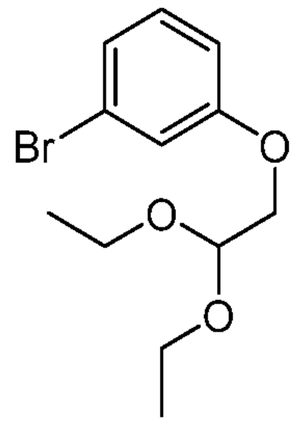
In the following Examples, some synthesis products are listed as having been isolated as a residue. It will be understood by one of ordinary skill in the art that the term "residue" does not limit the physical state in which the product was isolated and may include, for example, a solid, an oil, a foam, a gum, a syrup, and the like.

Example 1

1-(Benzofuran-4-yl)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 34**



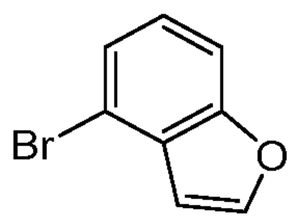
A. 1-Bromo-3-(2,2-diethoxyethoxy)benzene, **1a**



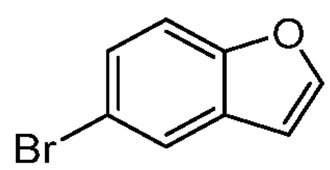
, **1a**

Sodium hydride in mineral oil (7.6 g, 60% purity, 0.19 mol) was added in portions to a 0 °C (ice/water) solution consisting of 3-bromophenol (30 g, 0.17 mmol) and DMF (200 mL), and the resultant mixture was stirred for 10 min at 0 °C. 2-Bromo-1,1-diethoxyethane (31 mL, 0.21 mmol) was added to the mixture at 0 °C, and the resulting mixture was stirred at 120 °C for 16 h before cooling to room temperature. The resulting solution was poured into water and extracted with ethyl acetate. The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 10:1) to afford compound **1a** (50 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 - 7.04 (m, 3H), 6.89 - 6.82 (m, 1H), 4.82 (t, *J* = 5.2 Hz, 1H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.83 - 3.72 (m, 2H), 3.69 - 3.58 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 6H).

B. 4-Bromobenzofuran (**1b**) and 5-Bromobenzofuran (**1c**)



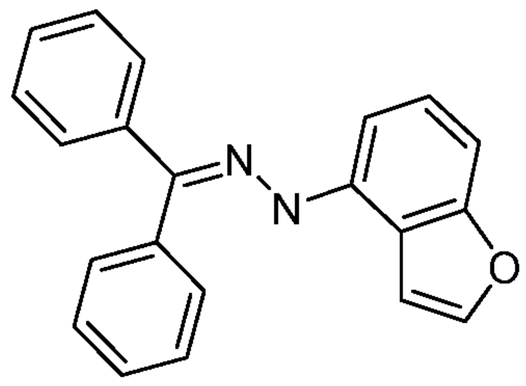
1b



1c

Polyphosphoric acid (PPA) (175 g, 519 mmol) was added to a solution consisting of 1-bromo-3-(2,2-diethoxyethoxy)benzene**, 1a** (50.0 g, 173 mmol) and toluene (200 mL) at room temperature under an $Ar_{(g)}$ atmosphere. The resulting mixture was stirred at 110 °C for 4 h before cooling to room temperature. The resulting mixture was quenched with cooled water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 20:1) to give a mixture of compounds **1b** and **1c** (21 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.43 - 7.34 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 1.2 Hz, 1H), 6.76 (d, *J* = 1.2 Hz, 1H).

C. 1-(Benzofuran-4-yl)-2-(diphenylmethylene)hydrazine, **1d**

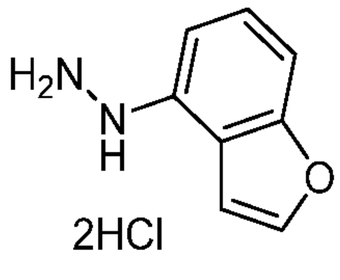


, **1d**

A mixture consisting of compounds **1b** and **1c** (21 g, 53 mmol), (diphenylmethylene)hydrazine (13 g, 64 mmol), palladium(II) acetate (1.2 g, 5.3 mmol), Xphos (5.1 g, 11 mmol), sodium hydroxide (4.3 g, 0.11 mol), and *t*-AmOH (150 mL) was stirred at 100 °C for 16 h before cooling to room temperature. The suspension was filtered and the pad was washed with ethyl acetate. The filtrate was concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 10:1) to afford compound **1d** (5.8 g, 17%) as a brown oil. LCMS (ESI): mass calcd. for $C_{21}H_{16}N_2O$ 312.13, m/z found 313.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$)

δ ppm 7.77 (s, 1H), 7.66 - 7.60 (m, 4H), 7.59 - 7.52 (m, 2H), 7.43 - 7.29 (m, 5H), 7.22 - 7.16 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.98 - 6.95 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H). LCMS (ESI) m/z M+1: 313.0.

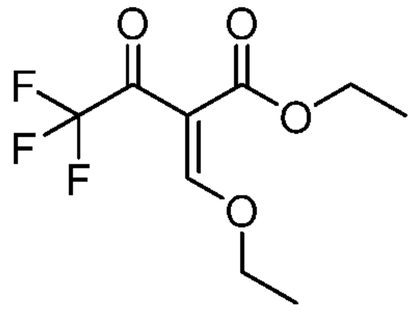
D. Benzofuran-4-ylhydrazine dihydrochloride, **1e**



, **1e**

Conc. HCl (50 mL) was added to a solution consisting of 1-(benzofuran-4-yl)-2-(diphenylmethylene)hydrazine, **1d** (4.8 g, 15 mmol) and EtOH (5 mL). The resulting mixture was stirred at room temperature for 16 h, concentrated to dryness under reduced pressure to afford a residue, which was added into water (10 mL). The resulting mixture was basified with 2 M NaOH to pH 13, and extracted with ethyl acetate (30 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford a crude product **1e** (1.1 g, crude), which was used in the following reaction without further purification.

E. Ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f**

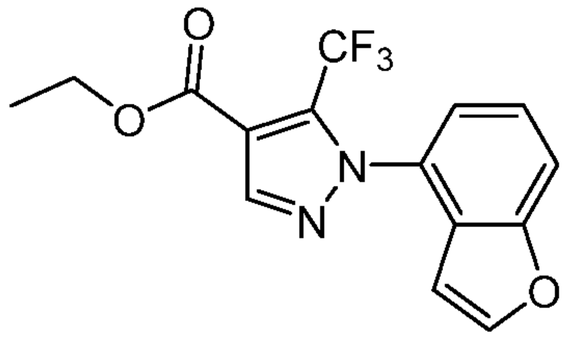


, **1f**

Ethyl 4,4,4-trifluoro-3-oxobutanoate (30 g, 162.9 mmol) was added to a solution of triethoxymethane (72.4 g, 488.8 mmol) in acetic anhydride (50 mL). The mixture was stirred at 135 °C for 18 h. The brown mixture was concentrated to afford ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (38 g, 97.1%) as a brown oil, which was used in the following reaction without further purification. ^{1}H NMR (400 MHz,

$CDCl_3$) δ ppm 1.23 - 1.33 (m, 3 H) 1.40 (dt, J=14.18, 7.19 Hz, 3 H) 4.19 - 4.36 (m, 4 H) 7.66 - 7.87 (m, 1 H).

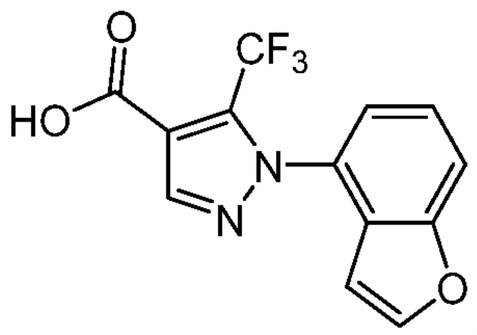
F. Ethyl 1-(benzofuran-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **1g**



, 1g

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (1.43 g, 5.97 mmol), benzofuran-4-ylhydrazine dihydrochloride, **1e** (1.10 g, 4.98 mmol), triethylamine (1.39 mL, 9.95 mmol), and ethanol (20 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The resulting solution was concentrated to dryness under reduced pressure, diluted with water (15 mL), and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 3:1) to afford compound **1g** (250 mg, 15 %) as a yellow oil. LCMS (ESI): mass calcd. for $C_{15}H_{11}F_3N_2O_3$ 324.07, m/z found 324.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.20 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.68 - 7.63 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.61 (dd, *J* = 0.8, 2.4 Hz, 1H), 4.43 - 4.36 (m, 2H), 1.42 - 1.38 (m, 3H). LCMS (ESI) m/z M+1: 324.9.

G. 1-(Benzofuran-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **1h**

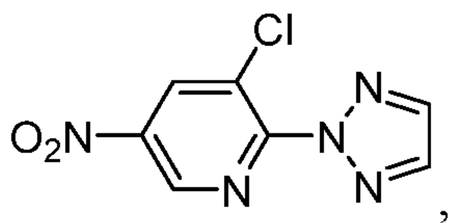


, 1h

A solution consisting of lithium hydroxide hydrate (97.1 mg, 2.31 mmol) and water (5 mL) was added to a solution consisting of ethyl 1-(benzofuran-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **1g** (250 mg, 0.771 mmol) and ethanol (10 mL). The mixture

was stirred at room temperature for 16 h. The resulting solution was concentrated to dryness under reduced pressure to afford the crude product, which was poured into water (5 mL) and acidified with 3N HCl to about pH 5. The resulting mixture was filtered and the filter cake was washed with water (5 mL), and then dried under reduced pressure to afford compound **1h** (200 mg, 88%) as a yellow solid. LCMS (ESI): mass calcd. for $C_{13}H_7F_3N_2O_3$ 296.04, m/z found 337.9 $[M+H+CH_3CN]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 13.40 (br.s., 1H), 8.32 (s, 1H), 8.14 (d, J = 2.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.53 - 7.41 (m, 2H), 6.76 (dd, J = 1.2, 2.4 Hz, 1H).

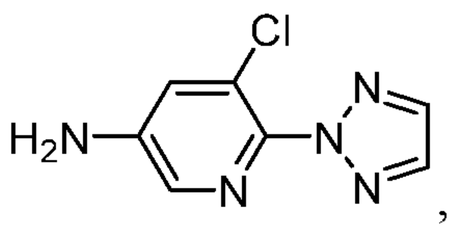
H. 3-Chloro-5-nitro-2-(2*H*-1,2,3-triazol-2-yl)pyridine, **1i**



, **1i**

A mixture of 2,3-dichloro-5-nitropyridine (50 g, 259.08 mmol), 1*H*-1,2,3-triazole (19.683 g, 284.99 mmol), potassium carbonate (46.549 g, 336.81 mmol) and CH_3CN (200 mL) was heated to 40 °C and stirred overnight. Ethyl acetate (500 mL) was added. The mixture was washed with water (500 mL x 2) and brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure. The residue was triturated with DCM (100 mL), filtered, and the solid was collected to afford compound **1i** (40 g, 68%) as an off-white solid. LC-MS: (ES, *m/z*): $[M+1]^+$ 225.9. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (d, J=2.0Hz, 1H), 9.15 (d, J=2.0Hz, 1H), 8.33 (s, 2H).

I. 5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j**

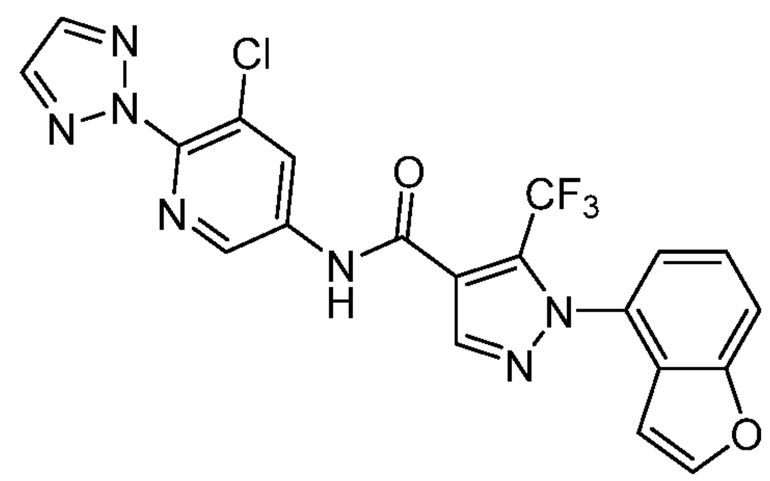


, **1j**

3-Chloro-5-nitro-2-(2*H*-1,2,3-triazol-2-yl)pyridine, **1i** (20 g, 88.656 mmol), MeOH (500 mL) and Pt/C (2 g, 5%, 0.513 mmol) were added to a 1000 mL hydrogenation bottle.

The resultant mixture was stirred under a H_2 atmosphere (30 psi) at 25 °C for 20 h. The suspension was filtered though a pad of diatomaceous earth and the filter cake was washed with ethyl acetate (100 mL). The filtrate was concentrated to dryness under reduced pressure to afford a crude product, which was purified by preparative reverse phase HPLC (0% to 50% (v/v) CH_3CN and water with 0.05% NH_3), followed by lyophilization to dryness to afford compound **1j** (10.4 g, 60 %) as an off-white solid. LC-MS: (ES, *m/z*): $[M+1]^+$ 196.1; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.05 (s, 2H), 7.83 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.19 (s, 2H).

J. 1-(Benzofuran-4-yl)-*N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 34**

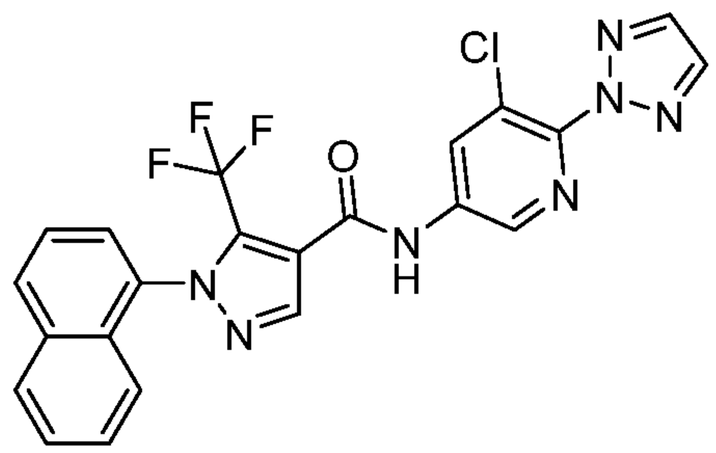


$POCl_3$ (112 mg, 0.729 mmol) was added dropwise to solution consisting of 1-(benzofuran-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **1h** (180 mg, 0.608 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (131 mg, 0.668 mmol), and pyridine (5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The resulting mixture was diluted with sat. aqueous $NaHCO_3$(10 mL) and extracted with ethyl acetate (15 mL x 3). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a crude residue, which was purified by FCC (petroleum ether: ethyl acetate = 1:1) to afford crude compound **34** (180 mg). Further purification by preparative reverse phase HPLC (43% to 73% (v/v) CH_3CN and water with 0.05% NH_3) afforded compound **34**, which was then suspended in water (10 mL), frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **34** (166.10 mg, 57 %). LCMS (ESI): mass calcd. for $C_{20}H_{11}ClF_3N_7O_2$ 473.06, m/z found

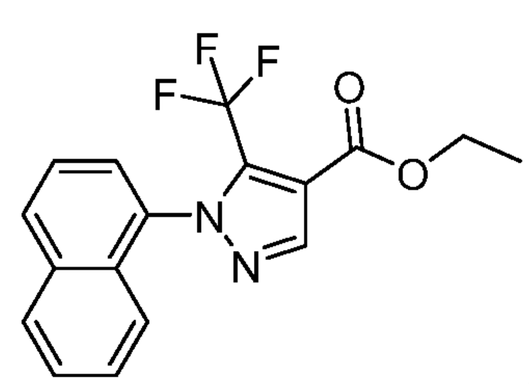
473.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.77 (d, J = 2.4 Hz, 1H), 8.51 (d, J = 2.0 Hz, 1H), 8.26 (s, 1H), 8.16 (s, 1H), 7.95 (s, 2H), 7.76 - 7.68 (m, 2H), 7.47 - 7.41 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H), 6.63 (d, J = 1.6 Hz, 1H).

Example 2

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 2**



A. Ethyl 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **2a**

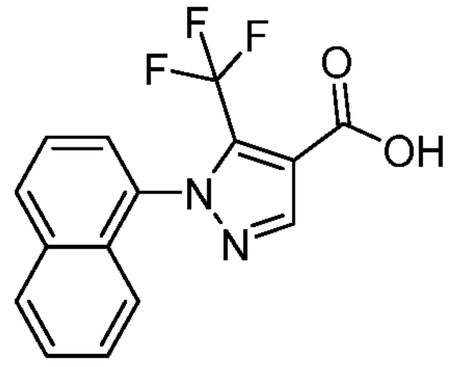


, **2a**

Ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (200 mg, 0.833 mmol) was added to a solution consisting of naphthalen-1-ylhydrazine (162 mg, 0.833 mmol), triethylamine (168 mg, 1.67 mmol) and ethanol (5 mL). The mixture was heated to reflux at 80 °C for 16 h. The resulting mixture was concentrated to dryness under reduced pressure to give a crude residue, which was purified by preparative high performance liquid chromatography using Phenomenex Gemini 150 x 25 mm x 10 μm (50% to 80% (v/v) ACN and water with 0.05% NH_3) to afford compound **2a**. Compound **2a** was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **2a** (129.80 mg, 47 %). LCMS (ESI): mass calcd. for $C_{17}H_{13}F_3N_2O_2$ 334.293, m/z found 335.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.26

(s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.59 - 7.50 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H). LCMS (ESI) m/z M+1: 335.0.

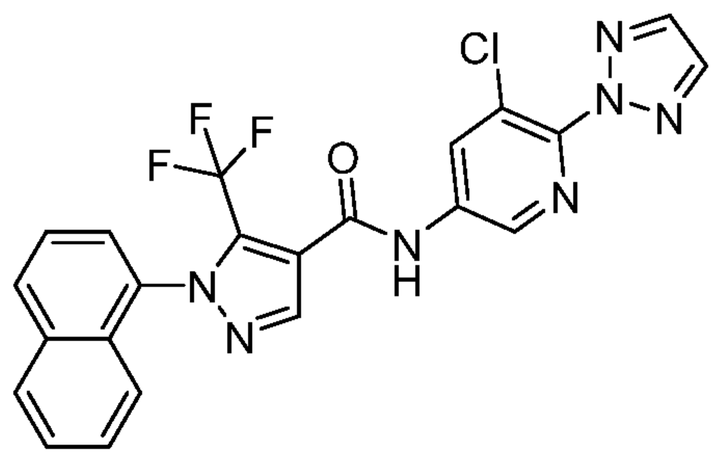
B. 1-(Naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **2b**



, 2b

A solution consisting of ethyl 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **2a** (1.20 g, 3.59 mmol), LiOH (452 mg, 10.8 mmol) and a water: EtOH mixture (12 mL, 1:2) was stirred at room temperature for 16 h. The solution was neutralized to about pH 7 with 4 M HCl, extracted with ethyl acetate (30 mL x 3), and dried over anhydrous Na_2SO_4. The extracts were concentrated to dryness under reduced pressure to afford compound **2b** (1.00 g, 78 %), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. For $C_{15}H_9F_3N_2O_2$ 306.239, m/z found 306.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 13.43 (br.s., 1H), 8.38 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.72 - 7.55 (m, 4H), 7.09 (d, *J* = 8.0 Hz, 1H).

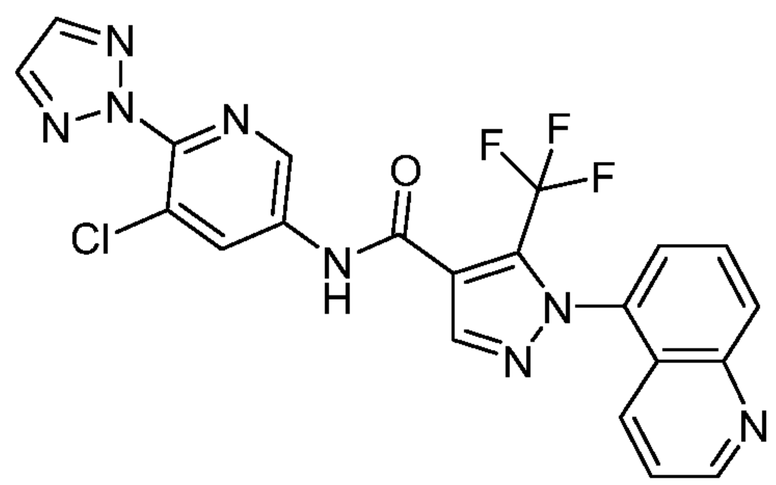
C. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 2**



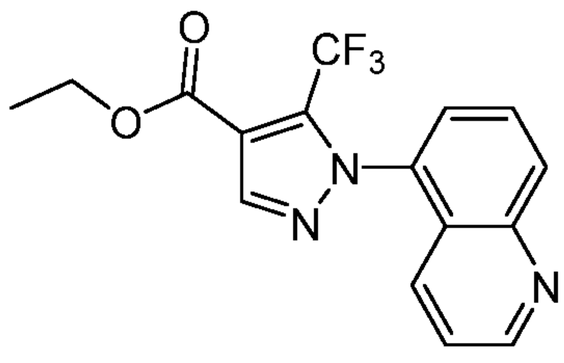
$POCl_3$ (90.1 mg, 0.588 mmol) was added dropwise to a solution consisting of 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **2b** (150 mg, 0.490 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (105 mg, 0.539 mmol) and pyridine (2 mL). The mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated to dryness under reduced pressure to give a crude product, which was purified by preparative reverse phase HPLC (46% to 76% (v/v) ACN and water with 0.05% NH_3) to afford compound **2**, which was then suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **2** (102.30 mg, 43 %). LCMS (ESI): mass calcd. for $C_{22}H_{13}ClF_3N_7O$ 483.833, m/z found 484.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (br.s., 1H), 8.86 (d, J = 2.0 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.57 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.20 (s, 2H), 8.15 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.76 - 7.62 (m, 3H), 7.13 (d, J = 8.0 Hz, 1H). LCMS (ESI) m/z M+1: 483.9.

Example 3

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 8**



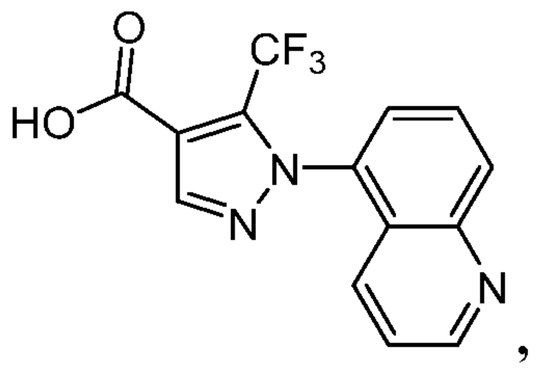
A. Ethyl 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **3a**



, **3a**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (905 mg, 3.77 mmol), 5-hydrazinylquinoline (500 mg, 3.14 mmol), and ethanol (20 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The resulting solution was concentrated to dryness under reduced pressure, and then purified by FCC (petroleum ether: ethyl acetate = 1:1) to afford compound **3a** (530 mg, 84 %) as a brown solid. LC-MS (ESI): mass calcd. for $C_{16}H_{12}F_3N_3O_2$ 335.09, m/z found 335.8 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 7.86 - 7.79 (m, 1H), 7.64 - 7.56 (m, 2H), 7.46 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.43 (q, *J* = 6.8 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H). LCMS (ESI) m/z M+1: 335.8.

B. 1-(Quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b**

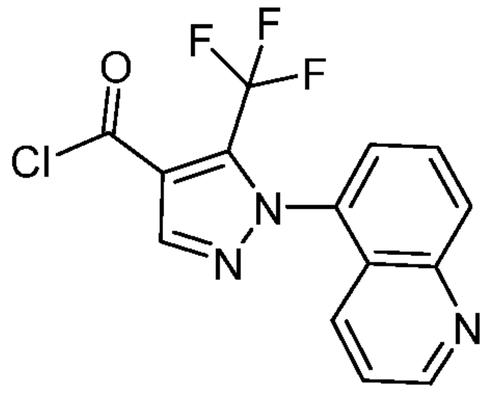


, **3b**

A solution consisting of lithium hydroxide hydrate (375 mg, 8.95 mmol) in water (5 mL) was added to a solution consisting of ethyl 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **3a** (1.00 g, 2.98 mmol) in ethanol (10 mL). The resulting solution was stirred at room temperature for 16 h, concentrated to dryness under reduced pressure, and the resulting mixture was poured into water (2 mL). The aqueous mixture was acidified with 3 N HCl to about pH 5, filtered, and the filter cake was washed with water (10 mL) and dried under reduced pressure to afford compound **3b** (910 mg, 99 %) as a yellow solid. LC-MS (ESI): mass calcd. for $C_{14}H_8F_3N_3O_2$ 307.06, m/z found 308.0

$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (s, 1H), 8.40 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.00 - 7.82 (m, 2H), 7.69 - 7.54 (m, 2H). LCMS (ESI) m/z M+1: 308.0.

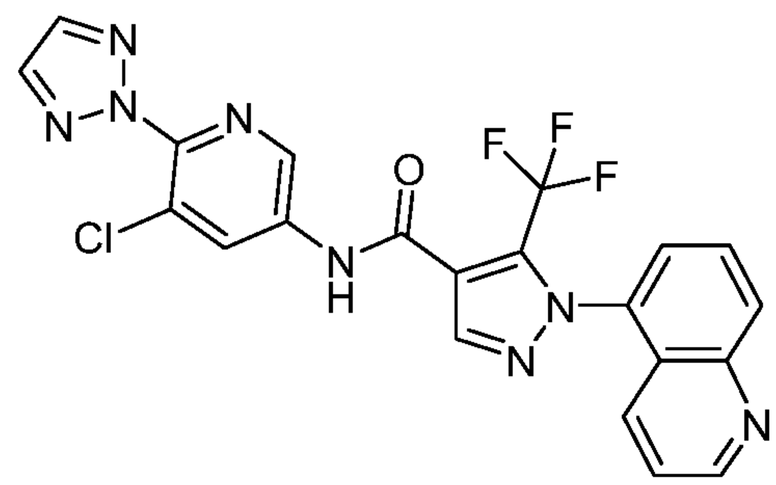
C. 1-(Quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride, **3c**



, 3c

Oxalyl dichloride (0.0830 mL, 0.976 mmol) was added to solution consisting of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (200 mg, 0.651 mmol), dichloromethane (15 mL), and DMF (catalytic amount). The solution was stirred at room temperature for 1 h. The resulting solution was concentrated to dryness to afford compound **3c** (200 mg, crude), which was used in the following reaction without further purification.

D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 8**

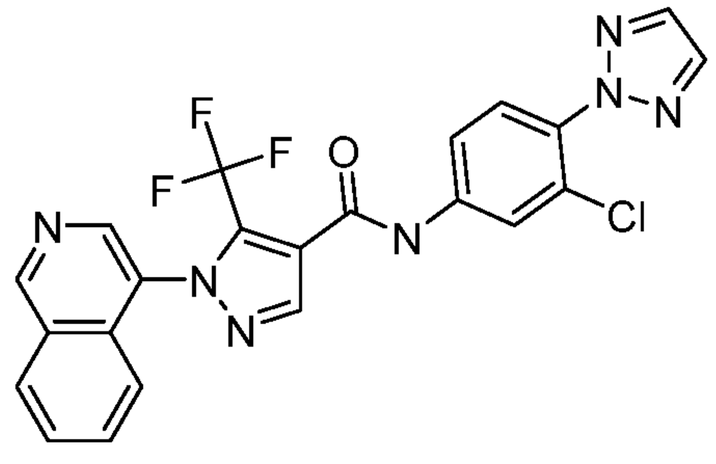


A solution consisting of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride, **3c** (200 mg, 0.614 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (144 mg, 0.737 mmol), and pyridine (10 mL) was stirred at 90 °C for 1 h before cooling to room temperature. The mixture was concentrated to dryness under reduced pressure, which was then purified by preparative HPLC using a Kromasil 150 x 25 mm x 10 μm column (32% to 62% (v/v) CH_3CN and water with 0.05% NH_3) to afford

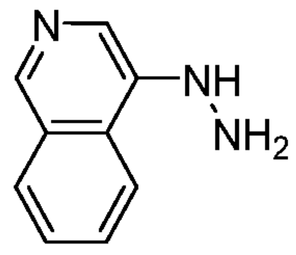
compound **8** (149.20 mg, 50 %) as a white solid. LCMS (ESI): mass calcd. for $C_{21}H_{12}ClF_3N_8O$ 484.08, m/z found 485.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.05 - 9.02 (m, 1H), 8.78 (d, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.4 Hz, 1H), 8.39 - 8.34 (m, 2H), 8.23 (s, 1H), 7.96 (s, 2H), 7.88 - 7.82 (m, 1H), 7.66 - 7.57 (m, 2H), 7.48 (dd, *J* = 4.0, 8.0 Hz, 1H). LCMS (ESI) m/z M+1: 485.0.

Example 4

N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 38**



A. 4-Hydrazinylisoquinoline, **4a**

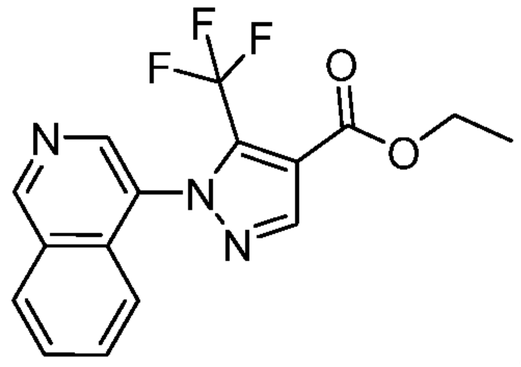


, **4a**

To a stirring solution of isoquinolin-4-amine (5.0 g, 34.68 mmol) in HCl (50 mL, 5N) at 0° C was added a solution of sodium nitrite ($NaNO_2$, 3.59 g, 52.02 mmol) in water at 0° C. The reaction mixture was stirred at 0° C for 30 min and a solution of tin (II) chloride dehydrate ($SnCl_2.2\ H_2O$, 19.56 g, 86.70 mmol) in concentrated hydrochloric acid (5 mL) was added dropwise. The mixture was stirred at room temperature for 2 h. The mixture was adjusted to about pH 12-14 with 20 % aqueous sodium hydroxide. At that time, the mixture was extracted with ethyl acetate (200 mL x 3). The combined organic extracts were washed with brine (300 mL). The organic portion was dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (petroleum ether/ ethyl acetate = 100:0 to ethyl

acetate/ methanol = 90:10) to afford compound **4a** (1.15 g, 20.8%) as a brown solid, which was used in the following reaction without further purification.

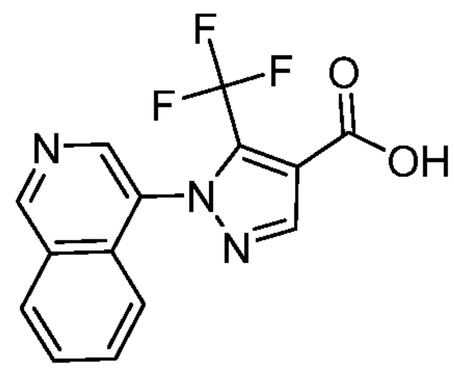
B. Ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **4b**



, **4b**

A mixture of 4-hydrazinylisoquinoline, **4a** (1.15 g, 7.224 mmol) and ethyl (*Z*)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (2.08 g, 8.669 mmol) in EtOH (30 mL) was stirred at 80 °C for 16 h. The resulting solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford compound **4b** (1.77 g, 72.98 %) as a yellow solid. LCMS (ESI) m/z M+1: 335.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.41 (t, J=7.06 Hz, 3 H) 4.42 (q, J=7.06 Hz, 2 H) 7.31 (d, J=8.38 Hz, 1 H) 7.70 - 7.80 (m, 1 H) 8.12 (dd, J=7.28, 1.10 Hz, 1 H) 8.28 (s, 1 H) 8.58 (s, 1 H) 9.41 (s, 1 H).

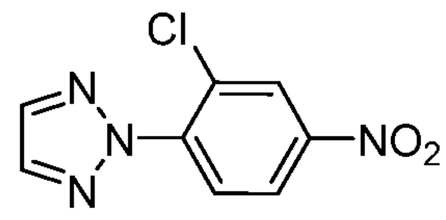
C. 1-(Isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c**



, **4c**

A solution of ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **4b** (500 mg, 1.49 mmol) in concentrated hydrochloric acid (5 mL) was stirred at 130 °C for 3 h. The solvent was concentrated under reduced pressure to afford compound **4c** (465.61 mg, 100 %) as a yellow solid. LCMS (ESI) m/z M+1: 307.9.

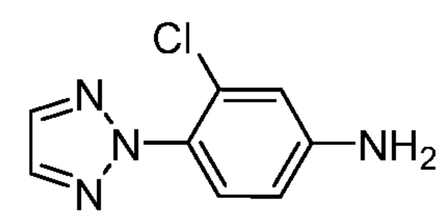
D. 2-(2-Chloro-4-nitrophenyl)-2*H*-1,2,3-triazole, **4d**



, **4d**

To a solution of 3-chloro-4-fluoronitrobenzene (1.2 g, 6.836 mmol) and 2*H*-1,2,3-triazole (0.567 g, 8.203 mmol) in anhydrous DMA (5 mL) was added K_2CO_3 (1.89 g, 13.7 mmol). The reaction mixture was stirred at 55 °C overnight. The reaction was concentrated to give a crude oil. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 20/80) to give compound **4d** (1 g, 65.1 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 - 8.02 (m, 3H), 8.28 (dd, J=8.93, 2.54 Hz, 1H), 8.49 (d, J=2.21 Hz, 1H).

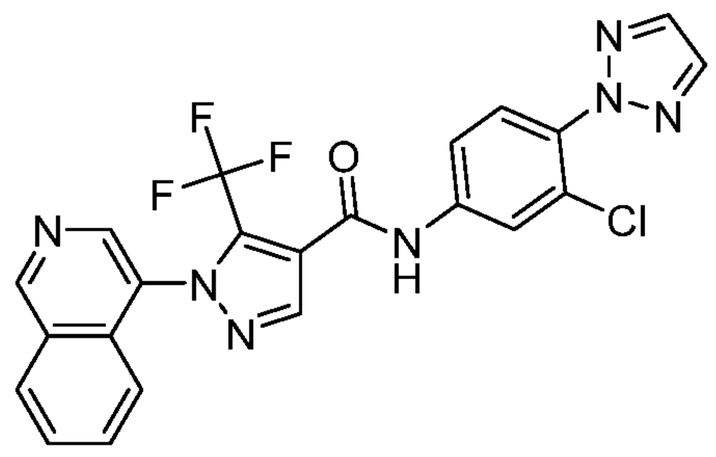
E. 3-Chloro-4-(2*H*-1,2,3-triazol-2-yl)aniline, **4e**



, **4e**

To a solution of 2-(2-chloro-4-nitrophenyl)-2*H*-1,2,3-triazole, **4d** (1 g, 4.45 mmol) in MeOH/THF/water (5 mL/10 mL/5 mL) was added Fe(0) (1.243 g, 22.26 mmol) and ammonium chloride (1.191 g, 22.26 mmol). The reaction mixture was stirred at 60 °C for 2 h. The reaction was filtered and the organic solvent was concentrated under reduced pressure. Water (10 mL) was added and the mixture was extracted with ethyl acetate (15 mL x 3). The organic extracts were dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to afford a crude product which was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 0/100) to afford 3-chloro-4-(2*H*-1,2,3-triazol-2-yl)aniline, **4e** (0.7 g, 80.8 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.96 (br. s., 2H) 6.63 (d, J=8.41 Hz, 1H), 6.81 (d, J=1.96 Hz, 1H), 7.31 (d, J=8.61 Hz, 1H), 7.84 (s, 2H).

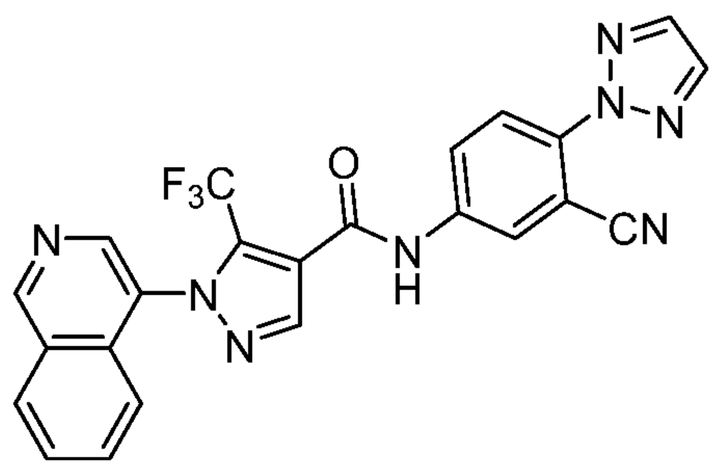
F. *N*-(3-Chloro-4-(2*H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 38**



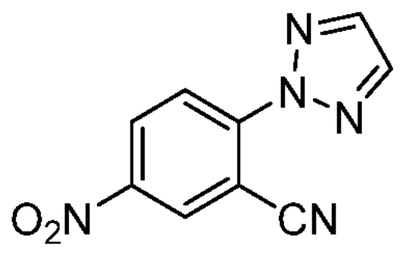
To a solution of 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (60 mg, 0.195 mmol), 3-chloro-4-(2*H*-1,2,3-triazol-2-yl)aniline, **4e** (45.6 mg, 0.234 mmol) and pyridine (77.2 mg, 0.98 mmol) in dichloromethane (5 mL) was added $POCl_3$ (89.8 mg, 0.59 mmol) dropwise. The reaction mixture was stirred at 20 °C for 1 h. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrates concentrated under reduced pressure to afford a yellow oil. The yellow oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate = 10:1 to petroleum ether/ ethyl acetate = 0:1) to afford compound **38** (35 mg, 35.8 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (d, J=8.41 Hz, 1 H), 7.58 - 7.68 (m, 2 H), 7.72 - 7.84 (m, 2 H), 7.89 (s, 2 H), 7.96 - 8.06 (m, 2 H), 8.15 (d, J=7.43 Hz, 1 H), 8.24 (s, 1 H), 8.60 (s, 1 H), 9.44 (s, 1 H); LCMS (ESI) m/z M+1: 483.9.

Example 5

N-(3-Cyano-4-(2*H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 59**



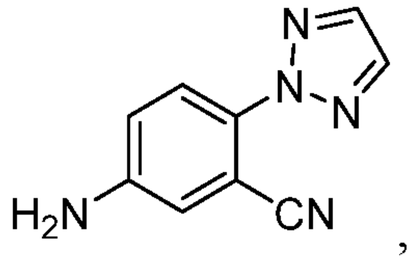
A. 5-Nitro-2-(2*H*-1,2,3-triazol-2-yl)benzonitrile, **5a**



, **5a**

2-Fluoro-5-nitrobenzonitrile (500 mg, 3.01 mmol), 2*H*-1,2,3-triazole (228.68 mg, 3.311 mmol) and K_2CO_3 (832.02 mg, 6.02 mmol) were added to THF (10 mL) and stirred at 25 °C for 16 h. The reaction mixture was filtered, and the collected solid was washed with ethyl acetate (30 mL x 3). The combined organic layers were concentrated under reduced pressure to afford a crude residue as a yellow solid which was purified by flash column chromatography over silica gel (petroleum ether/ ethyl acetate, 100:0 to 50:50) to afford 5-nitro-2-(2*H*-1,2,3-triazol-2-yl)benzonitrile, **5a** (140 mg, 21.6 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.72 (d, J=2.6 Hz, 1H), 8.56 (dd, J=2.5, 9.2 Hz, 1H), 8.42 (d, J=9.0 Hz, 1H), 8.03 (s, 2H).

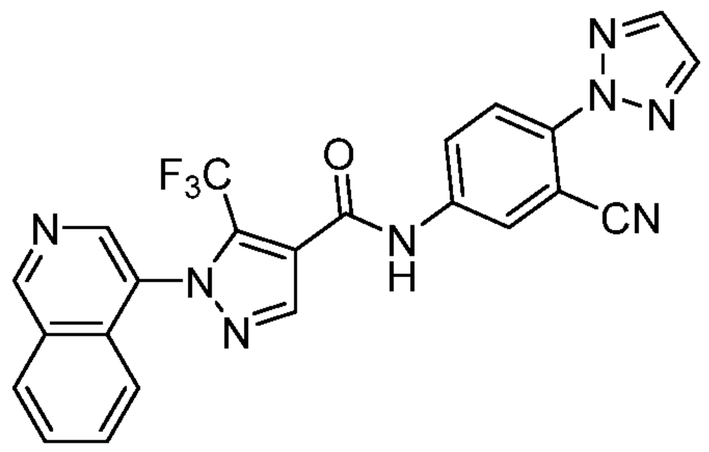
B. 5-Amino-2-(2*H*-1,2,3-triazol-2-yl)benzonitrile, **5b**



, **5b**

5-Nitro-2-(2*H*-1,2,3-triazol-2-yl)benzonitrile, **5a** (140 mg, 0.651 mmol) was dissolved in THF (8 mL), to which Fe(0) (363.36 mg, 6.507 mmol), NH_4Cl (348.04 mg, 6.507 mmol) and water (8 mL) were added. The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). Water (50 mL) was added and the organic layer was separated, dried over Na_2SO_4, filtered, and the filtrate concentrated to dryness to give crude compound **5b** (140 mg) as yellow solid, which was used in the following reaction without further purification. LCMS (ESI) m/z M+1: 186.1.

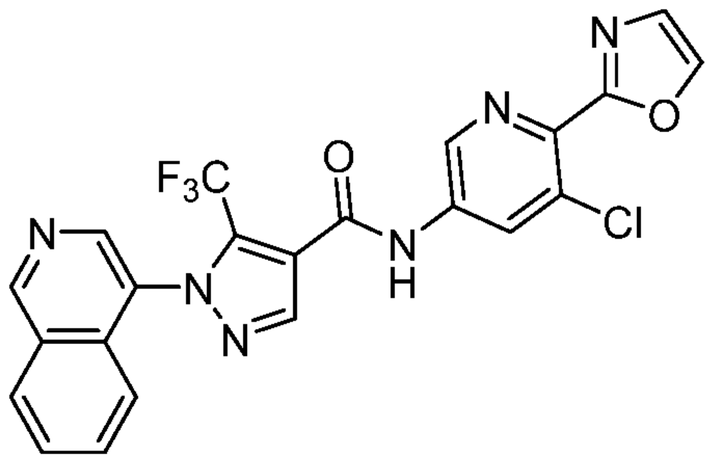
C. *N*-(3-Cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 59**



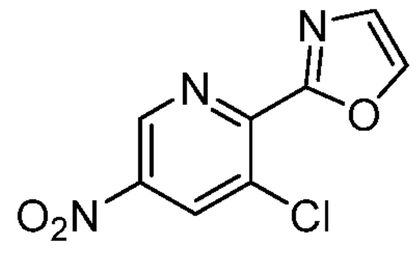
5-Amino-2-(2*H*-1,2,3-triazol-2-yl)benzonitrile , **5b** (67.03 mg, 0.21 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (66.95 mg, 0.315 mmol), and pyridine (74.84 mg, 0.946 mmol) were dissolved in dichloromethane (3 mL), and $POCl_3$ (48.36 mg, 0.315 mmol) was added to the mixture. The mixture was stirred at 25 °C for 16 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic extracts were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford a yellow oil. The oil was purified by flash column chromatography over silica gel (petroleum ether/ ethyl acetate from 100:0 to 40/60) to afford compound **59** (38 mg, 36.3 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.11 (br s, 1H), 9.59 (br s, 1H), 8.77 (br s, 1H), 8.58 (br s, 1H), 8.38 (br s, 2H), 8.29 - 8.04 (m, 4H), 8.01 - 7.69 (m, 2H), 7.27 (br d, J=5.5 Hz, 1H). LCMS (ESI) m/z M+1: 475.0.

Example 6

N-(5-Chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 50**

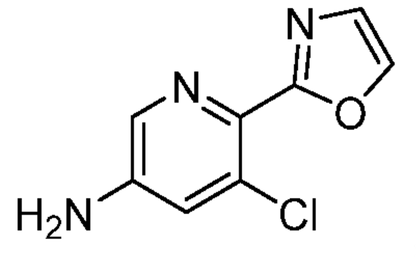


A. 2-(3-Chloro-5-nitropyridin-2-yl)oxazole, **6a**


, **6a**

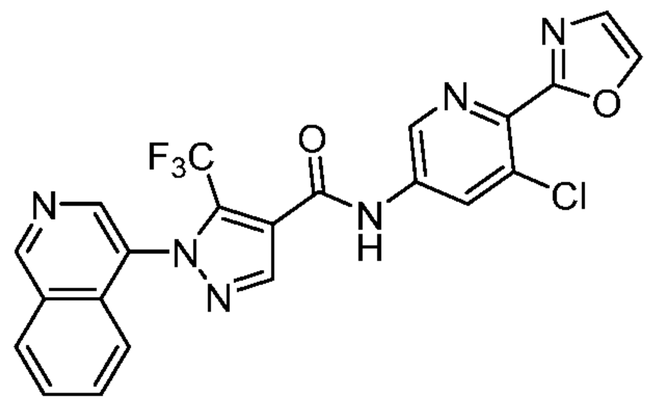
2,3-Dichloro-5-nitropyridine (216 mg, 1.119 mmol) and 2-(tributylstannyl)oxazole (400.1 mg, 1.119 mmol) were dissolved in DMF (3 mL) and purged with N_2. $Pd(PPh_3)_4$ (129 mg, 0.112 mmol) was added and the reaction was stirred at 110 °C for 16 h. The combined reaction mixture was concentrated under reduced pressure to afford a crude black oil. The oil was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 70/30) to afford 2-(3-chloro-5-nitropyridin-2-yl)oxazole, **6a** (150 mg, 59.4 %) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 - 7.55 (m, 1H) 7.93 - 7.99 (m, 1H) 8.66 - 8.72 (m, 1H) 9.40 - 9.47 (m, 1H); LCMS (ESI) m/z M+1: 225.9.

B. 5-Chloro-6-(oxazol-2-yl)pyridin-3-amine**, 6b**


, **6b**

2-(3-Chloro-5-nitropyridin-2-yl)oxazole , **6a** (88 mg ,0.39 mmol), Fe(0) (217.8 mg, 3.90 mmol), and NH_4Cl (208.6 mg, 3.90 mmol) were added to a mixture of THF (5 mL) and water (1 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). The combined filtrates were concentrated to dryness to give a crude yellow oil as product. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 50/50 to 0/100) to afford 5-chloro-6-(oxazol-2-yl)pyridin-3-amine , **6b** (50 mg, 65.5 %) as a yellow oil, which was used in the following reaction without further purification.

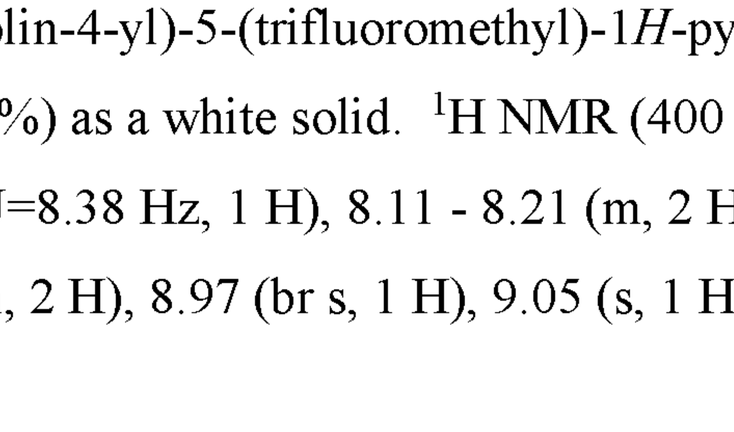
C. N-(5-Chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide**, Cpd 50**



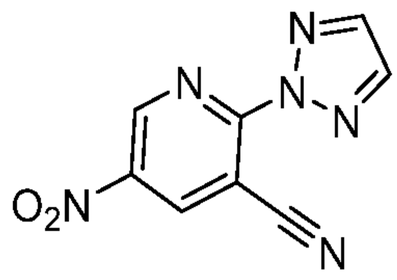
$POCl_3$ (78.4 mg, 0.511 mmol) was added to a mixture of 5-chloro-6-(oxazol-2-yl)pyridin-3-amine , **6b** (50 mg, 0.256 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (62.8 mg, 0.204 mmol), and pyridine (101 mg, 1.278 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 20 °C for 16 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic layer was concentrated under reduced pressure to afford a crude product, which was purified by preparative reverse phase HPLC (water (0.05% HCl):MeCN from 76 % to 46 %) and lyophilized to give *N*-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, compound **50** (28 mg, 22.6 %) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.50 (s, 1 H), 7.65 (d, J=8.38 Hz, 1 H), 8.11 - 8.21 (m, 2 H), 8.27 (t, J=7.20 Hz, 1 H), 8.53 (s, 1 H), 8.60 - 8.70 (m, 2 H), 8.97 (br s, 1 H), 9.05 (s, 1 H), 9.98 (s, 1 H); LCMS (ESI) m/z M+1: 484.9.

Example 7

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 47**



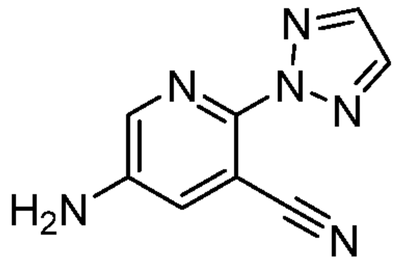
A. 5-Nitro-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7a**



, **7a**

A mixture of 2-chloro-5-nitronicotinonitrile (600 mg, 3.27 mmol), 1,2,3-triazole (270 mg, 3.92 mmol) and K_2CO_3 (1.35 g, 9.8 mmol) in CH_3CN (10 mL) was stirred at 30 °C for 2 h. A yellow solid was collected by filtration and was washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to give a crude product which was washed with dichloromethane (10 mL). The solid was dried under reduced pressure to give 5-nitro-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7a** (0.4 g, 56.6 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.44 (s, 2 H), 9.43 (d, J=2.35 Hz, 1 H), 9.59 (d, J=2.35 Hz, 1 H).

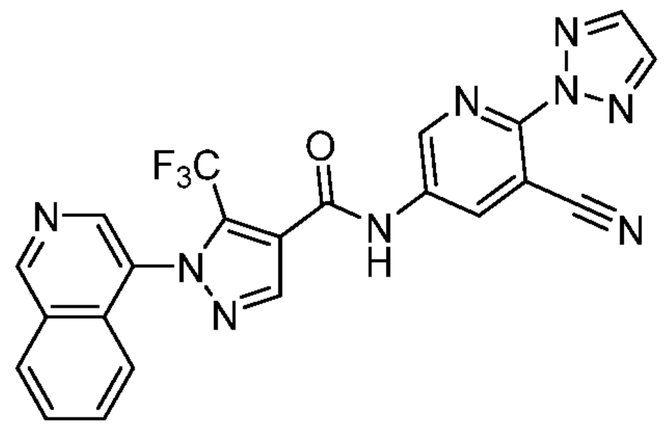
B. 5-Amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile**, 7b**



, **7b**

A solution of 5-nitro-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7a** (353 mg 1.6 mmol), Fe(0), (456 mg, 8.2 mmol) and NH_4Cl (437 mg, 8.2 mmol) in THF/MeOH/water (4:2:1, 35 mL) was stirred at 60 °C for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude product as a yellow oil. Water (20 mL) was added to the yellow oil. The mixture was extracted with ethyl acetate (30 x 3 mL), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to afford 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile**, 7b** (200 mg, 65.7 %) as a white solid, which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J=3.09 Hz, 1 H), 8.00 (s, 2 H), 8.10 (d, J=3.09 Hz, 1 H).

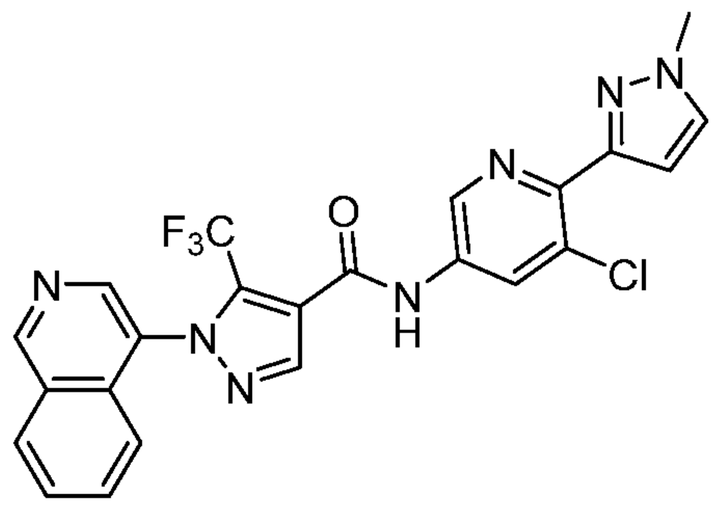
C. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 47**



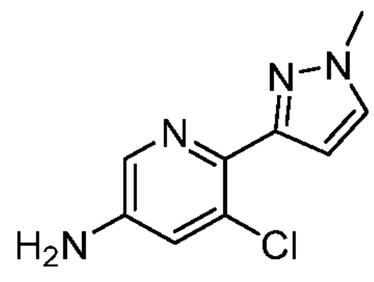
$POCl_3$ (82.36 mg, 0.537 mmol) was added to a mixture of 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile**,** 7**b** (50 mg, 0.269 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (66 mg, 0.215 mmol), and pyridine (106 mg, 1.343 mmol) in dichloromethane (5 mL), and the mixture was stirred at 20 °C for 2 h. Water (20 mL) was added and the mixture was extracted with dichloromethane (30 mL). The organic layer was concentrated under reduced pressure to afford a crude product. The crude product was purified by preparative high-performance liquid chromatography (water (0.05% HCl):MeCN from 84:16 to 66:44). The pure fractions were collected, the organic solvents concentrated under reduced pressure, and the mixture lyophilized to dryness to afford compound **47** (29 mg, 22.7 %) as a yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 7.51 (d, J=8.82 Hz, 1 H), 7.97 - 8.03 (m, 1 H), 8.07 - 8.16 (m, 3 H), 8.47 - 8.51 (m, 2 H), 8.85 (s, 1 H), 8.91 (d, J=2.43 Hz, 1 H), 9.08 (br s, 1 H), 9.75 (s, 1 H); LCMS (ESI) m/z M+1: 476.0.

Example 8

N-(5-chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 52**



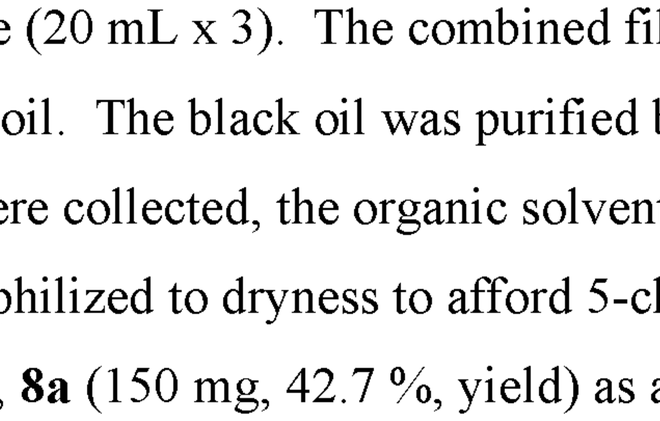
A. 5-Chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-amine, **8a**



, **8a**

6-Bromo-5-chloropyridin-3-amine (383.87 mg, 1.85 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (350 mg, 1.682 mmol) and Na_2CO_3 (356.58 mg, 3.364 mmol) were added to dioxane/water (9:1, 6 mL) and purged with N_2. $Pd(dppf)Cl_2$ (123.09 mg, 0.168 mmol) was added and the reaction was stirred at 120 °C for 16 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). The combined filtrates were concentrated to dryness to give a crude black oil. The black oil was purified by preparative reverse phase HPLC. The pure fractions were collected, the organic solvents concentrated under reduced pressure, and the mixture lyophilized to dryness to afford 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-amine, **8a** (150 mg, 42.7 %, yield) as a yellow oil. LCMS (ESI) m/z M+1: 209.1.

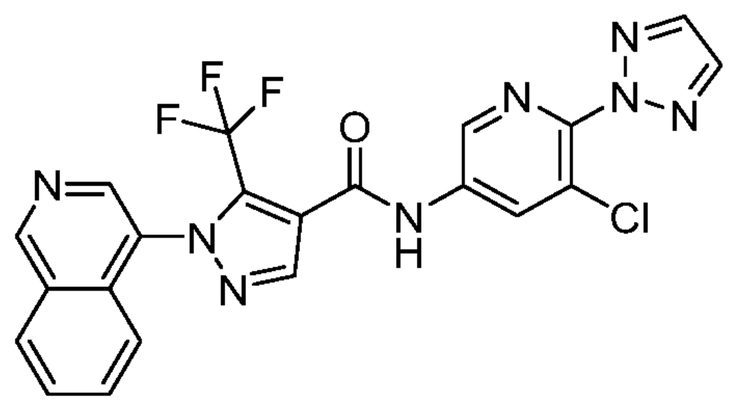
B. *N*-(5-Chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 52**



To a solution of ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **4b** (106.95 mg, 0.335 mmol), 5-chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-amine, **8a** (70 mg, 0.335 mmol) and pyridine (132.69 mg, 1.677 mmol) in dichloromethane (5 mL) was added $POCl_3$ (102.88 mg, 0.671 mmol) dropwise. The reaction mixture was stirred at 20 °C for 1 h. A solution of saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic phases were washed with brine and dried over Na_2SO_4. The mixture was filtered, and the filtrates concentrated under reduced pressure to afford a crude product as a yellow oil. The crude product was purified by flash column chromatography over silica gel (dichloromethane: MeOH = from 100:0 to 80:20) to afford a residue, which was further purified by preparative reverse phase HPLC. The pure fractions were collected, the organic solvents concentrated under reduced pressure, and the mixture lyophilized to dryness to give *N*-(5-chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, compound **52** (45 mg, 26.7 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.03 (br s, 1H), 9.60 (s, 1H), 8.83 (d, *J*=2.0 Hz, 1H), 8.77 (s, 1H), 8.58 (s, 1H), 8.42 (d, *J*=2.0 Hz, 1H), 8.36 (d, *J*=8.2 Hz, 1H), 7.96 - 7.89 (m, 1H), 7.88 - 7.82 (m, 1H), 7.77 (d, *J*=2.2 Hz, 1H), 7.27 (d, *J*=8.4 Hz, 1H), 6.75 (d, *J*=2.0 Hz, 1H), 3.91 (s, 3H). LCMS (ESI) m/z M+1: 497.9.

Example 9

N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 32**

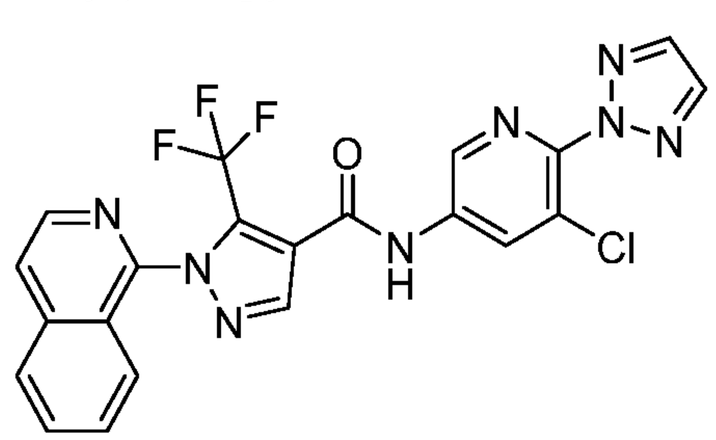


A 20 mL vial equipped with a stirbar was charged with ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **4b** (67 mg, 0.2 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (39.9 mg, 0.204 mmol), and THF (0.67 mL, 0.3 M,

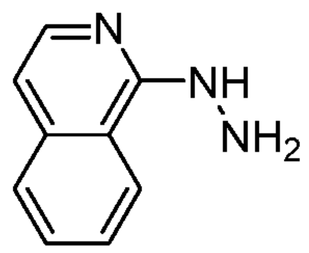
0.201 mmol). The resulting solution was treated with 1.01 M KOtBu/THF (0.32 mL, 1.01 M, 0.323 mmol) in one portion at room temperature and then stirred for 25 min. The reaction was then partitioned between 5 M NH_4Cl (1 mL) and ethyl acetate (2 mL), and the organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated to dryness to provide a beige foam (78 mg). The foam was purified by flash column chromatography on a 12 g Silicycle HP column (10 - 100% EtOAc in heptane over 25 CVs, then isocratic EtOAc) to provide compound **32** as a foam (27.4 mg, 28 %). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.45 (s, 1H), 8.80 (d, *J*=2.53 Hz, 1H), 8.66 (br s, 1H), 8.49-8.59 (m, 2H), 8.25 (s, 1H), 8.16 (dd, *J*=1.52, 7.07 Hz, 1H), 7.92-8.00 (m, 2H), 7.71-7.83 (m, 2H); MS m/e 485.0 (M+H).

Example 10

N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 57**



A. 1-Hydrazinylisoquinoline, **10a**

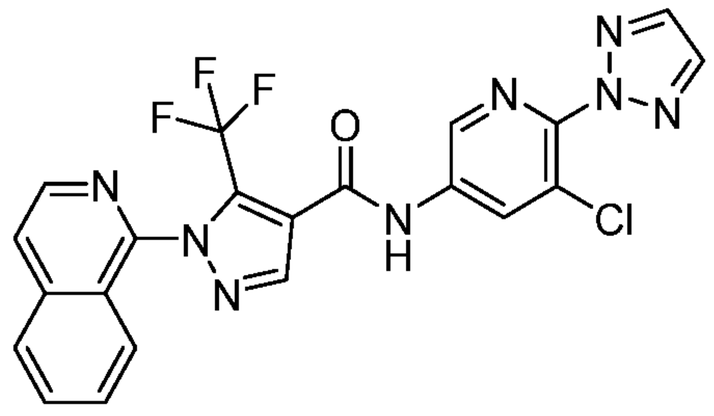


, **10a**

A 2-5 mL Biotage microwave vial equipped with a stirbar was charged with 1-chloroisoquinoline (341.8 mg, 2.089 mmol) and hydrazine (0.66 mL, 1.021 g/mL, 21.028 mmol) at room temperature, and the vial was evacuated/flushed with Argon (4x) and the reaction was stirred at 150 °C for 20 min. The resulting dark yellow homogeneous solution was allowed to cool to room temperature, at which time a precipitate formed.

This was taken up in a 3:1 water/CH_3CN mixture (2 mL) and the solids were collected by filtration. The yellow filter cake was washed with water (2 mL x 3) and then dissolved in DCM (6 mL). The DCM mixture was dried over Na_2SO_4, filtered, and the filtrate concentrated to provide compound **10a** as a yellow solid (189 mg, 57 %).

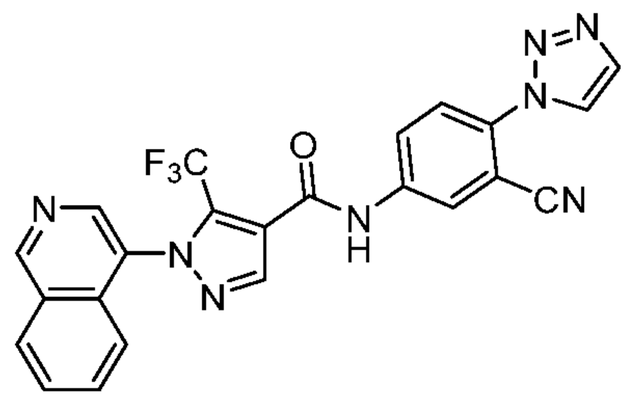
B. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 57**



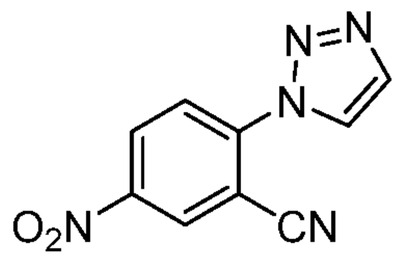
A 4 mL vial equipped with a with stirbar was charged with 1-hydrazinylisoquinoline, **10a** (45.5 mg, 0.286 mmol), THF (0.41 mL, 0.7 M, 0.287 mmol), and 0.5 M ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f**/THF (0.57 mL, 0.5 M, 0.285 mmol), and the reaction was stirred at room temperature for 10 min, followed by 90 min of stirring at 70 °C. The reaction was then charged with calcium sulfate (183 mg, 1.34 mmol) and stirred at 70 °C for 10 min. The reaction was then cooled to room temperature, treated with 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (56.6 mg, 0.288 mmol) and 1.01 M KOtBu/THF (0.42 mL, 1.01 M, 0.424 mmol) in single portions at room temperature, and the resulting dark reaction was stirred at room temperature for 30 min. The dark reaction was then partitioned between 5 M NH_4Cl (1 mL) and ethyl acetate (1 mL), and the organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (50 - 100% EtOAc in heptane over 10 CVs) followed by (1:1 acetone/heptane; isocratic) to afford compound **57** (21.3 mg, 15 %). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.77 (d, *J*=2.02 Hz, 1H), 8.50-8.53 (m, 2H), 8.26 (s, 1H), 7.91-8.02 (m, 4H), 7.83 (ddd, *J*=2.78, 5.56, 8.34 Hz, 1H), 7.67-7.72 (m, 2H); MS m/e 485.1 (M+H).

Example 11

N-(3-cyano-4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 62**



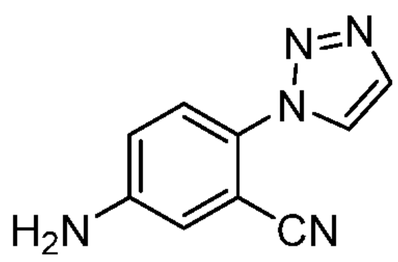
A. 5-Nitro-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11a**



, **11a**

2-Fluoro-5-nitrobenzonitrile (500 mg, 3.01 mmol), triazole (228.7 mg, 3.31 mmol) and K_2CO_3 (832.0 mg, 6.02 mmol) were added to THF (10 mL) and stirred at 25 °C for 16 h. The reaction mixture was filtered and the residue was washed with ethyl acetate (30 mL x 3). The combined organic layers were concentrated under reduced pressure to afford a crude yellow solid. The crude solid was purified by flash column chromatography over silica gel (petroleum ether/ ethyl acetate from 100:0 to 50:50) to afford 5-nitro-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11a** (500 mg, 77.2 %) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3) δ ppm 8.74 (d, J=2.6 Hz, 1H), 8.65 (dd, J=2.4, 9.0 Hz, 1H), 8.48 (d, J=0.9 Hz, 1H), 8.27 (d, J=9.0 Hz, 1H), 7.98 (d, J=0.9 Hz, 1H).

B. 5-Amino-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11b**

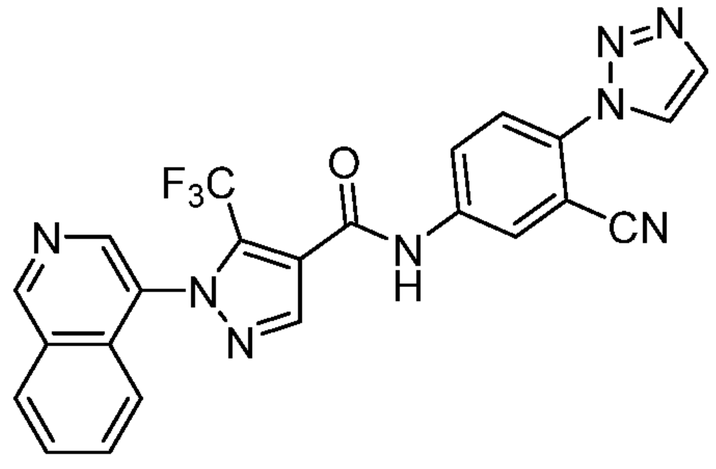


, **11b**

5-Nitro-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11a** (500 mg, 2.32 mmol) was dissolved in THF (10 mL), to which Fe(0) (1297.7 mg, 23.24 mmol), NH_4Cl (1243.0 mg,

23.24 mmol) and water (10 mL) were added. The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). Water (30 mL) was added and the organic layer was separated, dried over Na_2SO_4, filtered and the filtrate concentrated to dryness to give crude 5-amino-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11b** (460 mg, 104.4 %, crude) as a yellow solid. LCMS (ESI) m/z M+1: 185.9.

C. *N*-(3-cyano-4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 62**



1-(Isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (75.1 mg, 0.23 mmol), 5-amino-2-(1*H*-1,2,3-triazol-1-yl)benzonitrile, **11b** (66.4 mg, 0.35 mmol), and pyridine (83.1 mg, 1.05 mmol) were dissolved in dichloromethane (3 mL), and $POCl_3$ (53.7 mg, 0.35 mmol) was added. The mixture was stirred at 25 °C for 16 h. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The crude oil was purified by reverse phase HPLC (A: water (0.05%HCl), B: MeCN, then: A (62%) and B (38%) at the end: A: (32%) and B (68%)). The pure fractions were collected, concentrated under reduced pressure, and lyophilized to dryness to afford compound **62** (35 mg, 29 %) as a white solid. LCMS (ESI) m/z M+1: 185.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.48 (s, 1H), 9.69 (s, 1H), 8.86 (s, 1H), 8.77 (br d, J=4.0 Hz, 2H), 8.53 (br d, J=1.3 Hz, 1H), 8.43 (br d, J=8.3 Hz, 1H), 8.31 (br d, J=8.8 Hz, 1H), 8.07 (s, 1H), 8.03 - 7.96 (m, 1H), 7.96 - 7.87 (m, 2H), 7.35 (br d, J=8.5 Hz, 1H).

Example 12

N-(5-cyano-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 78**

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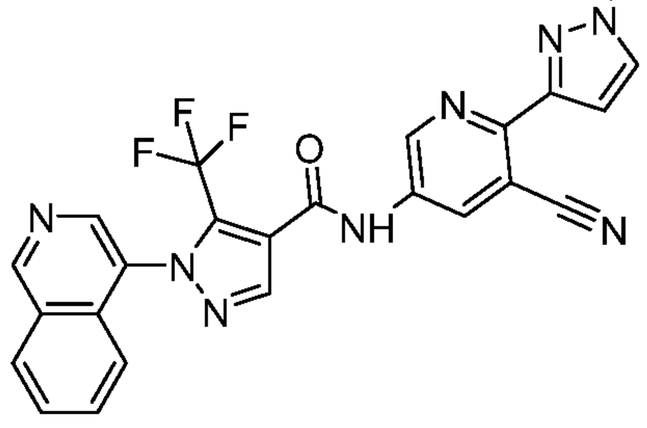
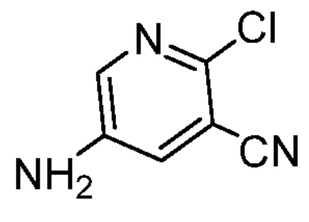
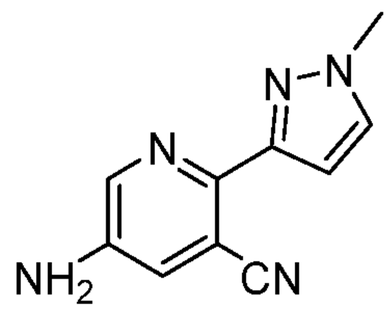


A. 5-Amino-2-chloronicotinonitrile, **12a**


, **12a**

2-Chloro-5-nitronicotinonitrile (500 mg, 2.72 mmol) was dissolved in THF (10 mL), to which was added Fe (0) (1521.2 mg, 27.24 mmol), NH_4Cl (1457.1 mg, 27.24 mmol) and water (10 mL). The reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). Water (50 mL) was added and the organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was concentrated to dryness to give a crude yellow solid. The crude solid was purified by flash column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 80/20) to afford 5-amino-2-chloronicotinonitrile, **12a** (270 mg, 64.5 %) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (d, J=2.8 Hz, 1H), 7.04 (d, J=2.8 Hz, 1H), 4.96 (br s, 2H).

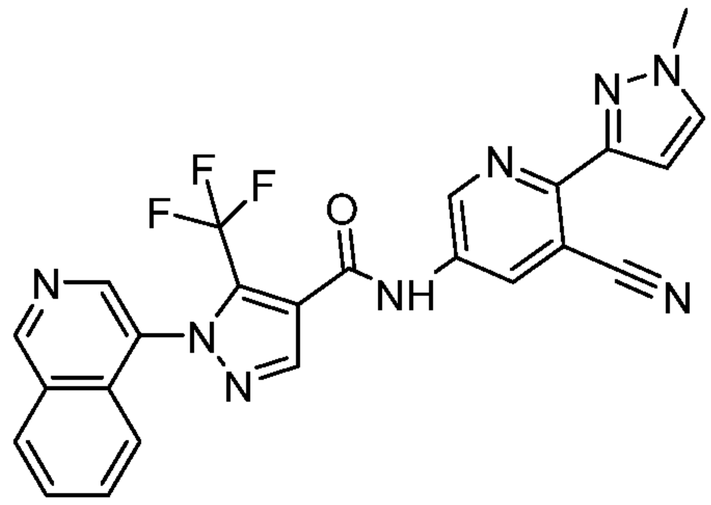
B. 5-Amino-2-(1-methyl-1*H*-pyrazol-3-yl)nicotinonitrile, **12b**



, **12b**

5-Amino-2-chloronicotinonitrile, **12a** (100 mg, 0.65 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (135.5 mg, 0.65 mmol) and Na_2CO_3 (138.0 mg, 1.30 mmol) were added to a dioxane/water mixture (9:1, 6 mL) and the reaction was purged with N_2. $Pd(dppf)Cl_2$ (47.6, 0.065 mmol) was added and the reaction was stirred at 100 °C for 16 h. The reaction mixture was concentrated to dryness to give a crude black oil. The crude oil was purified by flash column chromatography over silica gel (dichloromethane / MeOH from 100/0 to 90/10) to afford 5-amino-2-(1-methyl-1*H*-pyrazol-3-yl)nicotinonitrile, **12b** (100 mg, 51.3 %) as a black solid. LCMS (ESI) m/z M+1: 200.1.

C. *N*-(5-cyano-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 78**

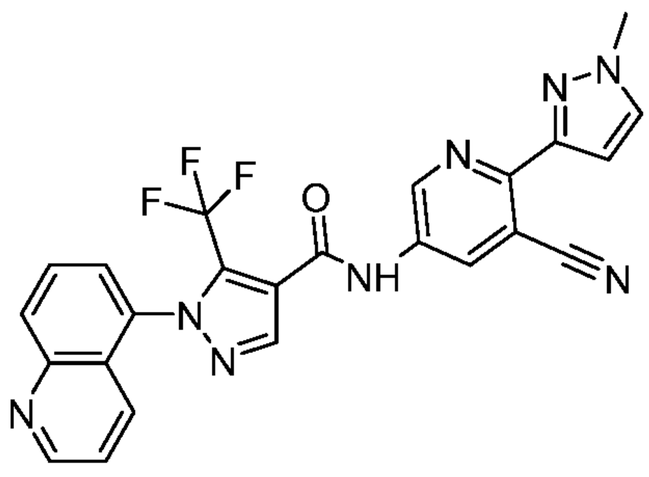


1-(Isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (70 mg, 0.22 mmol), 5-amino-2-(1-methyl-1*H*-pyrazol-3-yl)nicotinonitrile, **12b** (97.8 mg, 0.33 mmol), and pyridine (74.5 mg, 0.98 mmol) were dissolved in dichloromethane (3 mL), and $POCl_3$ (50.0 mg, 0.32 mmol) was added. The mixture was stirred at 25 °C for 16 h. Sat. aqueous $NaHCO_3$ (20 mL) was added and the mixture extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The oil was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (75%/25%

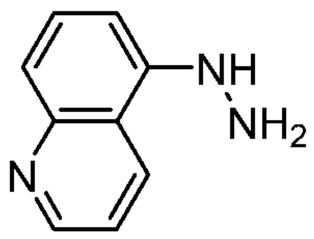
to 48%/52 %). The pure fractions concentrated under reduced pressure and lyophilized to dryness to give compound **78** (50 mg, 46 %) as a yellow solid. LCMS (ESI) m/z M+1: 489.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.33 (s, 1H), 9.64 (s, 1H), 9.13 (d, J=1.8 Hz, 1H), 8.81 (s, 1H), 8.67 (br s, 2H), 8.39 (br d, J=8.2 Hz, 1H), 7.99 - 7.91 (m, 1H), 7.90 - 7.80 (m, 2H), 7.29 (br d, J=8.2 Hz, 1H), 6.85 (d, J=1.8 Hz, 1H), 3.94 (s, 3H).

Example 13

N-(5-cyano-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 89**



A. 5-Hydrazinylquinoline, **13a**

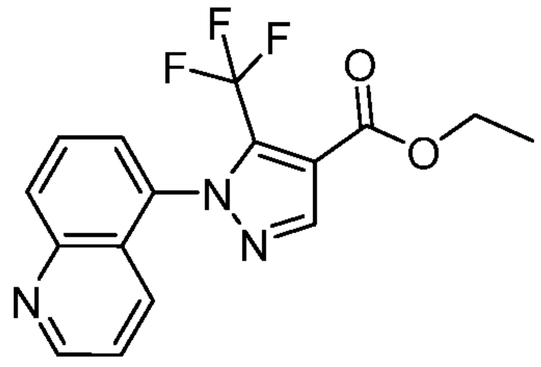


, **13a**

To a stirring solution of isoquinolin-4-amine (3.5 g, 24.28 mmol) in HCl (35 mL, 5 N) at 0° C, was added a solution of sodium nitrite ($NaNO_2$, 2.51 g, 36.42 mmol) in water at 0° C. The reaction mixture was stirred at 0 °C for 30 min and a solution of tin (II) chloride dihydrate ($SnCl_2.2\ H_2O$, 13.695 g, 60.69 mmol) dissolved in concentrated hydrochloric acid (6.5 mL) was added dropwise. The mixture was stirred at room temperature for 2 h. The mixture was adjusted to pH 12-14 with 20% aqueous sodium hydroxide. The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (300 mL). The organic layers were dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resulting crude product was purified by flash

chromatography (petroleum ether/ ethyl acetate=100:0 to ethyl acetate/ methanol=90:10) to afford compound **13a** (1.5 g, 39 %) as a brown solid.

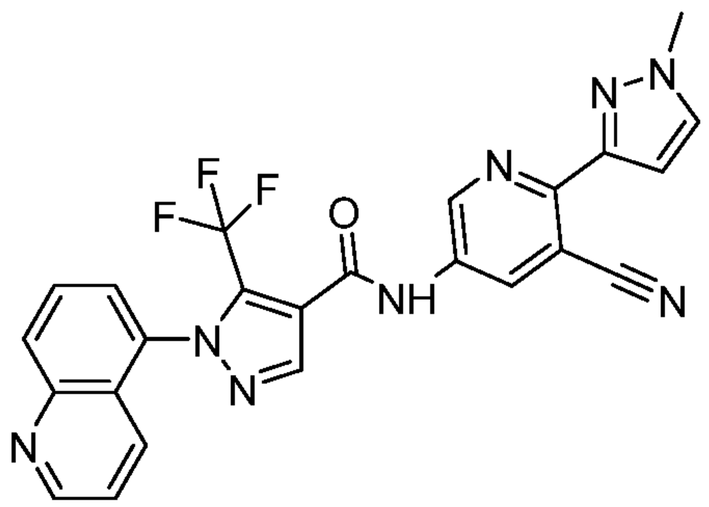
B. Ethyl 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **13b**



, **13b**

A solution of 5-hydrazinylquinoline, **13a** (1.5 g, 9.42 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (2.716 g, 11.31 mmol) in EtOH (40 mL) was stirred at 80 °C for 16 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford a crude product, which was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate, 100:0 to 70:30) to afford crude compound **13b** (2.56 g, 80.9 %) as a yellow solid. LCMS (ESI) m/z M+1: 336.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 - 1.47 (m, 3 H), 4.36 - 4.48 (m, 2 H), 7.41 - 7.50 (m, 1 H), 7.55 - 7.67 (m, 2 H), 7.77 - 7.86 (m, 1 H), 8.25 (s, 1 H), 8.29 - 8.38 (m, 1 H), 8.96 - 9.06 (m, 1 H).

C. *N*-(5-cyano-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 89**

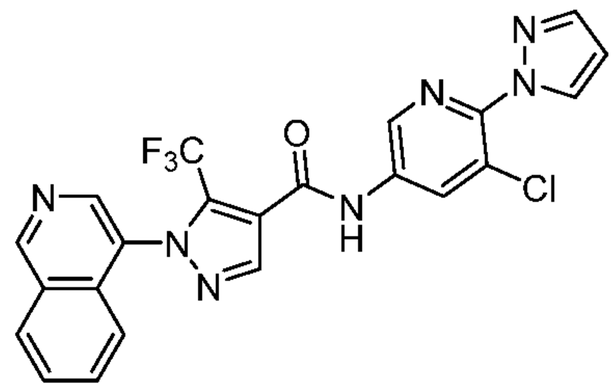


1-(Quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **3b** (102.2 mg, 0.33 mmol), 5-amino-2-(1-methyl-1*H*-pyrazol-3-yl)nicotinonitrile, **12b** (150 mg, 0.50 mmol), and pyridine (118.47 mg, 1.50 mmol) were dissolved in dichloromethane (3 mL),

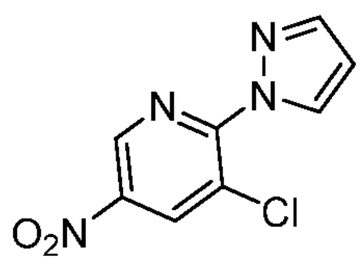
and $POCl_3$ (76.496 mg, 0.499 mmol) was added. The mixture was stirred at 25 °C for 16 h. Sat. aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The oil was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (75%/25% to 45%/55 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **89** (85 mg, 52 %) as a yellow solid. LCMS (ESI) m/z M+1: 489.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 9.14 (dd, J=2.4, 11.9 Hz, 2H), 8.74 - 8.61 (m, 2H), 8.39 (d, J=8.6 Hz, 1H), 8.07 - 7.95 (m, 2H), 7.86 - 7.73 (m, 3H), 6.84 (d, J=1.8 Hz, 1H), 3.94 (s, 3H).

Example 14

N-(5-Chloro-6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 46**



A. 3-Chloro-5-nitro-2-(1*H*-pyrazol-1-yl)pyridine, **14a**

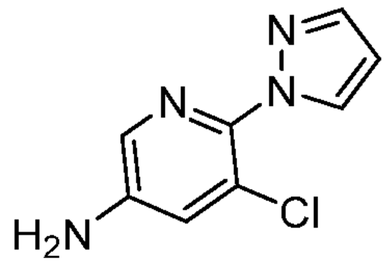


, **14a**

2,3-Dichloro-5-nitropyridine (1g, 5.18 mmol), pyrazole (529 mg, 7.77 mmol), and Cs_2CO_3 (5.06 g, 15.50 mmol) were added to DMF (15 mL) and stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The yellow oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=1:0 to petroleum ether/ ethyl acetate=10:1) to give compound **14a** (511 mg, 43.907 %) as a yellow solid. LCMS (ESI) m/z M+1: 224.8;

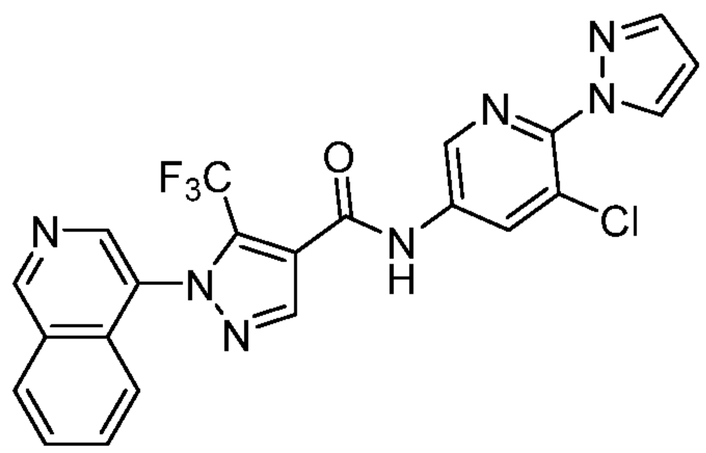
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.57 (d, J=1.76 Hz, 1 H), 7.90 (s, 1 H), 8.37 - 8.46 (m, 1 H), 8.42 (d, J=2.65 Hz, 1 H), 8.71 (d, J=2.21 Hz,1 H), 9.21 (d, J=2.21 Hz, 1 H).

B. **5**-Chloro-6-(1*H*-pyrazol-1-yl)pyridin-3-amine, **14b**



3-Chloro-5-nitro-2-(1*H*-pyrazol-1-yl)pyridine, **14a** (500 mg, 2.26 mmol) was added to a mixture of Fe (0) (621.6 mg, 11.13 mmol), NH_4Cl (595.4 mg, 11.13 mmol) in MeOH (10 mL), water (5 mL), and THF (20 mL). The reaction was stirred at 60 °C for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=1:0 to petroleum ether/ ethyl acetate=0:1) to give compound **14b** (300 mg, 69.2 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.44 (s, 1 H), 7.15 (d, J=2.35 Hz, 1 H), 7.75 (s, 1 H), 7.85 - 7.91 (m, 2 H).

C. *N*-(5-chloro-6-(1*H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide**, Cpd 46**

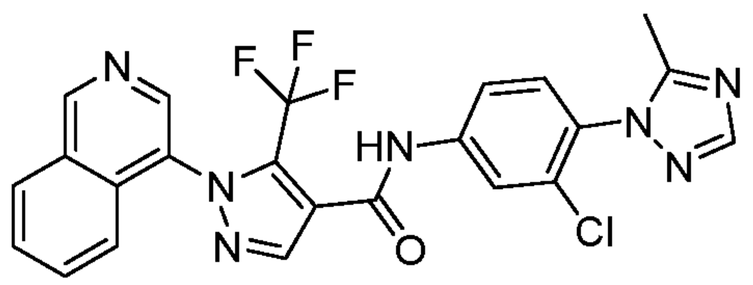


$POCl_3$ (78.8 mg, 0.514 mmol) was added to a mixture of 5-chloro-6-(1*H*-pyrazol-1-yl)pyridin-3-amine, **14b** (50 mg,0.26 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (63.1 mg, 0.21 mmol), and pyridine (101.6 mg, 1.3 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 20 °C for 16 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic layer was concentrated under reduced pressure to

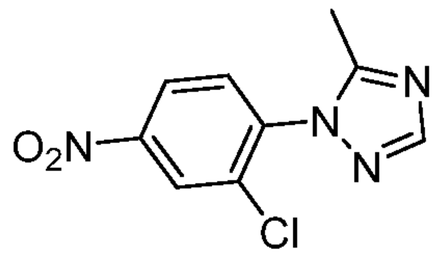
afford a crude product which was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (57%/43% to 27%/73 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **46** (55 mg, 44 %) as a pale white solid. LCMS (ESI) m/z M+1: 483.9; ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm 6.57 (t, J=2.09 Hz, 1 H), 7.38 (d, J=8.60 Hz, 1 H), 7.78 - 7.95 (m, 3 H), 8.16 (d, J=2.43 Hz, 1 H), 8.33 (d, J=8.16 Hz, 1 H), 8.41 (s, 1 H), 8.61 - 8.66 (m, 2 H), 8.77 (d, J=2.21 Hz, 1 H), 9.51 (s, 1 H).

Example 15

N-(3-Chloro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 51**



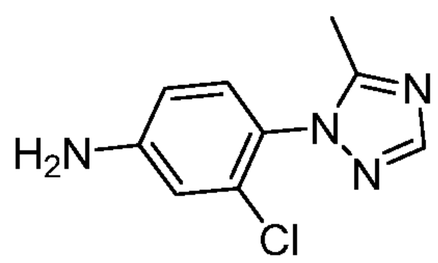
A. 1-(2-Chloro-4-nitrophenyl)-5-methyl-1*H*-1,2,4-triazole, **15a**



, **15a**

2-Chloro-1-fluoro-4-nitrobenzene (1.6 g, 9.11 mmol), 5-methyl-1*H*-1,2,4-triazole (1.14 g, 13.7 mmol) and Cs_2CO_3 (8.9 g, 27.3 mmol) were added to DMF (15 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=7:3 to petroleum ether/ ethyl acetate=3:7) to afford compound **15a** (1.5 g, 69 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.38 - 2.56 (m, 1 H), 2.39 - 2.44 (m, 1 H), 2.51 (s, 2 H), 7.60 - 7.67 (m, 1 H), 7.90 (d, J=8.82 Hz, 1 H), 8.02 (s, 1 H), 8.23 - 8.33 (m, 1 H), 8.43 - 8.50 (m, 1 H), 8.69 (s, 1 H).

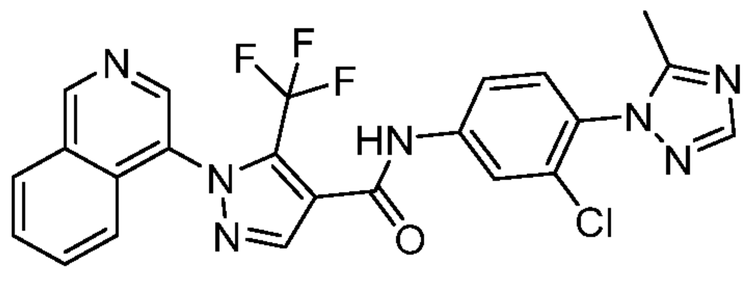
B. 3-Chloro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)aniline, **15b**



, **15b**

1-(2-Chloro-4-nitrophenyl)-5-methyl-1*H*-1,2,4-triazole, **15a** (1500 mg, 2.26 mmol) was added to the mixture of Fe (0) (877 mg, 15.71 mmol), NH_4Cl (840 mg, 15.71 mmol) in MeOH (10 mL), water (5 mL), and THF (20 mL). The reaction was stirred at 60 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=1:1 to petroleum ether/ ethyl acetate=0:1) afford compound **15b** (1200 mg, 91.5 %) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.90 (s, 3 H), 6.52 - 6.61 (m, 1 H), 6.69 - 6.77 (m, 1 H), 7.06 (d, J=8.61 Hz, 1 H), 7.16 (d, J=8.61 Hz, 1H), 7.87 (s, 1 H), 7.96 (s, 1 H), 8.15 (s, 1 H).

C. *N*-(3-chloro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide**, Cpd 51**

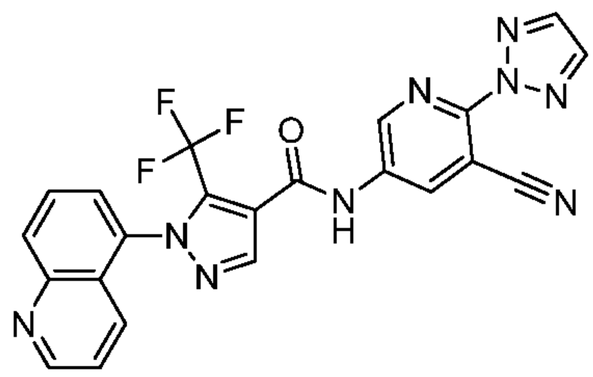


$POCl_3$ (110.23 mg, 0.719 mmol) was added to a mixture of 3-chloro-4-(5-methyl-1*H*-1,2,4-triazol-1-yl)aniline, **15b** (150 mg, 0.36 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (88.3 mg,0.29 mmol), and pyridine (142.2 mg, 1.8 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at 20 °C for 16 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic layer was concentrated under reduced pressure to afford a crude product, which was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (62%/38% to 32%/68 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound compound **51** (31 mg, 17 %) as a pale white solid. LCMS (ESI) m/z M+1: 497.9; ^1H NMR (400 MHz,

METHANOL-d_4) δ ppm 2.50 (s, 3 H), 7.48 (d, J=8.38 Hz, 1 H), 7.64 (d, J=8.82 Hz, 1 H), 7.84 (dd, J=8.60, 2.20 Hz, 1 H), 7.92 - 7.98 (m, 1H), 8.00 - 8.06 (m, 1 H), 8.22 (d, J=2.20 Hz, 1 H), 8.39 - 8.48 (m, 2 H), 8.67 (br s, 1 H), 8.82 (br s, 1 H), 9.01 (s, 1 H), 9.53 - 9.91 (m, 1 H), 9.72 (br s, 1 H).

Example 16

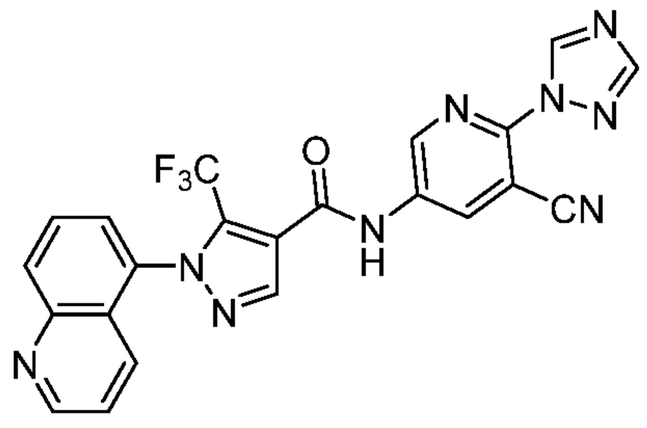
N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 83**



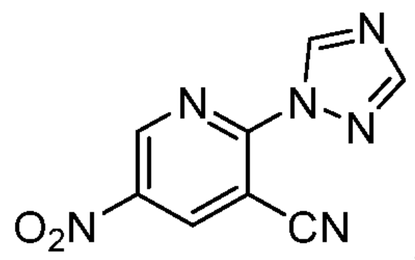
$POCl_3$ (49.4 mg, 0.32 mmol) was added to a mixture of 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (30 mg, 0.161 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (49.5 mg,0.16 mmol), and pyridine (63.7 mg, 0.81 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at 20 °C for 2 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic layers were concentrated under reduced pressure to afford a crude product, which was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (67%/33% to 37%/63 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **83** (33 mg, 42 %) as a white solid. LCMS (ESI) m/z M+1: 475.9. ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.07 - 8.21 (m, 4 H), 8.32 (t, J=8.03 Hz, 1 H), 8.48 - 8.57 (m, 3 H), 8.94 (d, J=2.26 Hz, 1 H), 9.10 - 9.18 (m, 1 H), 9.35 (d, J=4.02 Hz, 1 H).

Example 17

N-(5-cyano-6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 86**



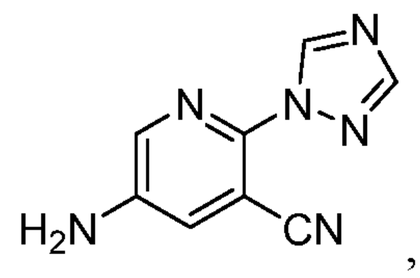
A. 5-Nitro-2-(1*H*-1,2,4-triazol-1-yl)nicotinonitrile**, 17a**



, **17a**

K_2CO_3 (564.7 mg, 4.09 mmol) was added to a solution of 2-chloro-5-nitronicotinonitrile (250 mg, 1.36 mmol) 1,2,4-triazole (141.1 mg, 2.04 mmol) in MeCN (5 mL). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=1:2) to afford compound **17a** (200 mg, 67.9 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.31 (s, 1 H), 9.02 (d, J=2.51 Hz, 1 H), 9.28 (s, 1 H), 9.48 (d, J=2.51 Hz, 1 H).

B. 5-Amino-2-(1*H*-1,2,4-triazol-1-yl)nicotinonitrile, **17b**

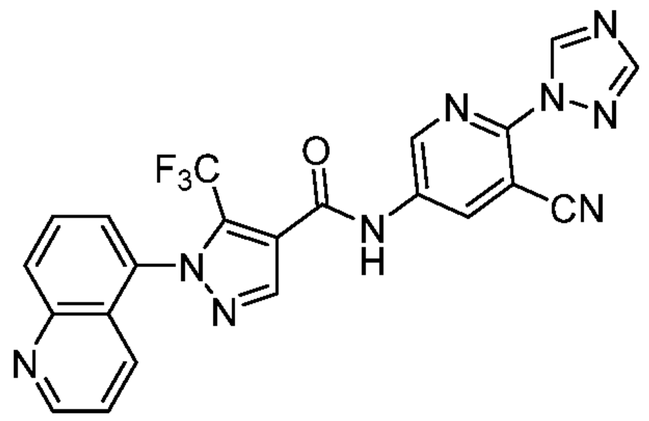


, **17b**

5-Nitro-2-(1*H*-1,2,4-triazol-1-yl)nicotinonitrile, **17a** (100 mg, 0.46 mmol) was added to a mixture of Fe(0) (206.7 mg, 3.7 mmol), NH_4Cl (198.0 mg, 3.70 mmol) in THF (4 mL), and water (1 mL). The reaction was stirred at 60 °C for 1 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). The combined filtrates were concentrated to dryness to give a crude yellow solid. The crude solid was purified by flash column chromatography over silica gel

(petroleum ether/ethyl acetate from 50/50 to 0/100) to afford compound **17b** (55 mg, 64 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.08 - 4.17 (m, 2 H), 7.35 - 7.42 (m, 1 H), 7.39 (d, J=2.65 Hz, 1 H), 8.17 (s, 1 H), 8.93 (s, 1 H).

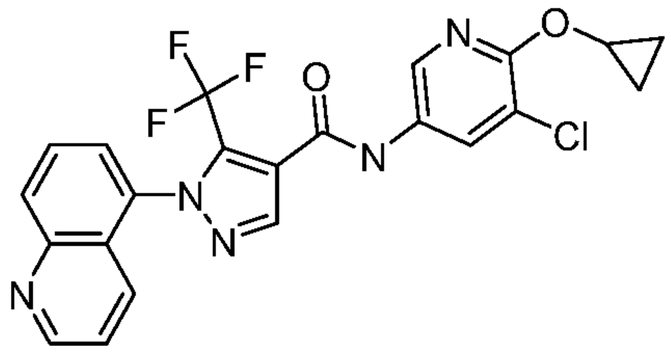
C. *N*-(5-cyano-6-(1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 86**



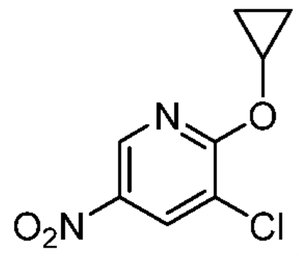
$POCl_3$ (82.4 mg, 0.54 mmol) was added to a mixture of 5-amino-2-(1*H*-1,2,4-triazol-1-yl)nicotinonitrile, **17b** (50 mg, 0.269 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (82.5 mg,0.27 mmol), and pyridine (106.2 mg, 1.34 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at 20 °C for 2 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic layer was concentrated under reduced pressure to afford a crude product, which was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (65%/35% to 35%/65 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **86** (84 mg, 66 %) as a white solid. LCMS (ESI) m/z M+1: 475.9; ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 8.16 - 8.24 (m, 2 H), 8.31 - 8.39 (m, 2 H), 8.50 (s, 1 H), 8.55 (d, J=8.82 Hz, 1 H), 8.64 (d, J=8.60 Hz, 1 H), 8.88 (d, J=2.43 Hz, 1 H), 9.09 (d, J=2.65 Hz, 1 H), 9.35 - 9.43 (m, 2 H).

Example 18

N-(5-Chloro-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 79**



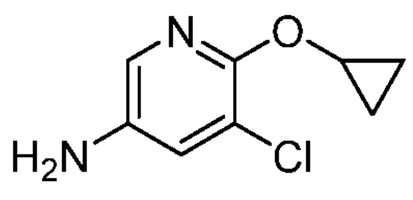
A. 3-Chloro-2-cyclopropoxy-5-nitropyridine, **18a**



, **18a**

Cyclopropanol (4.304 g, 74.10 mmol) was slowly added to a mixture of NaH (4.042 g, 101.0 mmol) in THF (30 mL) at room temperature. The mixture was stirred at 40 °C for 1 h. 2,3-Dichloro-5-nitropyridine in THF (20 mL) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (50 mL). The mixture was extracted with ethyl acetate (200 mL x 3). The organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 90/10) to afford 3-chloro-2-cyclopropoxy-5-nitropyridine, **18a** (9 g, 53 %) as a yellow solid.

B. 5-Chloro-6-cyclopropoxypyridin-3-amine, **18b**

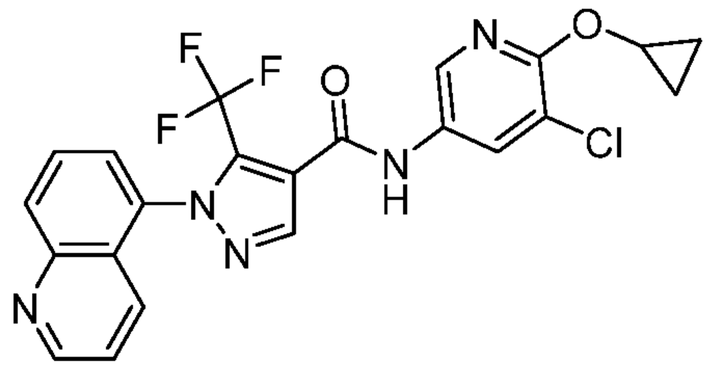


, **18b**

3-Chloro-2-cyclopropoxy-5-nitropyridine, **18a** (18 g, 76.79 mmol) was dissolved in a mixture of MeOH/THF/water (2:4:1, 100 mL). Fe(0) (21.47 g, 384 mmol) and NH_4Cl (20.54 g, 384 mmol) were added. The reaction mixture was stirred at 60 °C for 2 h. Ethyl acetate (200 mL) was added to the mixture. A precipitate was removed by filtration. The precipitate was washed with ethyl acetate (100 mL), and the filtrate was concentrated under reduced pressure. A 10% $NaHCO_3$ solution (100 mL) was added to the mixture and

the mixture was extracted with ethyl acetate (100 mL x 2). The organic portion was dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a crude yellow oil. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=1:2) to afford compound **18b** (12 g, 78.3 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.78 (d, J=4.52 Hz, 4 H), 3.43 (br. s., 2 H), 4.22 (quin, J=4.58 Hz, 1 H), 7.10 (d, J=2.76 Hz, 1 H), 7.62 (d, J=2.51 Hz, 1 H).

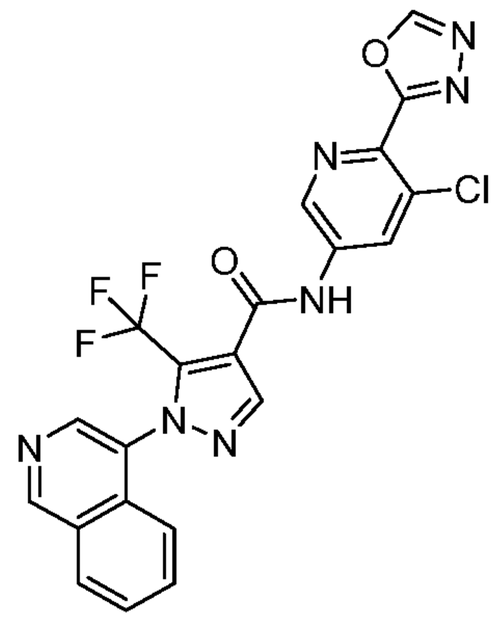
C. *N*-(5-chloro-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 79**



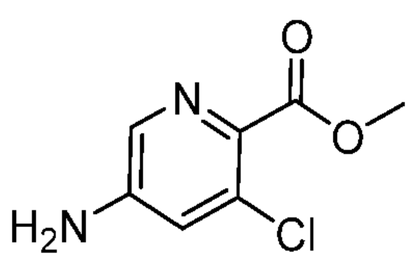
HATU (111.6 mg, 0.294 mmol) was added to a mixture of 5-chloro-6-cyclopropoxypyridin-3-amine, **18b** (58.7 mg, 0.29 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (75.1 mg, 0.245 mmol) and DIEA (94.85 mg, 0.73 mmol) in DMF (3 mL). The mixture was stirred at room temperature for 2 h. Water (10 mL) was added to the mixture and the mixture was extracted with ethyl acetate (30 mL x 2). The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate concentrated to dryness to give a crude yellow solid. The crude solid was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=0:1) to give compound **79** (90 mg, 76 %) as a white solid. LCMS (ESI) m/z M+1: 473.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.73 (br s, 2 H), 0.77 - 0.83 (m, 2 H), 4.33 (dt, J=6.21, 3.04 Hz, 1 H), 7.56 - 7.63 (m, 1 H), 7.65 - 7.71 (m, 1 H), 7.87 - 7.93 (m, 1 H), 7.95 - 8.00 (m, 1 H), 8.29 (d, J=2.26 Hz, 1 H), 8.33 (d, J=8.28 Hz, 1 H), 8.45 (d, J=2.51 Hz, 1 H), 8.51 (s, 1 H), 9.06 (dd, J=4.39, 1.38 Hz, 1 H), 10.80 (s, 1 H).

Example 19

N-(5-Chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 69**



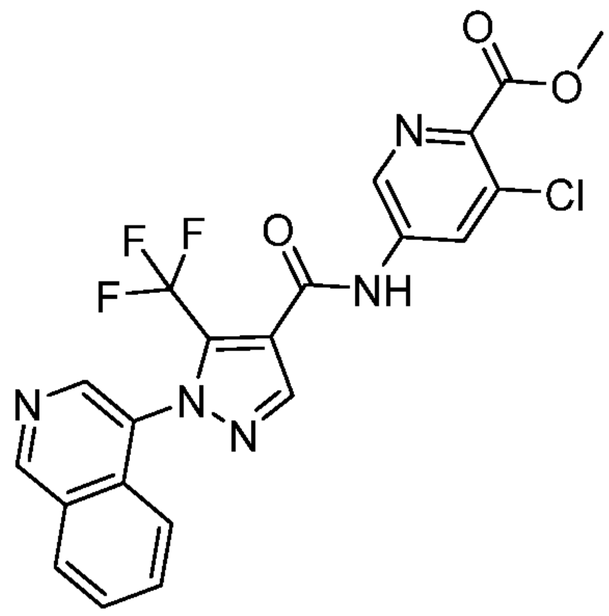
A. Methyl 5-amino-3-chloropicolinate, **19a**



, **19a**

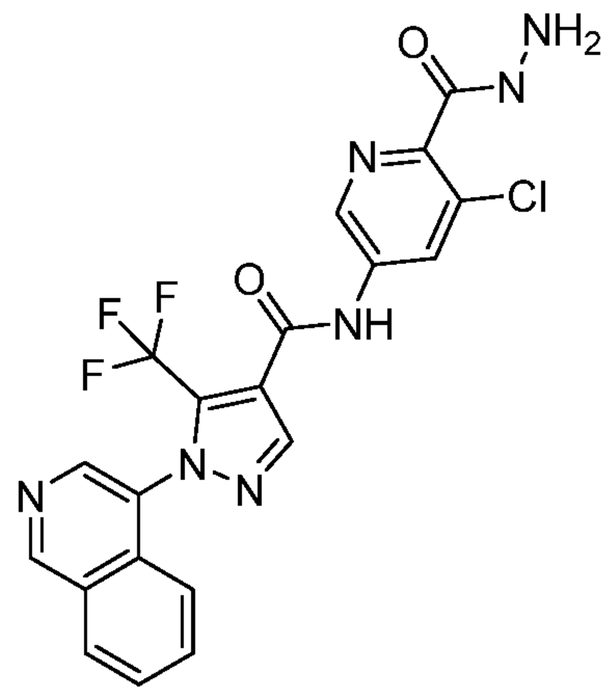
A stirring solution of 5-amino-2-bromo-3-chloropyridine (800 mg, 3.856 mmol), dppf (213.8 mg, 0.386 mmol) and NEt_3 (1.17 g, 11.6 mmol) in MeOH (4 mL) and toluene (20 mL) was carbonylated at 70 °C (35 psi) with $Pd(dppf)Cl_2.CH_2Cl_2$ (314.9 mg, 0.386 mmol) as a catalyst for 16 h. After uptake of CO (1 equiv), the catalyst was removed by filtration, and the filtrate was concentrated to give a crude product. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 70/30) to afford methyl 5-amino-3-chloropicolinate, **19a** (400 mg, 56 %) as a red solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.95 (s, 3 H), 4.20 (br s, 2 H), 7.02 (d, J=2.43 Hz, 1 H), 8.01 (d, J=2.43 Hz, 1 H).

B. Methyl 3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamido)picolinate, **19b**



To a solution of methyl 5-amino-3-chloropicolinate, **19a** (270 mg, 1.45 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (387.9 mg, 1.206 mmol) and pyridine (388 µL, 4.82 mmol) in dichloromethane (3 mL), $POCl_3$ (221 µL, 2.41 mmol) was added dropwise. The reaction mixture was stirred at 20 °C for 1 h. Sat. aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to afford a crude yellow oil. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=0:1) to give methyl 3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamido) picolinate, **19b** (190 mg, 33 %) as a yellow solid. LCMS (ESI) m/z M+1: 475.9.

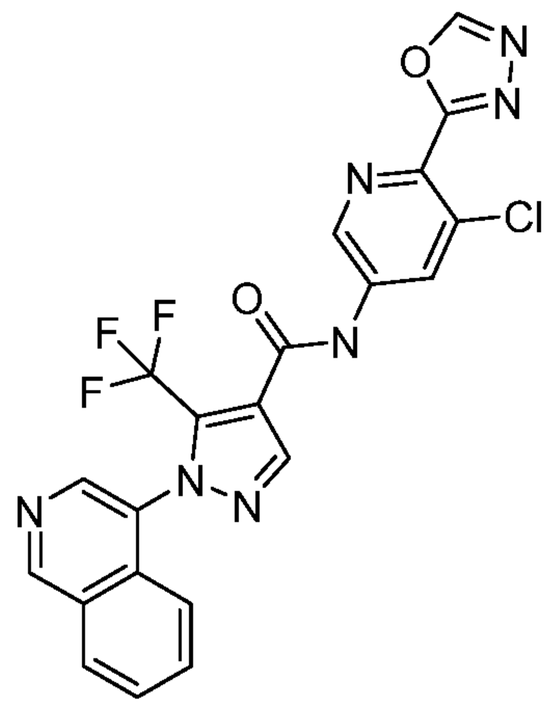
C. *N*-(5-Chloro-6-(hydrazinecarbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide**, 19c**



, 19c

To a solution of methyl 3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamido)picolinate, **19b** (170 mg, 0.36 mmol) in EtOH (5 mL) was added 85 % $NH_2NH_2.H_2O$ (2 mL) at room temperature. The mixture was heated to 80 °C and stirred for 4 h. The solvent was concentrated under reduced pressure to give a red solid. The red solid was washed with a mixture of petroleum ether (5 mL) and ethyl acetate (1 mL) to give compound **19c** (160 mg, 83 %) as a red solid. LCMS (ESI) m/z M+1: 476.0.

D. *N*-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 69**



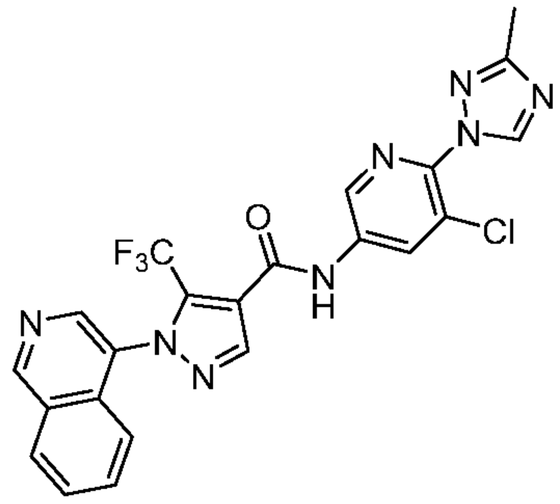
To a solution of *N*-(5-chloro-6-(hydrazinecarbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide**, 19c** (160 mg, 0.296 mmol) and triethyl orthoformate (131.6 mg, 0.888 mmol) in toluene (3 mL) was added HOAc (5.3 mg, 0.09 mmol) at room temperature. The mixture was heated to 100 °C for 2 h. The solvent was concentrated to afford a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to ethyl acetate / methanol=5:1) to afford compound **69** (26.8 mg, 17 %) as a white solid. LCMS (ESI) m/z M+1: 485.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (d, J=7.72 Hz, 1 H), 7.75 - 7.83 (m, 2 H), 8.16 (d, J=8.16 Hz, 1 H), 8.29 (s, 2 H) 8.60 (s, 2 H), 8.75 (d, J=3.97 Hz, 2 H), 9.45 (s, 1 H).

Example 20

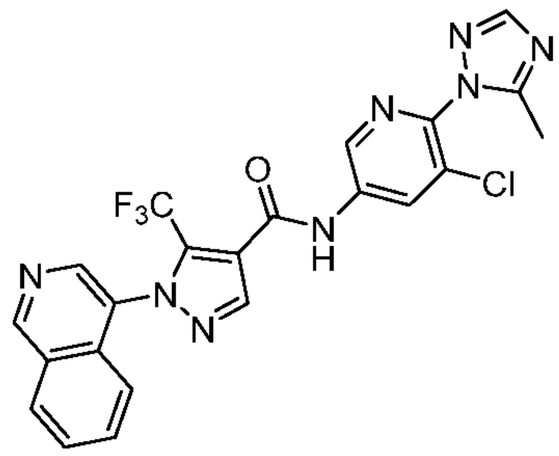
N-(5-Chloro-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 53**

and

N-(5-Chloro-6-(5-methyl-1*H* -1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H* -pyrazole-4-carboxamide, **Cpd 54**

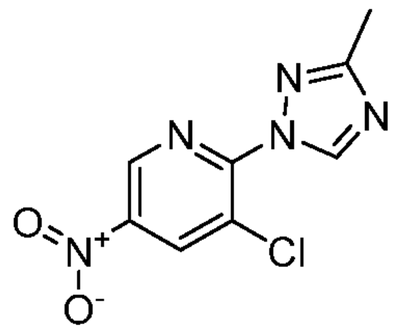


Cpd 53

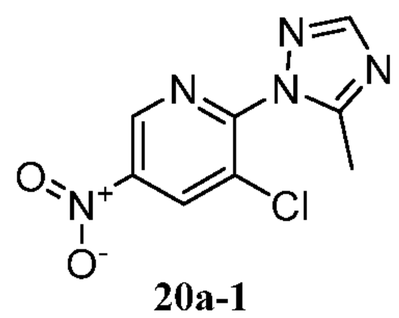


Cpd 54

A. 3-Chloro-2-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-nitropyridine (**20a**) and 3-chloro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)-5-nitropyridine (**20a-1**)



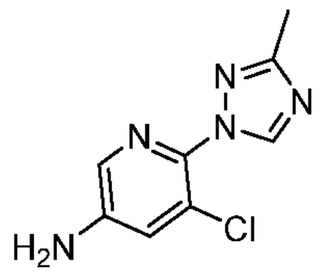
20a



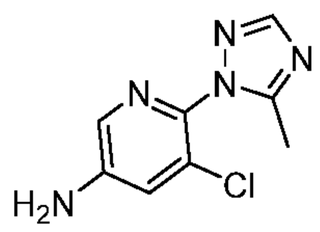
20a-1

2,3-Dichloro-5-nitropyridine (2 g, 10.36 mmol), 3-methyl-1*H*-1,2,4-triazole (1.722 g, 20.73 mmol) and Cs_2CO_3 (6.798 g, 20.73 mmol) were added to DMF (30 mL) and the reaction was stirred at rt for 12 h. The reaction mixture was quenched with water (200 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The crude residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100:0 to 50:50) to afford a mixture of compounds **20a** and **20a-1** (780 mg, 31 %) as a white solid.

B. 5-Chloro-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine (**20b**) and 5-chloro-6-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine (**20b-1**)



20b



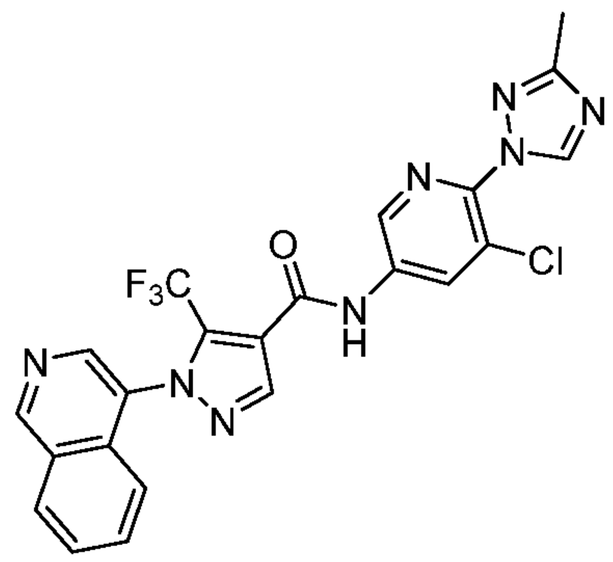
20b-1

A mixture of 3-chloro-2-(3-methyl-1*H*-1,2,4-triazol-1-yl)-5-nitropyridine, **20a** and 3-chloro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)-5-nitropyridine, **20a-1** (780 mg, 1.63 mmol) was dissolved in MeOH (20 mL), and Zn (0) (1.058 g, 16.28 mmol) and aqueous NH_4Cl (20 mL) were added. The reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad washed with ethyl acetate (20 mL x 3). Water (50 mL) was added and the organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was concentrated to dryness to give a crude mixture of compounds **20b** and **20b-1** (400 mg, 59 %) as a yellow solid. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm 2.43 (s, 3 H), 2.85 (d, J=0.66 Hz, 1 H), 2.99 (s, 1 H), 7.21 - 7.23 (m, 1 H), 7.82 (d, J=2.65 Hz, 1 H) ,7.86 (dd, J=4.85, 2.43 Hz, 1 H), 8.02 (s, 1 H), 8.61 - 8.65 (m, 1 H), 8.63 (s, 1 H).

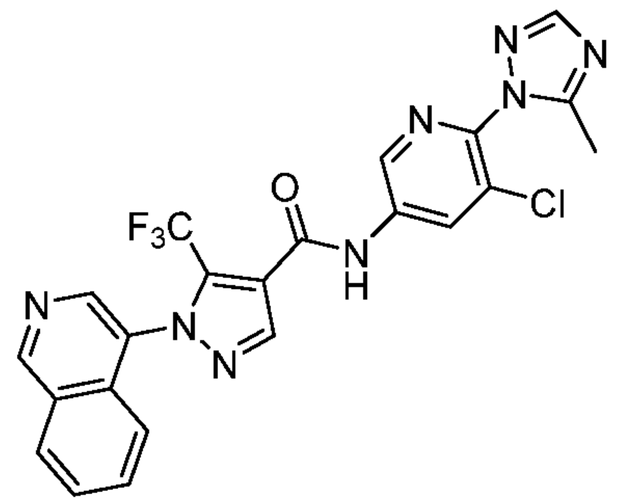
C. *N*-(5-Chloro-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 53**

and

N-(5-chloro-6-(5-methyl-1*H* -1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H* -pyrazole-4-carboxamide, **Cpd 54**



Cpd 53



Cpd 54

A mixture of compounds 5-chloro-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine, **20b** and 5-chloro-6-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-amine, **20b-1** (100 mg, 0.31 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (263.0 mg, 0.63 mmol), and pyridine (62.0 mg, 0.78 mmol) were dissolved in dichloromethane (10 mL), and $POCl_3$ (96.2 mg, 0.63 mmol) was added. The mixture was stirred at rt for 2.5 h. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The crude oil was purified by reverse phase HPLC (A: water (0.05%HCl)-CAN, B: MeCN, A/B : (48%/52%). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford a mixture of compounds **53** and **54** (90 mg). The mixture was separated by Supercritical Fluid Chromatography (0.1% NH_3H_2O: MEOH. Mobile phase: A: CO_2 B: 0.1%NH_3H_2O: MEOH; A/B 75/25).

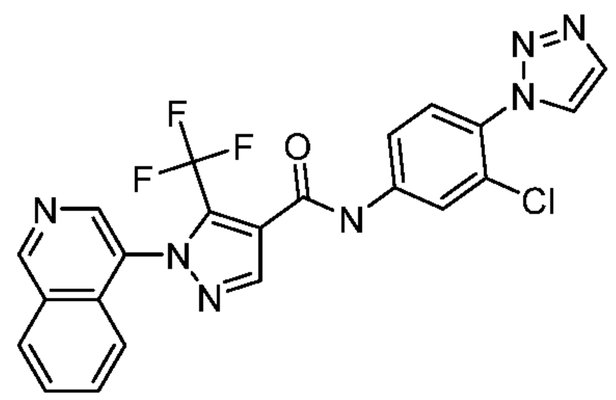
Cpd 53: *N*-(5-chloro-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, (37.8 mg, 24.1%) as a white solid. LCMS (ESI) m/z M+1: 498.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 - 2.40 (m, 3 H), 7.27 - 7.30 (m, 1 H), 7.81 - 7.90 (m, 1 H), 7.90 - 7.97 (m, 1 H), 8.33 - 8.41 (m, 1 H), 8.66 - 8.72 (m, 1 H), 8.74 - 8.82 (m, 2 H), 8.86 - 8.98 (m, 2 H), 9.60 (s, 1 H).

Cpd 54: *N*-(5-chloro-6-(5-methyl-1*H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide (18.4 mg, 11.7%) as a white solid. LCMS (ESI) m/z M+1: 499.0. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 - 2.37 (m, 3 H), 7.23 - 7.32 (m, 1 H), 7.82 - 7.90 (m, 1 H), 7.91 - 7.98 (m, 1 H), 8.06 - 8.12

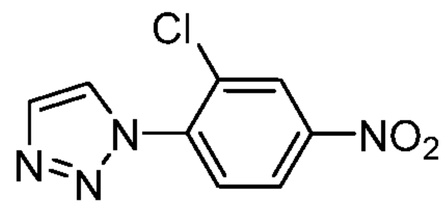
(m, 1 H), 8.33 - 8.41 (m, 1 H), 8.59 - 8.64 (m, 1 H), 8.65 - 8.70 (m, 1 H), 8.75 - 8.81 (m, 1 H), 8.85 - 8.90 (m, 1 H), 9.58 - 9.64 (m, 1 H).

Example 21

N-(3-chloro-4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 18**

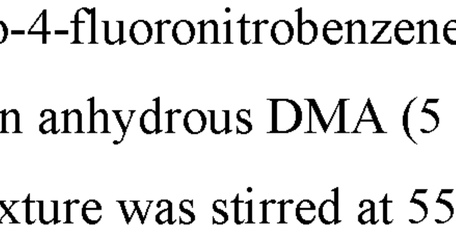


A. 1-(2-Chloro-4-nitrophenyl)-1H-1,2,3-triazole, **21a**


, **21a**

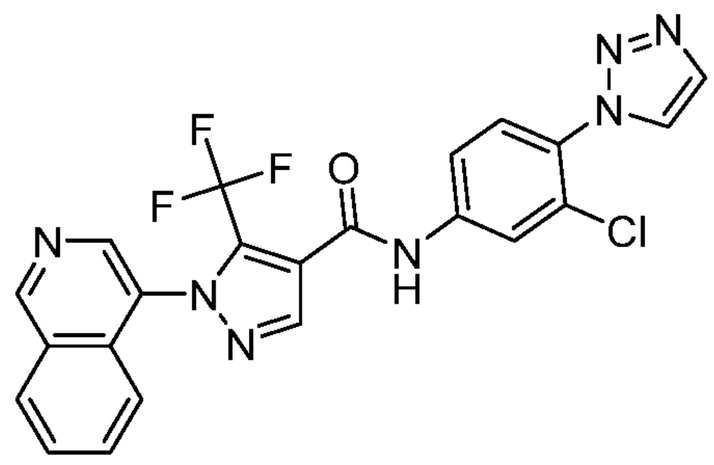
To a solution of 3-chloro-4-fluoronitrobenzene (1.2 g, 6.836 mmol) and 2*H*-1,2,3-triazole (0.567 g, 8.203 mmol) in anhydrous DMA (5 mL) was added K_2CO_3 (1.89 g, 13.672 mmol). The reaction mixture was stirred at 55 °C overnight. The reaction was concentrated to give a crude product as an oil. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 20/80 to afford 1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazole, **21a** (400 mg, 26.1 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.92 - 8.00 (m, 2 H), 8.20 (s, 1 H), 8.35 (dd, J=8.71, 2.32 Hz, 1 H), 8.51 (d, J=2.43 Hz, 1 H)

B. 3-Chloro-4-(1*H*-1,2,3-triazol-1-yl)aniline, **21b**


, **21b**

To a solution of 1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazole, **21a** (400 mg, 1.781 mmol) in MeOH/THF/water (5 mL/10 mL/5 mL) was added Fe (0) (497 mg, 8.905 mmol) and ammonium chloride (476 mg, 8.905 mmol). The reaction mixture was stirred at 60 °C for 2 h. The reaction was filtered and the organic solvent was concentrated. Water (10 mL) was added and the mixture was extracted with ethyl acetate (15 mL x 3). The separated organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to give a crude solid. The crude solid was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 0/100 to afford 3-chloro-4-(1*H*-1,2,3-triazol-1-yl)aniline, **21b** (300 mg, 86.6 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.03 (br. s., 2 H), 6.66 (dd, J=8.41, 2.15 Hz, 1 H), 6.82 (d, J=1.96 Hz, 1 H), 7.32 (d, J=8.61 Hz, 1 H), 7.85 (d, J=14.09 Hz, 2 H)

C. *N*-(3-Chloro-4-(1*H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 18**

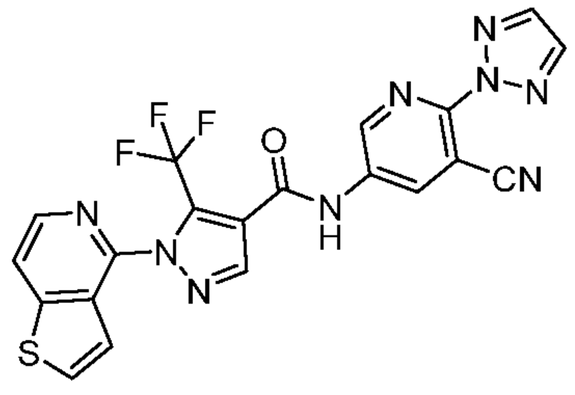


To a solution of 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (50 mg, 0.16 mmol), 3-chloro-4-(1*H*-1,2,3-triazol-1-yl)aniline, **21b** (37 mg, 0.19 mmol) and pyridine (63 mg, 0.8 mmol) in dichloromethane (2 mL), was added $POCl_3$ (49.4 mg, 0.32 mmol) dropwise to the mixture. The reaction mixture was stirred at 20 °C for 1 h. Water (5 mL) was added and the reaction mixture was extracted with dichloromethane (5 mL x 3). The combined organic extracts were washed with brine and dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The crude oil was purified by reverse phase HPLC (A: water (0.05% ammonia hydroxide v/v), B: MeCN; then: A/B (60%/40% to 70%/30 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford

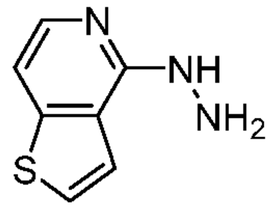
compound **18** (30 mg, 39 %) as a white solid. LCMS (ESI) m/z M+1: 483.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (d, J=8.38 Hz, 1 H), 7.61 - 7.69 (m, 2 H), 7.75 - 7.85 (m, 2 H), 7.90 (s, 1 H), 7.96 (s, 1 H), 8.03 (s, 1 H), 8.12 - 8.20 (m, 2 H), 8.27 (s, 1 H), 8.64 (s, 1 H), 9.46 (s, 1 H).

Example 22

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 90**



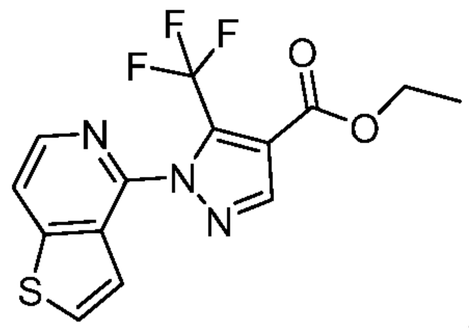
A. 4-Hydrazinylthieno[3,2-c]pyridine, **22a**



, **22a**

A mixture of 4-chlorothieno[3,2-*c*]pyridine (150 mg, 0.88 mmol) in hydrazine hydrate (4 mL) was stirred at 80 °C for 12 h. The mixture was extracted with dichloromethane (30 mL x 2). The organic portion was concentrated under reduced pressure to afford a crude product (120 mg, 82 %) as a yellow solid.

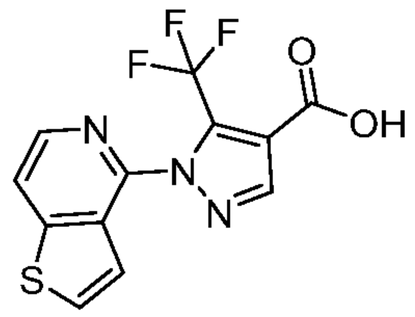
B. Ethyl 1-(thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **22b**



, **22b**

A solution of 4-hydrazinylthieno[3,2-c]pyridine, **22a** (120 mg, 7.26 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (227 mg, 0.944 mmol) in EtOH (50 mL) was stirred at 80 °C for 16 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford a crude product, which was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford compound **22b** (120 mg, 48 %) as a yellow solid. LCMS (ESI) m/z M+1: 341.9.

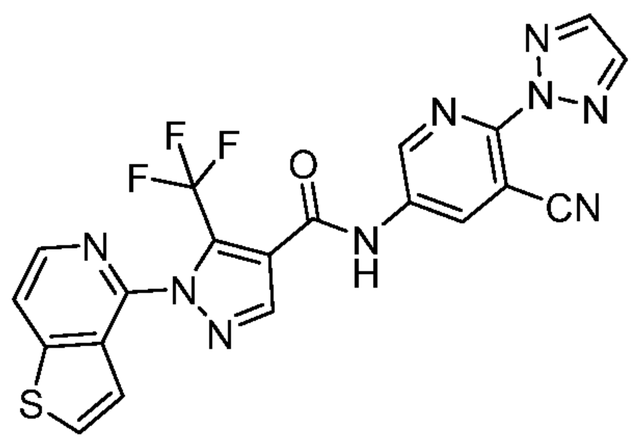
C. 1-(Thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **22c**



, **22c**

A solution of ethyl 1-(thieno[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **22b** (120 mg, 0.352 mmol) in concentrated hydrochloric acid (3 mL) was stirred at 130 °C for 3 h. The solvent was concentrated under reduced pressure to afford a crude product (110 mg, 100 %) as a yellow solid, which was used in the following reaction without further purification. LCMS (ESI) m/z M+1: 313.8.

D. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 90**

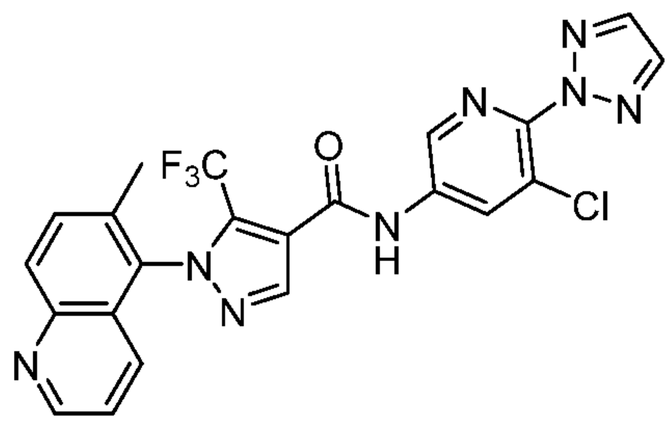


To a solution of 1-(thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **22c** (90 mg, 0.29 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile,

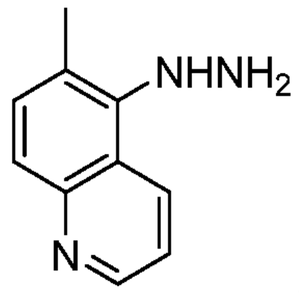
7b (45.6 mg, 0.23 mmol) and pyridine (115.9 μL, 1.44 mmol) in dichloromethane (5 mL), was added $POCl_3$ (52.6 μL, 0.575 mmol) dropwise to the mixture. The reaction mixture was stirred at 20 °C for 1 h. Sat. aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a crude yellow oil. The crude oil was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=0:1) to afford compound **90** (71.2 mg, 51 %) as a white solid. LCMS (ESI) m/z M+1: 481.9. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.45 (d, J=5.51 Hz, 1 H), 8.11 (d, J=5.51 Hz, 1 H), 8.30 (s, 2 H), 8.39 (d, J=5.51 Hz, 1 H), 8.46 (d, J=5.51 Hz, 1 H), 8.60 (s, 1 H), 8.88 (d, J=2.43 Hz, 1 H), 9.11 (d, J=2.43 Hz, 1 H), 11.46 (s, 1 H).

Example 23

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 27**



A. 5-Hydrazinyl-6-methylquinoline, **23a**

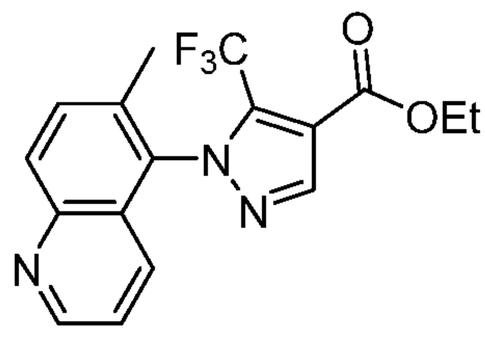


, **23a**

A solution of 6-methylquinolin-5-amine (800 mg, 5.06 mmol) in concentrated hydrochloric acid (5 mL) was stirred at 0 °C for 10 min. A solution of sodium nitrite (419 mg, 6.07 mmol) and water (0.5 mL) was added slowly, then stirred at 0 °C for 1 h. *L*-

ascorbic acid (935 mg, 5.31 mmol) was then added to the reaction mixture over 10 min. The mixture was warmed to room temperature and stirred for 1 h before heating at 80 °C for 30 min. Water (4 mL) was added. The suspension was cooled to 0 °C and stirred for 2 h. The resulting mixture was basified to pH 10 with 4 M aq. NaOH, extracted with ethyl acetate (30 mL x 3), and dried over anhydrous Na_2SO_4. The mixture was filtered and the filtrate concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 30:70) to afford compound **23a** (150 mg, 17 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.93 - 8.89 (m, 1H), 8.75 - 8.72 (m, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 6.8 Hz, 1H), 7.40 - 7.35 (m, 1H), 4.87 - 4.60 (m, 1H), 2.52 - 2.50 (m, 2 H), 2.42 (s, 3H).

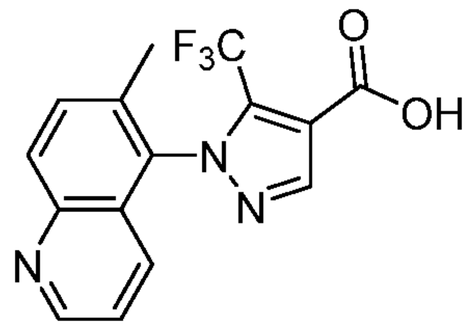
B. Ethyl 1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **23b**



, **23b**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (130 mg, 0.541 mmol), 5-hydrazinyl-6-methylquinoline, **23a** (113 mg, 0.541 mmol) and ethanol (5 mL) was refluxed at 80 °C for 16 h before cooling to room temperature. The mixture was concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 50:50) to give compound **23b** (130 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.91 (d, J = 3.2 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 8.8 Hz 1H), 7.42 - 7.29 (m, 2H), 4.41 (q, J = 6.8 Hz, 2H), 2.21 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

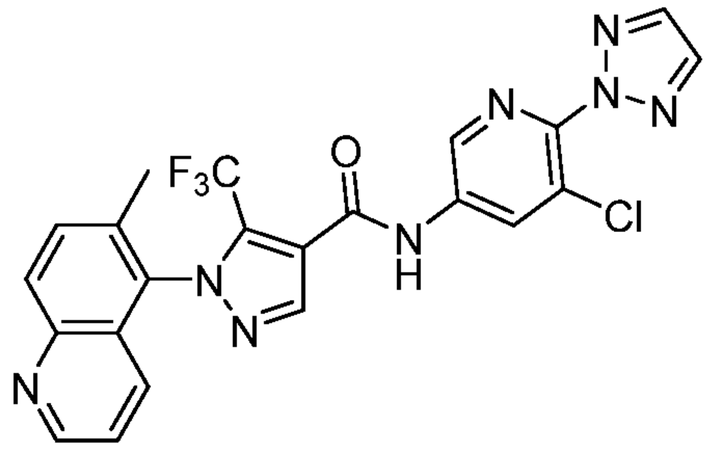
C. 1-(6-Methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, 23c



, **23c**

A solution consisting of ethyl 1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **23b** (100 mg, 0.286 mmol), NaOH (34.4 mg, 0.859 mmol) and water:EtOH (3 mL, 1:2) was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure, neutralized to pH 7 with 4 N aq. HCl, and a solid, compound **23**, was collected by filtration (90 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): R_T = 0.65 min, mass calcd. for $C_{15}H_{10}F_3N_3O_2$ 321.254, m/z found 322.0 $[M+H]^+$.

D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 27**

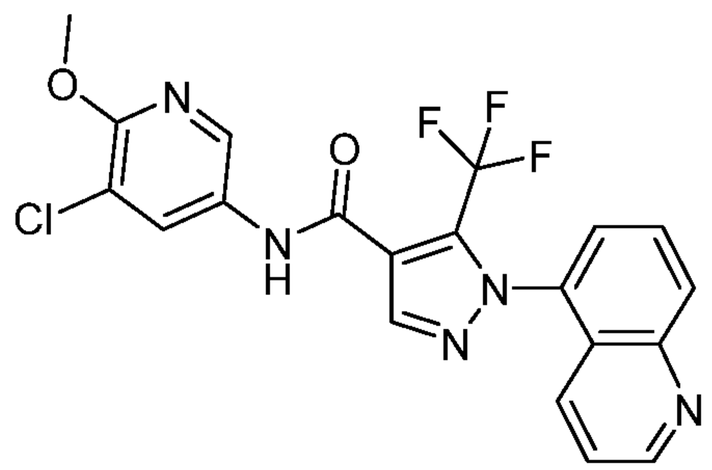


$POCl_3$ (45.8 mg, 0.299 mmol) was added dropwise to a solution consisting of 1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **23c** (80.0 mg, 0.249 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (97.4 mg, 0.498 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resultant mixture was poured into sat. aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product, which was purified by preparative high performance liquid chromatography using Boston Green ODS 150 x 30 mm x 5 μm (27% to 57% (v/v) ACN and water with 0.05% HCl) to afford compound **27**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to give compound **27** (23.5

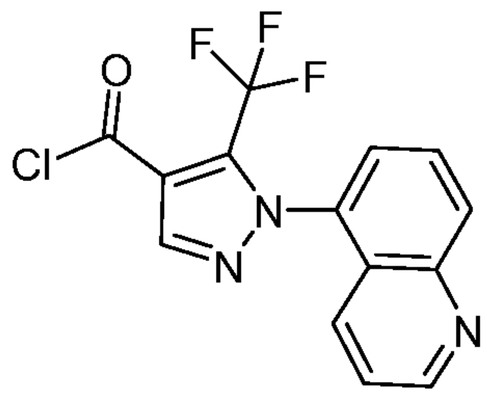
mg, 18 %). LCMS (ESI): mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.848, m/z found 499.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.50 (s, 1H), 9.08 (dd, J = 1.2, 4.0 Hz, 1H), 8.95 (d, J = 2.0 Hz, 1H), 8.79 - 8.73 (m, 2H), 8.32 (d, J = 8.8 Hz, 1H), 8.21 (s, 2H), 7.98 (d, J = 8.8 Hz, 1H), 7.74 (dd, J = 4.4, 8.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 2.24 (s, 3H).

Example 24

N-(5-Chloro-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 7**



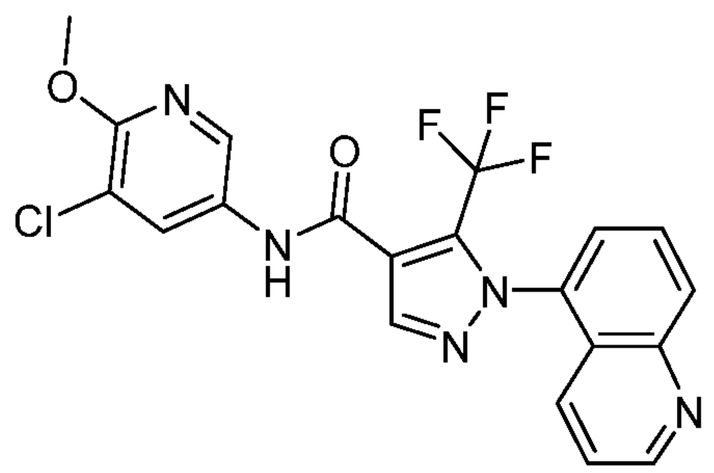
A. 1-(Quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride, **24a**



, **24a**

Oxalyl dichloride (0.0830 mL, 0.976 mmol) was added to solution consisting of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (200 mg, 0.651 mmol), dichloromethane (15 mL), and DMF (catalytic amount). The resultant solution was stirred at room temperature for 1 h. The resultant solution was concentrated to dryness to afford compound **24a** (200 mg, crude), which was used in the following reaction without further purification.

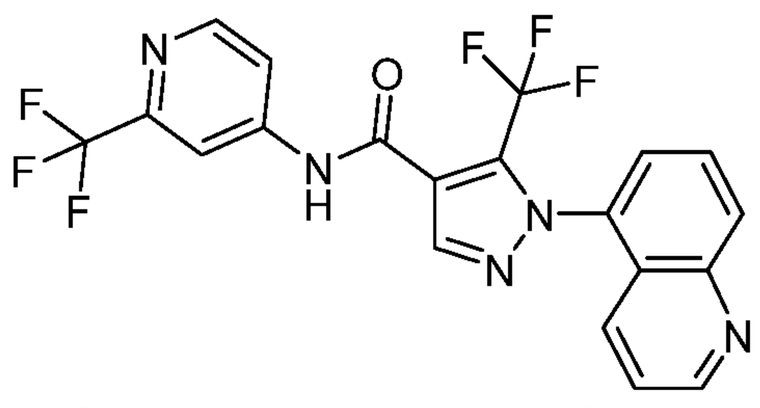
B. *N*-(5-Chloro-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 7**



A solution consisting of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride, **24a** (200 mg, 0.614 mmol), 5-chloro-6-methoxypyridin-3-amine (117 mg, 0.737 mmol), and pyridine (10 mL) was stirred at 90 °C for 1 h before cooling to room temperature. The resultant mixture was concentrated to dryness under reduced pressure to give the crude product, which was purified by reverse phase HPLC (38% to 68% (v/v) CH_3CN and water with 0.05% NH_3) to afford compound 7 (74.80 mg, 27 %) as a brown solid. LCMS (ESI): mass calcd. for $C_{20}H_{13}ClF_3N_5O_2$ 447.07, m/z found 448.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.03 (dd, J = 1.6, 4.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.28 - 8.10 (m, 3H), 7.88 - 7.80 (m, 1H), 7.70 (s, 1H), 7.66 - 7.59 (m, 2H), 7.47 (dd, J = 4.4, 8.4 Hz, 1H), 4.04 (s, 3H).

Example 25

1-(Quinolin-5-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 6**

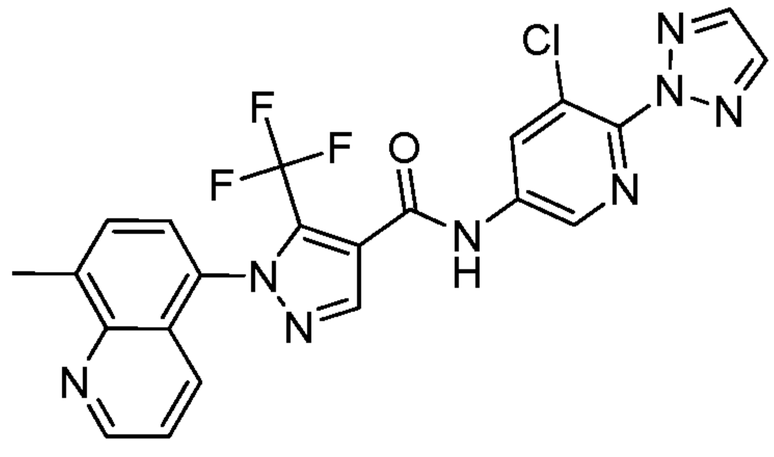


A solution consisting of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride, **24a** (200 mg, 0.614 mmol), 2-(trifluoromethyl)pyridin-4-amine (119 mg, 0.737 mmol), and pyridine (10 mL) was stirred at 90 °C for 1 h before cooling to room temperature. The resultant mixture was concentrated to dryness under reduced pressure to

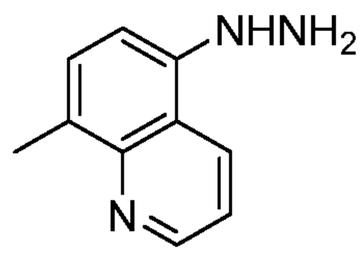
give the crude product, which was purified by reverse phase HPLC (43% to 63% (v/v) CH_3CN and water with 0.05% NH_3) to afford compound **6** (107.30 mg, 39 %) as a white solid. LCMS (ESI): mass calcd. for $C_{20}H_{11}F_6N_5O$ 451.09, m/z found 452.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.04 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.88 - 7.81 (m, 2H), 7.67 - 7.57 (m, 2H), 7.49 (dd, *J* = 4.4, 8.4 Hz, 1H).

Example 26

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 28**



A. 5-Hydrazinyl-8-methylquinoline, **26a**

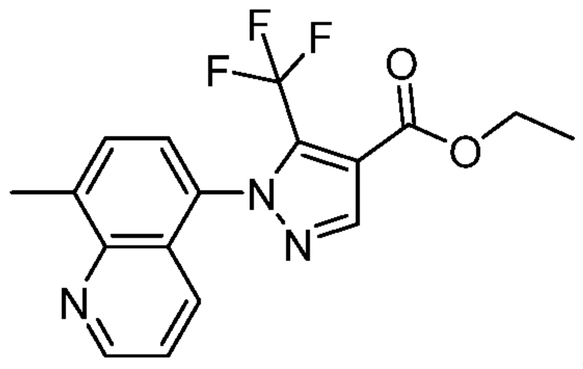


, **26a**

A solution of sodium nitrite (65.4 mg, 0.948 mmol) and water (0.5 mL) was added dropwise to a solution consisting of 8-methylquinolin-5-amine (100 mg, 0.632 mmol) and concentrated hydrochloric acid (4 mL) at a temperature between -10 °C and 0 °C. The mixture was stirred at a temperature between -10 °C and 0 °C for 1.5 h. A solution consisting of $SnCl_2$ (285 mg, 1.26 mmol) and concentrated hydrochloric acid (0.5 mL) was added dropwise at a temperature between -10 °C and 0 °C, then the mixture was stirred at room temperature for 16 h before filtration. The collected solid was washed with MeOH (2 mL x 2) to give compound **26a** (90 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{10}H_{11}N_3$ 173.214, m/z

found 174.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.72 (br. s., 2H), 9.82 - 9.31 (m, 1H), 9.14 (d, J = 4.4 Hz, 1H), 9.05 (d, J = 8.4 Hz, 1H), 7.98 - 7.85 (m, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 2.71 (s, 3H).

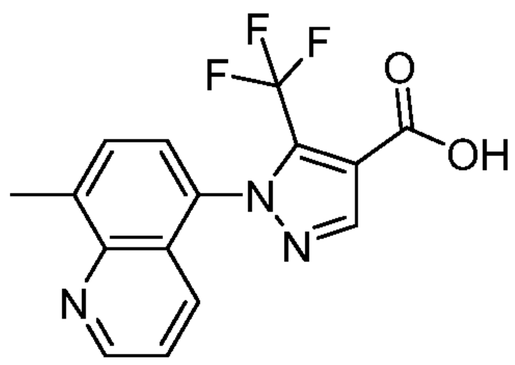
B. Ethyl 1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **26b**



, **26b**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (87.8 mg, 0.366 mmol), 5-hydrazinyl-8-methylquinoline, **26a** (90.0 mg, 0.366 mmol) and ethanol (3 mL) was refluxed at 80 °C for 16 h before cooling to room temperature. The mixture was concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to afford compound **26b** (90 mg, 70 %). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.06 - 8.98 (m, 1H), 8.24 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.58 - 7.43 (m, 3H), 4.41 (d, J = 6.8 Hz, 2H), 2.90 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

C. 1-(8-Methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **26c**

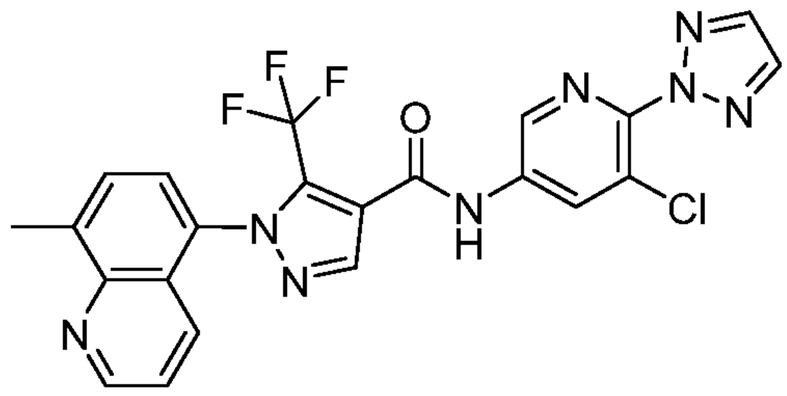


, **26c**

A solution of ethyl 1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **26b** (70 mg, 0.20 mmol), NaOH (24.0 mg, 0.601 mmol) and water: EtOH (3 mL, 1:2) was stirred at room temperature for 16 h. The reaction mixture was neutralized to pH 7 with 4 M aq. HCl, and then concentrated to dryness under reduced pressure to give

the crude compound **26c** (110 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{15}H_{10}F_3N_3O_2$ 321.254, m/z found 322.0 $[M+H]^+$.

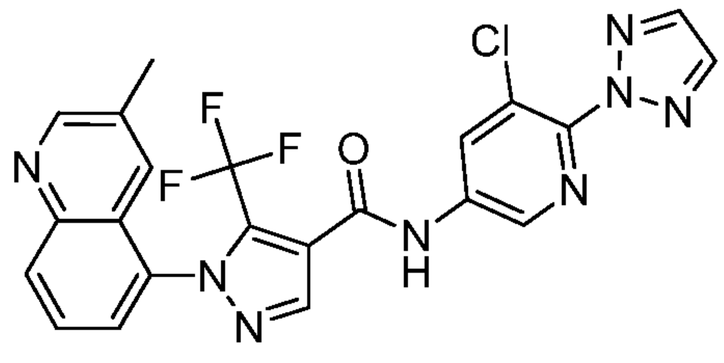
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 28**



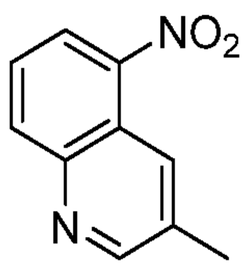
$POCl_3$ (52.7 mg, 0.344 mmol) was added dropwise to a solution of ethyl 1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **26c** (100 mg, 0.286 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (112 mg, 0.573 mmol) and pyridine (3 mL). The mixture was stirred at 0 °C for 1 h. T he resultant mixture was poured into sat. aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to give a crude product, which was purified by reverse phase HPLC (48% to 78% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **28**. The compound was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to give compound **28** (39.20 mg, 27 %). LCMS (ESI): mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.848, m/z found 498.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (dd, J = 1.6, 4.0 Hz, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.57 (s, 1H), 8.19 (s, 2H), 7.85 - 7.79 (m, 2H), 7.68 (dd, J = 4.4, 8.4 Hz, 1H), 7.57 (dd, J = 1.6, 8.4 Hz, 1H), 2.85 (s, 3H).

Example 27

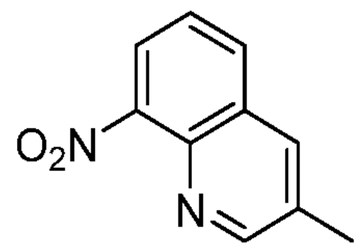
N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, Cpd 65



A. 3-Methyl-5-nitroquinoline (**27a**) and 3-methyl-8-nitroquinoline (**27a-1**)



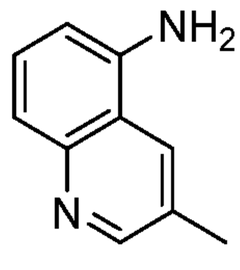
27a



27a-1

HNO_3 (4.72 mL, 105 mmol) was added dropwise to a mixture consisting of 3-methylquinoline (5.0 g, 35 mmol) and H_2SO_4 (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The resultant mixture was neutralized to pH 7 with 1 M aq. NaOH, extracted with ethyl acetate (30 mL x 3), and the extracts were concentrated under reduced pressure and purified by FCC (petroleum ether: ethyl acetate = 100:0 to 50:50) to afford a mixture of compounds **27a** and **27a-1** (4 g, 30 %). LCMS (ESI): mass calcd. for $C_{10}H_8N_2O_2$ 188.18, m/z found 189.0 $[M+H]^+$.

B. 3-Methylquinolin-5-amine, **27b**

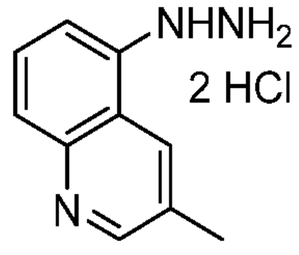


, **27b**

A mixture of 3-methyl-5-nitroquinoline (**27a**) and 3-methyl-8-nitroquinoline (**27a-1**) (3.50 g, 9.30 mmol), MeOH (30 mL) and dry Pd/C (350 mg, 5%) was added to a 500 mL hydrogenation bottle. The mixture was stirred under a H_2 (30 psi) atmosphere at room temperature for 16 h. The suspension was filtered though a pad of diatomaceous earth and the pad was washed with MeOH (100 mL). The filtrate was concentrated to dryness under reduced pressure to give crude compound **27b**, which was purified by FCC (ethyl acetate: methanol = 100:0 to 95:5) to afford compound **27b** (300 mg, 20 %). ^1H NMR (400 MHz,

DMSO-d_6) δ ppm 8.64 (d, J = 1.6 Hz, 1H), 8.30 (s, 1H), 7.37 - 7.30 (m, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 7.2 Hz, 1H), 5.83 (s, 2H), 2.46 (s, 3H).

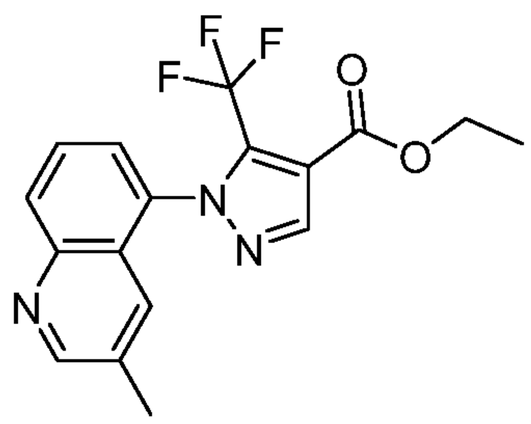
C. 5-Hydrazinyl-3-methylquinoline, **27c**



, **27c**

A solution of sodium nitrite (131 mg, 1.90 mmol) and water (1 mL) was added dropwise to a solution of 3-methylquinolin-5-amine, **27b** (200 mg, 1.26 mmol) and concentrated hydrochloric acid (1 mL) at a temperature between -10 °C and 0 °C. The mixture was stirred at a temperature between -10 °C and 0 °C for 1.5 h. A solution consisting of $SnCl_2$ (571 mg, 2.53 mmol) and concentrated hydrochloric acid (1 mL) was added dropwise at a temperature between -10 °C and 0 °C, then the mixture was stirred at room temperature for 16 h. The suspension was filtered to give compound **27c** (200 mg, crude), which was used in the next step without purification. LCMS (ESI): mass calcd. for $C_{10}H_{11}N_3$ 173.214, m/z found 174.0 $[M+H]^+$.

D. Ethyl 1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **27d**

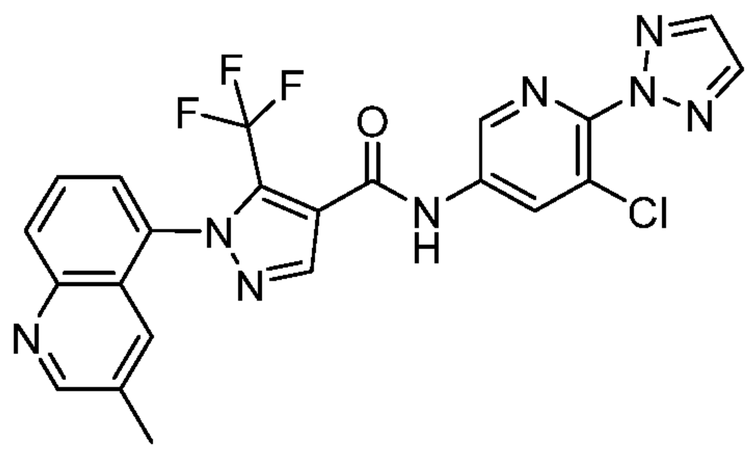


, **27d**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (195 mg, 0.813 mmol), 5-hydrazinyl-3-methylquinoline, **27c** (200 mg, 0.813 mmol), triethylamine (164 mg, 1.63 mmol), and ethanol (2 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The reaction was concentrated to dryness under

reduced pressure to give crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 60:40) to give compound **27d** (100 mg, 35 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.85 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 8.0 Hz, 2H), 7.76 - 7.70 (m, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.33 - 7.29 (m, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.48 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

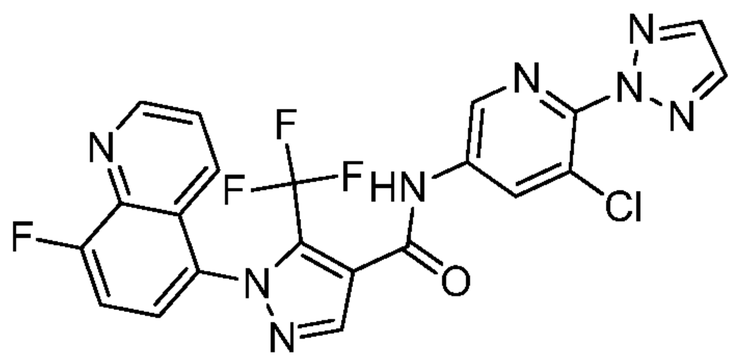
E. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 65**



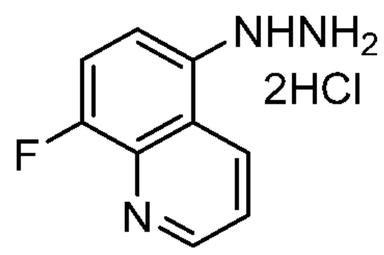
A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (44.8 mg, 0.229 mmol) and THF (0.5 mL) was added to potassium *tert*-butoxide in THF (0.687 mL, 0.687 mmol, 1 M) at 0 °C, then a solution consisting of ethyl 1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **27d** (60.0 mg, 0.229 mmol) and THF (0.5 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by reverse phase HPLC (41% to 71% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **65**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **65** (45.40 mg, 40 %). LCMS (ESI): mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.848, m/z found 499.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.28 (br.s., 1H), 8.93 (d, *J* = 2.0 Hz, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 8.60 (s, 1H), 8.31 - 8.27 (m, 1H), 8.20 (s, 2H), 7.92 - 7.85 (m, 2H), 7.40 - 7.38 (m, 1H), 2.47 (s, 3H).

Example 28

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 40**



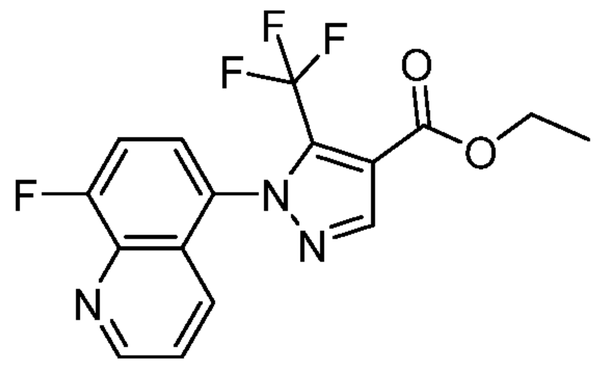
A. 8-Fluoro-5-hydrazinylquinoline, **28a**



, **28a**

A solution of sodium nitrite (95.7 mg, 1.39 mmol) and water (0.5 mL) was added dropwise to a solution consisting of 8-fluoroquinolin-5-amine (150 mg, 0.925 mmol) and conc. hydrochloric acid (4 mL, 36 %) at a temperature between -10 °C and 0 °C. The mixture was stirred at a temperature between -10 °C and 0 °C for 1.5 h. A solution of $SnCl_2$ (417 mg, 1.85 mmol) and conc. hydrochloric acid (1 mL) was added dropwise at a temperature between -10 °C and 0 °C and the reaction was stirred at room temperature for 16 h. The mixture was filtered. The resultant solid was washed with MeOH (1 mL x 2) and dried under reduced pressure to afford compound **28a** (220 mg, crude) as a yellow solid, which was used in the next step without further purification. LCMS (ESI): mass calcd. for $C_9H_8FN_3$ 177.178, m/z found 178.1 $[M+H]^+$.

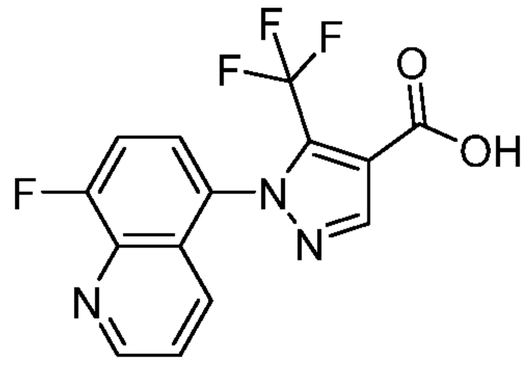
B. Ethyl 1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, 28b



, **28b**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (207 mg, 0.864 mmol), 8-fluoro-5-hydrazinylquinoline HCl salt, **28a** (360 mg, 0.864 mmol), triethylamine (175 mg, 1.73 mmol), and ethanol (5 mL) was refluxed at 80 °C for 16 h before cooling to room temperature. The reaction was concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to give compound **28b** (100 mg, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.06 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.25 (s, 1H), 7.61 - 7.48 (m, 4H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

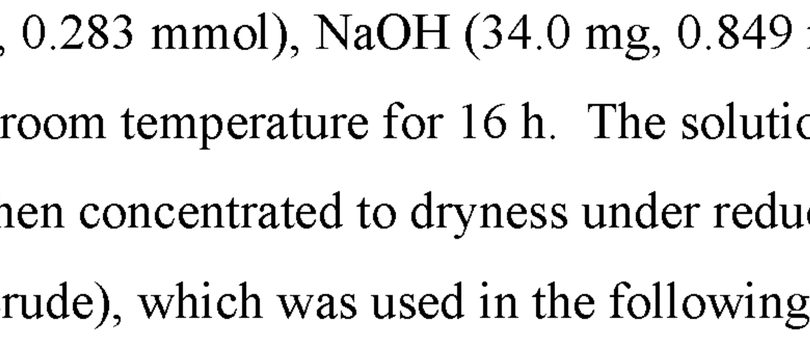
C. 1-(8-Fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **28c**



, **28c**

A solution of ethyl 1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **28b** (100 mg, 0.283 mmol), NaOH (34.0 mg, 0.849 mmol) and water: EtOH (3 mL, 1:2) was stirred at room temperature for 16 h. The solution was neutralized to pH 7 with 4 M aq. HCl, and then concentrated to dryness under reduced pressure to give compound **28c** (120 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{14}H_7F_4N_3O_2$ 325.218, m/z found 325.9 $[M+H]^+$.

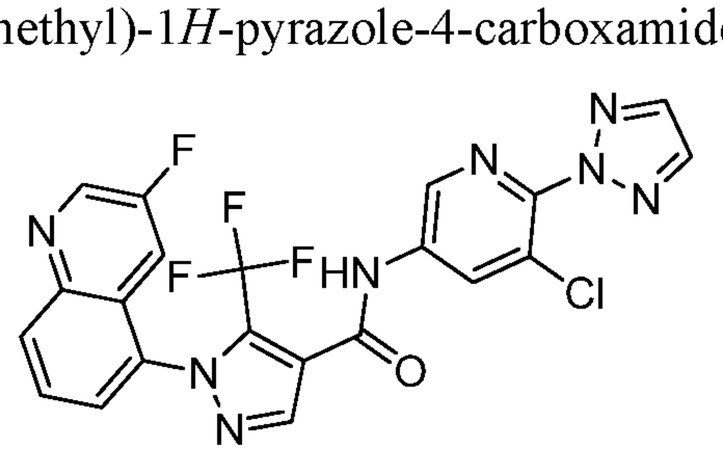
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 40**



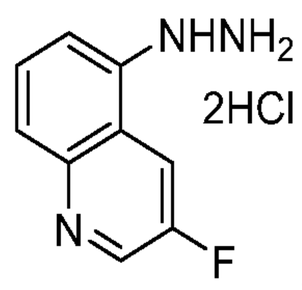
$POCl_3$ (56.6 mg, 0.369 mmol) was added dropwise to a solution of 1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **28c** (100 mg, 0.307 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (120 mg, 0.615 mmol) and pyridine (5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by reverse phase HPLC (38% to 68% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **40**. Compound was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to give compound **40** (20.10 mg, 13 %). LCMS (ESI): mass calcd. for $C_{21}H_{11}ClF_4N_8O$ 502.812, m/z found 502.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.28 (br.s., 1H), 9.13 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.87 (d, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.60 (s, 1H), 8.20 (s, 2H), 8.00 (dd, *J* = 4.4, 8.4 Hz, 1H), 7.87 - 7.78 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H).

Example 29

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 25**



A. 3-Fluoro-5-hydrazinylquinoline, **29a**

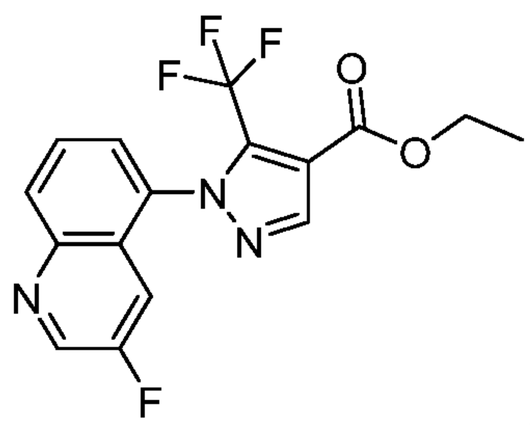


, **29a**

A solution of sodium nitrite (95.7 mg, 1.39 mmol) and water (0.5 mL) was added dropwise to a solution consisting of 3-fluoroquinolin-5-amine (150 mg, 0.925 mmol) and concentrated hydrochloric acid (4 mL, 36%) at -10 °C - 0 °C. The mixture was stirred at a

temperature between -10 °C and 0 °C for 1.5 h. A solution of $SnCl_2$ (417 mg, 1.85 mmol) and concentrated hydrochloric acid (1 mL) was added dropwise at a temperature between -10 °C and 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was filtered. The resultant solid was washed with MeOH (1 mL x 2) and dried under reduced pressure to afford compound **29a** (220 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_9H_8FN_3$ 177.178, m/z found 178.1 $[M+H]^+$.

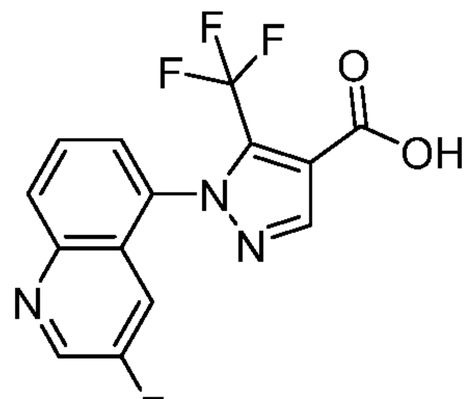
B. Ethyl 1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **29b**



, **29b**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (211 mg, 0.880 mmol), 3-fluoro-5-hydrazinylquinoline, **29a** (220 mg, 0.880 mmol), triethylamine (178 mg, 1.76 mmol), and ethanol (5 mL) was refluxed at 80 °C for 16 h before cooling to room temperature. The reaction mixture was concentrated to dryness under reduced pressure to afford crude compound **29b**, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to give compound **29b** (160 mg, 51 %). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.94 - 8.89 (m, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), 7.83 - 7.76 (m, 1H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.25 - 7.19 (m, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

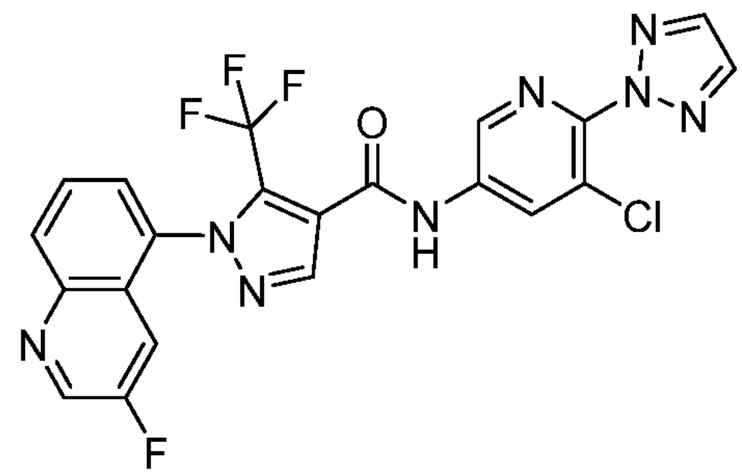
C. 1-(3-Fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **29c**



, **29c**

A solution consisting of ethyl 1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **29b** (160 mg, 0.453 mmol), NaOH (54.3 mg, 1.54 mmol) and water: EtOH (3 mL, 1:2) was stirred at room temperature for 16 h. The solution was neutralized to pH 7 with 4 M aq. HCl, and the resultant solid was collected by filtration to afford compound **29c** (150 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{14}H_7F_4N_3O_2$ 325.218, m/z found 325.9 $[M+H]^+$.

D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 25**

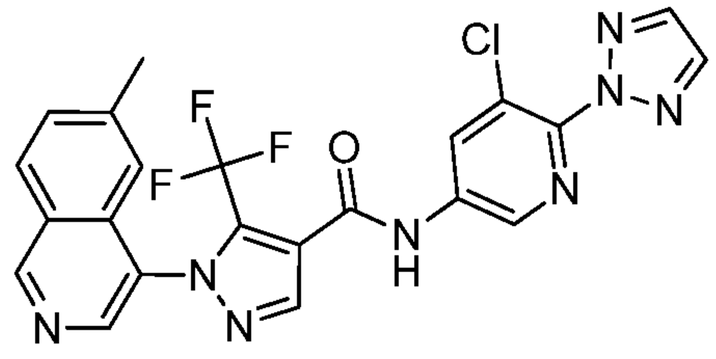


$POCl_3$ (5.7 mg, 0.037 mmol) was added dropwise to a solution of 1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **29c** (160 mg, 0.492 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (192 mg, 0.984 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resultant mixture was poured into sat. aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to give the crude compound **25**, which was purified by reverse phase HPLC (42% to 72%

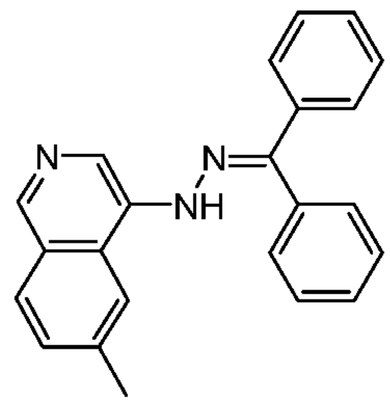
(v/v) ACN and H_2O with 0.05% NH_3) to afford pure compound **25**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to give compound **25** (53.60 mg, 21 %). LCMS (ESI): mass calcd. for $C_{21}H_{11}ClF_4N_8O$ 502.812, m/z found 502.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.24 (br.s., 1H), 9.14 (d, J = 2.8 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.61 (s, 1H), 8.40 (d, J = 7.6 Hz, 1H), 8.21 (s, 2H), 8.03 - 7.96 (m, 2H), 7.52 - 7.49 (m, 1H).

Example 30

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 36**



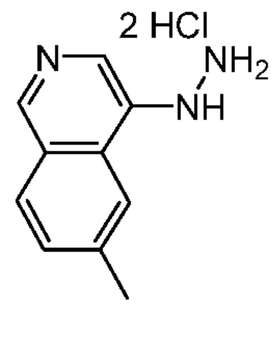
A. 4-(2-(Diphenylmethylene)hydrazinyl)-6-methylisoquinoline, **30a**



, **30a**

A mixture of 4-bromo-6-methylisoquinoline (500 mg, 2.25 mmol), benzophenone hydrazone (442 mg, 2.25 mmol), BINAP (140 mg, 0.225 mmol), palladium(II) acetate (50.5 mg, 0.225 mmol), sodium *tert*-butoxide (325 mg, 3.38 mmol), and toluene (3 mL) was heated to 100 °C and stirred for 20 h under a N_2 atmosphere before cooling to room temperature. The mixture was filtered and concentrated to give a black oil, which was purified by FCC (petroleum ether: ethyl acetate = 30 :70) to afford compound **30a** (280 mg, 37 %) as a yellow solid. LCMS (ESI): mass calcd. for $C_{23}H_{19}N_3$ 337.4, m/z found 338.0 $[M+H]^+$.

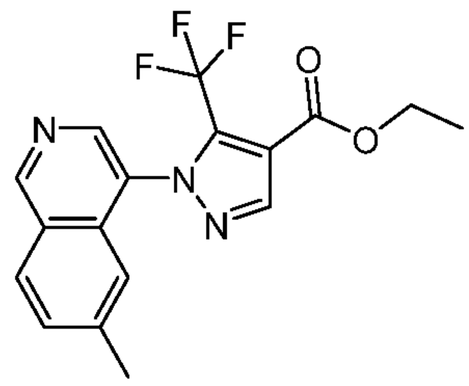
B. 4-Hydrazinyl-6-methylisoquinoline hydrochloride, **30b**



, **30b**

A mixture of 4-(2-(diphenylmethylene)hydrazinyl)-6-methylisoquinoline, **30a** (260 mg, 0.771 mmol), conc. hydrochloride (10 mL, 12 M in water, 43 mmol), and EtOH (1 mL) was stirred for 20 h at room temperature. The solid was collected by filtration, washed with DCM (3 mL x 2), and dried under reduced pressure to afford compound **30b** (145 mg, 76 %) as a yellow solid, which was used in the following reaction without further purification. LCMS (ESI): Mass calcd. for $C_{10}H_{11}N_3$ 173.2, m/z found 174.1 $[M+H]^+$.

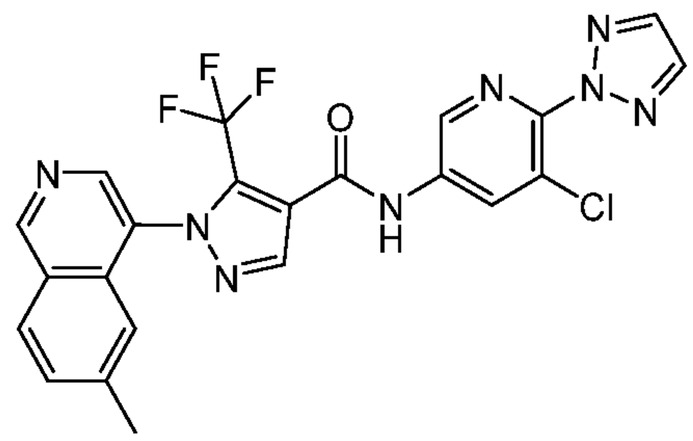
C. Ethyl 1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **30c**



, **30c**

A mixture of 4-hydrazinyl-6-methylisoquinoline hydrochloride, **30b** (145 mg, 0.589 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (200 mg, 0.707 mmol), triethylamine (0.246 mL, 1.77 mmol), and EtOH (5 mL) was heated to 90 °C and stirred for 20 h before cooling to room temperature. The mixture was concentrated under reduced pressure to afford a yellow oil, which was purified by FCC (ethyl acetate: petroleum ether = 40: 60) to afford compound **30c** (96 mg, 47 %) as a yellow solid. LCMS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O_2$ 349.3, m/z found 350.1 $[M+H]^+$.

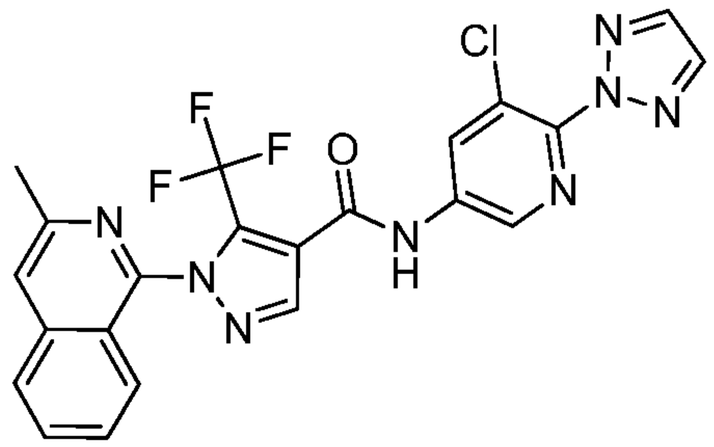
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 36**



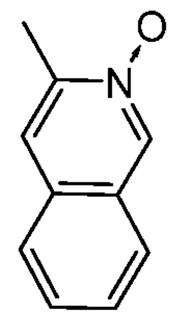
Ethyl 1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **30c** (90.0 mg, 0.258 mmol) in THF (0.5 mL) and 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (50.4 mg, 0.258 mmol) in THF (0.5 mL) were added into a suspension of potassium *tert*-butoxide (43.4 mg, 0.386 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at room temperature for 20 h before evaporating under reduced pressure to give a yellow solid, which was purified by reverse phase HPLC (CH_3CN in Basic water (0.05% $NH_3•H_2O$) from 45% to 75%, v/v). The resultant residue was re-suspended in water (50 mL) and the resulting mixture was lyophilized to dryness to remove the solvent residue completely. Compound **36** (40.40 mg, 31 %) was obtained as an off-white solid. LCMS (ESI): mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.8, m/z found 498.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.28 (br s, 1H), 9.53 (s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.70 (d, J = 2.4 Hz, 1H), 8.63 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.20 (s, 2H), 7.72 (dd, J = 1.6, 8.8 Hz, 1H), 7.08 (s, 1H), 2.53 - 2.52 (m, 3H).

Example 31

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 9**



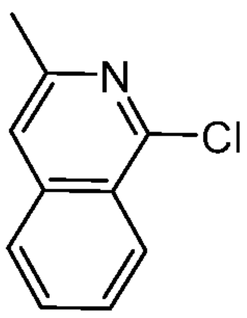
A. 3-Methylisoquinoline 2-oxide, **31a**



, **31a**

3-Chloroperoxybenzoic acid (2.53 g, 14.7 mmol) was added in portions into a mixture consisting of 3-methylisoquinoline (1.91 g, 13.3 mmol) and DCM (10 mL). The resultant mixture was stirred for 2 days at room temperature before diluting with DCM (100 mL), washing with aqueous $NaHCO_3$ (70 mL x 2) and brine (70 mL), drying over anhydrous Na_2SO_4, filtering, and the filtrate concentrating under reduced pressure to afford compound **31a** (1.4 g, 66 %) as a yellow solid, which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{10}H_9NO$ 159.2, m/z found 160.0 $[M+H]^+$.

B. 1-Chloro-3-methylisoquinoline, **31b**

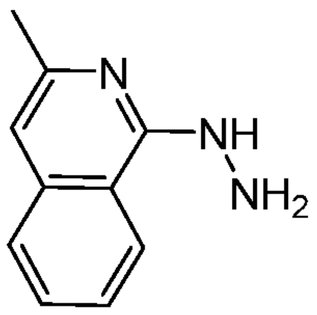


, **31b**

To a stirred solution of 3-methylisoquinoline 2-oxide, **31a** (1.40 g, 8.80 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C was added phosphorus oxychloride (0.902 mL, 9.67 mmol) followed by dropwise addition of DMF (0.338 mL, 4.40 mmol) under an Argon atmosphere. The resulting reaction mixture was warmed to room temperature and stirred

for 20 h. Saturated aqueous sodium carbonate solution was added to the reaction mixture slowly to adjust the pH to 7-8. The resulting mixture was separated and the aqueous phase was extracted with dichloromethane. The organic extracts were combined and washed with brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford a crude compound **31b**, which was purified by flash column chromatography (ethyl acetate: pretroleum ether = 20: 80) to afford compound **31b** (670 mg, 43 %) as a yellow oil. LCMS (ESI): mass calcd. for $C_{10}H_8ClN$ 177.6, m/z found 177.9 $[M+H]^+$.

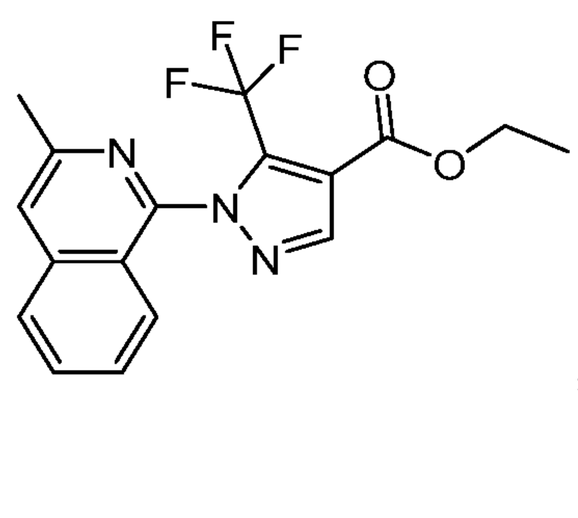
C. 1-Hydrazinyl-3-methylisoquinoline, **31c**



, **31c**

A mixture of 1-chloro-3-methylisoquinoline, **31b** (670 mg, 3.77 mmol), hydrazine hydrate (4.44 g, 75.4 mmol), and EtOH (5 mL) was heated to 90 °C and stirred for 20 h before cooling to room temperature. The mixture was concentrated to give a yellow solid, which was dissolved into ethyl acetate (100 mL), washed with water (100 mL x 2), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to afford compound **31c** (715 mg, 98 %) as a yellow solid. The crude product was used directly without further purification. LCMS (ESI): mass calcd. for $C_{10}H_{11}N_3$ 173.2, m/z found 174.0 $[M+H]^+$.

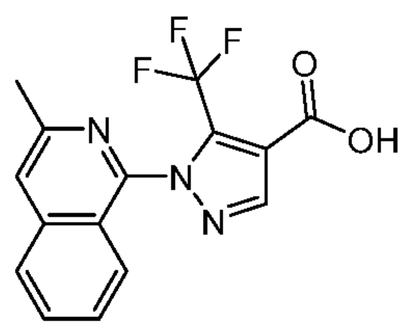
D. Ethyl 1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **31d**



, **31d**

A mixture of 1-hydrazinyl-3-methylisoquinoline, **31c** (710 mg, 4.10 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (1.27 g, 4.51 mmol), and EtOH (15 mL) was heated to 90 °C and stirred for 20 h before cooling to room temperature. The mixture was concentrated under reduced pressure to afford a yellow solid, which was treated with MeOH (5 mL) and stirred for 15 min. The solid was collected by filtration, washed with MeOH (3 mL x 2), and dried under reduced pressure at room temperature to afford compound **31d** (823.2 mg, 56 %). LCMS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O_2$ 349.3, m/z found 350.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.59 – 7.48 (m, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

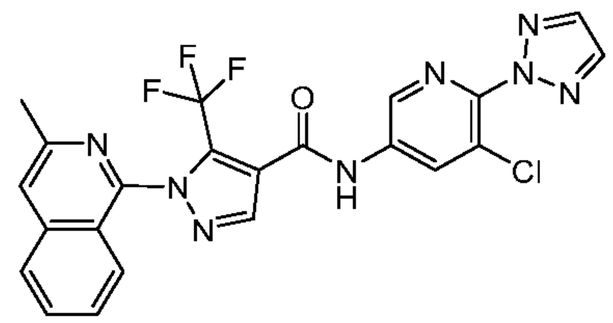
E. 1-(3-Methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **31e**



, **31e**

A mixture of ethyl 1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **31d** (220 mg, 0.630 mmol), lithium hydroxide (45.2 mg, 1.89 mmol), MeOH (1 mL), THF (1 mL), and water (1 mL) was stirred for 20 h at room temperature. The pH of the mixture was adjusted to 2 with 6 N aq. HCl. The organic solvents were removed under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 2). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to afford compound **31e** (140 mg, 69 %) as a yellow solid. LCMS (ESI): mass calcd. for $C_{15}H_{10}F_3N_3O_2$ 321.2, m/z found 322.0 $[M+H]^+$.

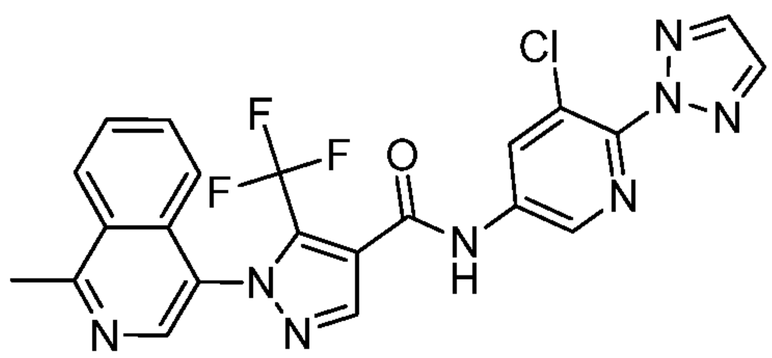
F. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 9**



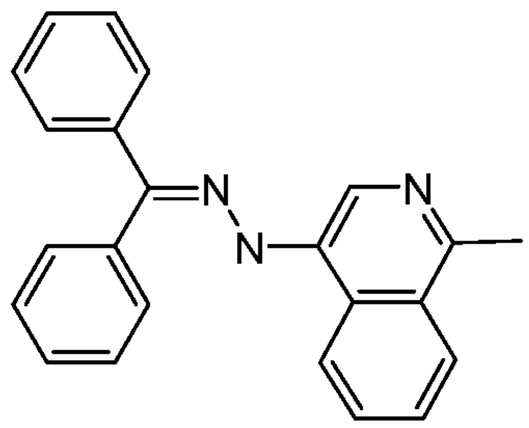
Phosphorus oxychloride (0.049 mL, 0.52 mmol) was added dropwise into a solution consisting of 1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **31e** (140 mg, 0.436 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (93.8 mg, 0.479 mmol), and pyridine (2 mL). The mixture was stirred at 0 °C for 1 h before concentrating to dryness under reduced pressure to give crude product, which was purified by preparative HPLC using a Phenomenex Gemini C18 150 x 25 mm x 5 μm column (50% to 80% (v/v) CH_3CN and water with 0.05% NH_3) to afford pure compound **9**. Compound was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **9** (96.10 mg, 44 %) as a white solid. LCMS (ESI): mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.8, m/z found 498.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.28 (br. s., 1H), 8.89 (s, 1H), 8.70 (s, 1H), 8.63 (s, 1H), 8.21 (s, 2H), 8.11 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.90 (m, 1H), 7.73 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 2.68 (s, 3H).

Example 32

N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 66**



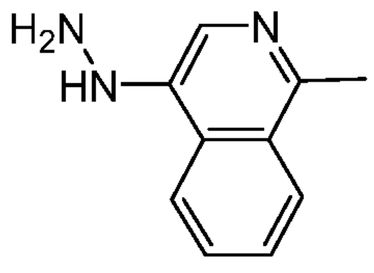
A. 4-(2-(Diphenylmethylene)hydrazinyl)-1-methylisoquinoline, **32a**



, **32a**

A mixture consisting of 4-bromo-1-methylisoquinoline (800 mg, 3.60 mmol), (diphenylmethylene)hydrazine (707 mg, 3.60 mmol), BINAP (224 mg, 0.360 mmol), palladium(II) acetate (80.9 mg, 0.360 mmol), *t*-BuONa (1.04 g, 10.8 mmol), and 1,4-dioxane (20 mL) was stirred at 100 °C for 16 h before cooling to room temperature. The suspension was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (30 mL). The filtrate was concentrated to dryness under reduced pressure to give a crude product, which was added into water (15 mL). The resultant mixture was extracted with ethyl acetate (20 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to dryness under reduced pressure to afford crude compound **32a**, which was purified by FCC (petroleum ether: ethyl acetate = 4:1) to afford compound **32a** (500 mg, 41 %) as a brown oil. LCMS (ESI): mass calcd. for $C_{23}H_{19}N_3$ 337.16, m/z found 337.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.74 (s, 1H), 8.11 - 8.05 (m, 1H), 7.87 (s, 1H), 7.70 - 7.64 (m, 4H), 7.63 - 7.59 (m, 1H), 7.58 - 7.53 (m, 2H), 7.49 - 7.43 (m, 2H), 7.41 - 7.31 (m, 4H), 2.91 (s, 3H).

B. 4-Hydrazinyl-1-methylisoquinoline, **32b**

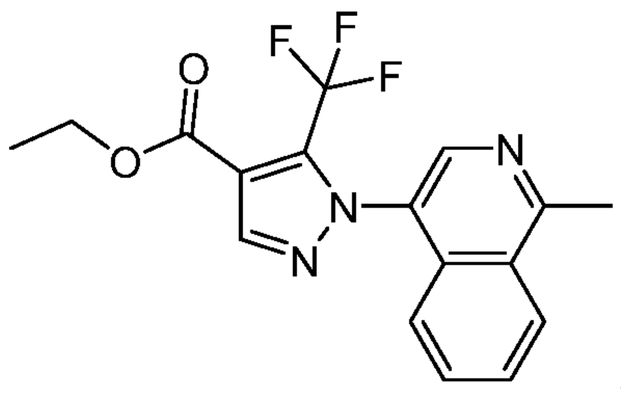


, **32b**

Conc. HCl (5 mL) was added to a solution consisting of 4-(2-(diphenylmethylene) hydrazinyl)-1-methylisoquinoline, **32a** (500 mg, 1.48 mmol) and EtOH (2 mL). The resultant solution was stirred at room temperature for 16 h. The resultant mixture was added into dichloromethane (20 mL), filtered and the pad was washed with

dichloromethane (10 mL). The organic solution was concentrated to dryness under reduced pressure to afford compound **32b** (940 mg, crude), which was used in the following reaction without further purification. LCMS (ESI): mass calcd. for $C_{10}H_{11}N_3$ 173.10, m/z found 174.1 $[M+H]^+$.

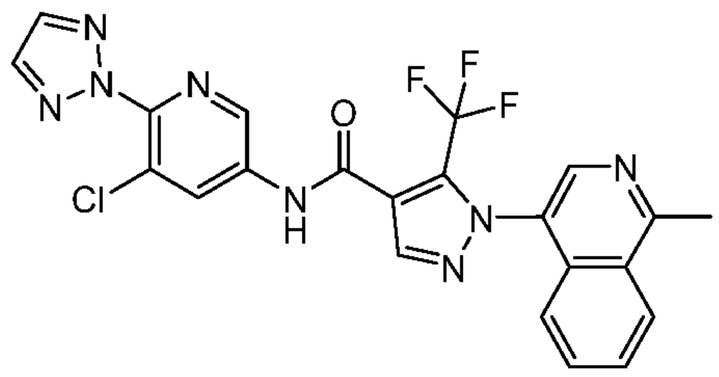
C. Ethyl 1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **32c**



, **32c**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (984 mg, 4.10 mmol), 4-hydrazinyl-1-methylisoquinoline, **32b** (840 mg, 3.41 mmol), triethylamine (0.950 mL, 6.83 mmol), and ethanol (20 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The resultant solution was concentrated to dryness under reduced pressure to afford a crude product, which was added into water (10 mL). The resultant mixture was extracted with ethyl acetate (20 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrated concentrated to dryness under reduced pressure to afford compound **32c**, which was purified by FCC (petroleum ether: ethyl acetate = 4:1) to afford compound **32c** (250 mg, 21 %) as a brown solid. LCMS (ESI): mass calcd. for $C_{17}H_{14}F_3N_3O_2$ 349.10, m/z found 349.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.45 (s, 1H), 8.29 – 8.21 (m, 2H), 7.77 – 7.68 (m, 2H), 7.28 – 7.23 (m, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.07 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

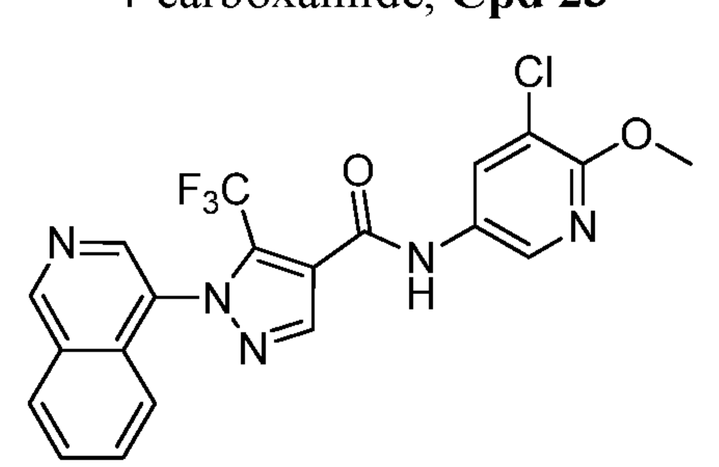
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, Cpd 66



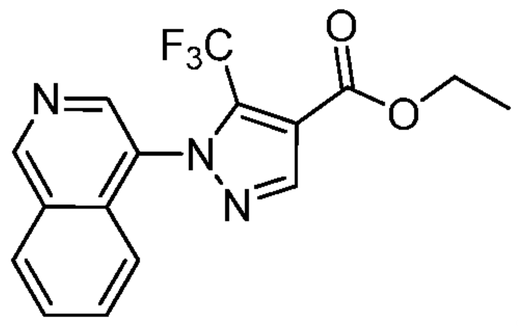
A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (193 mg, 0.988 mmol) and THF (1 mL), and a solution consisting of ethyl 1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **32c** (230 mg, 0.658 mmol) and THF (1 mL) were added to a solution consisting of potassium *tert*-butoxide (1.98 mL, 1.98 mmol, 1 M in THF) at 0 °C. The resultant mixture was stirred at room temperature for 16 h. The resultant mixture was added water (5 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to dryness under reduced pressure to afford a crude product, which was purified by preparative HPLC using a Kromasil 150 x 25 mm x 10 μm column (35% to 65% (v/v) CH_3CN and water with 0.05% NH_3) to afford pure compound **66**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **66** (126.40 mg, 38 %). LCMS (ESI): mass calcd. for $C_{22}H_{17}ClN_8O$ 444.12, m/z found 449.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.29 (s, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 8.62 (d, J = 9.2 Hz, 2H), 8.42 (d, J = 8.0 Hz, 1H), 8.20 (s, 2H), 7.94 - 7.83 (m, 2H), 7.23 (d, J = 8.4 Hz, 1H), 3.04 (s, 3H).

Example 33

N-(5-chloro-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 23**



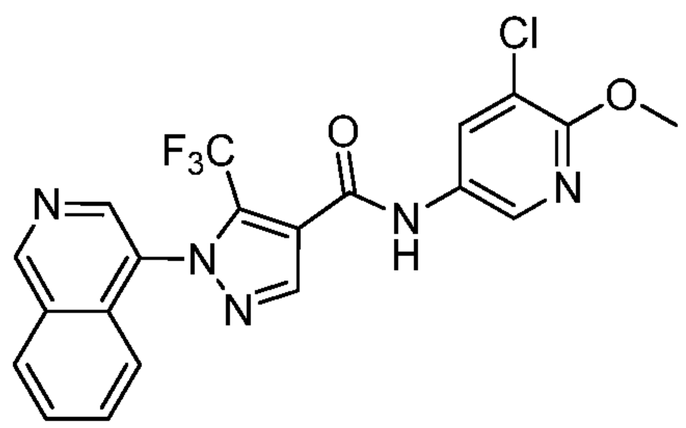
A. Ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **33a**



, 33a

A 20 mL vial with stirbar was charged with 4-chloroisoquinoline (103.6 mg, 0.633 mmol), palladium(II)(pi-cinnamyl) chloride dimer (9.1 mg, 0.0176 mmol), n-[2-(di-1-adamantylphosphino)phenyl]morpholine (22 mg, 0.0475 mmol), sodium tert-butoxide (110 mg, 1.145 mmol), hydrazine hydrate (0.0614 mL, 1.032 g/mL, 1.266 mmol), and toluene (6.3 mL) under air at room temperature. The dark yellow mixture was quickly bubbled with Argon gas for 1 min, and the vial was then sealed and stirred at 100 °C under an Argon atmosphere overnight (14 h). The reaction was then cooled to room temperature and treated with ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f**(0.123 mL, 1.235 g/mL, 0.633 mmol) and stirred at 100 °C under air (sealed). After 20 min at 100 °C, the reaction was concentrated at 46 °C under reduced pressure to give a light green residue. This was taken up in THF (3 mL) and stirred at 60 °C for 5 min to maximize dissolution of compound **33a** from the reaction mixture, and the reaction mixture was then cooled to room temperature. The amber solution in THF (assumed 0.2 M) was split into two (4 mL) vials and used in the next step immediately without further purification or characterization.

B. *N*-(5-chloro-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 23**

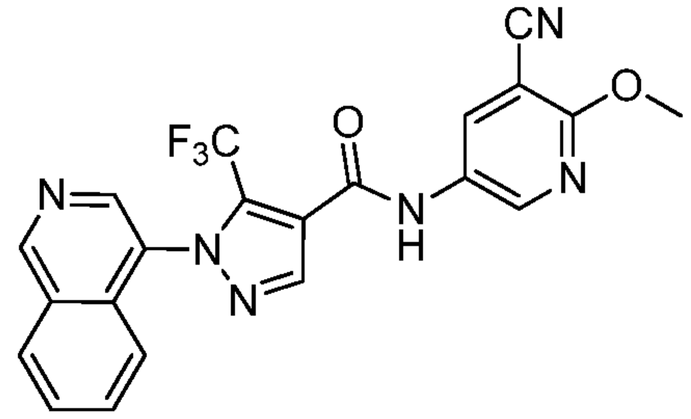


A solution of crude ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **33a** in THF, (Step A, assumed 106 mg, 0.316 mmol) was treated with 5-

chloro-6-methoxypyridin-3-amine (52.7 mg, 0.332 mmol) and the mixture was stirred until it was homogeneous. The mixture was then treated with KOtBu (56 mg, 0.499 mmol) in one portion, and the resulting dark reddish reaction was stirred at room temperature under air (sealed) for 45 min. About 100 mg of thiol-functionalized silica gel (1.2 mmol/g, ~3 eq) was then added, and the reaction stirred at room temperature for another 45 min. The mixture was then filtered and concentrated to provide a dark residue (136 mg) that was dissolved in a co-solvent (0.14 mL DMSO / 0.2 mL DCM), and purified by flash column chromatography (10 to 100% EtOAc in heptane over 24 CVs). Concentration from MeOH provided compound **23** as a white foam (11.6 mg, 8 % overall from 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.43 (s, 1H), 8.54 (s, 1H), 8.08-8.26 (m, 5H), 7.77 (quind, 2H), 7.34 (br d, *J*=7.58 Hz, 1H), 4.03 (s, 3H); MS m/e 448.0 (M+H).

Example 34

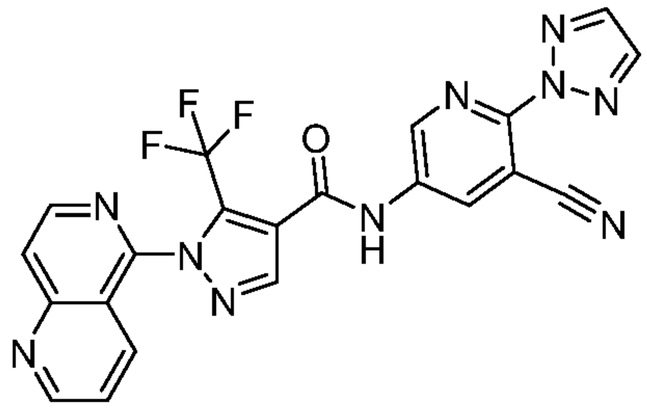
N-(5-cyano-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 24**



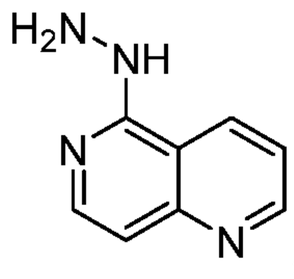
A solution of crude ethyl 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **33a** in THF, (assumed 106 mg, 0.316 mmol) was treated as described in Example 33, Step B, substituting 5-amino-2-methoxynicotinonitrile (47.4 mg, 0.318 mmol) for 5-chloro-6-methoxypyridin-3-amine, and the reaction was quenched with solid NH_4Cl rather than thiol-functionalized silica gel. Purification by flash column chromatography provided, following concentration from MeOH, compound **24** (18 mg, 13% overall in 3 steps) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.45 (s, 1H), 8.61 (s, 1H), 8.45 (s, 2H), 8.24 (s, 1H), 8.17 (d, *J*=7.58 Hz, 1H), 7.74-7.83 (m, 2H), 7.69 (s, 1H), 7.28-7.37 (m, 1H), 4.08 (s, 3H). MS m/e 439.2 (M+H).

Example 35

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 100**



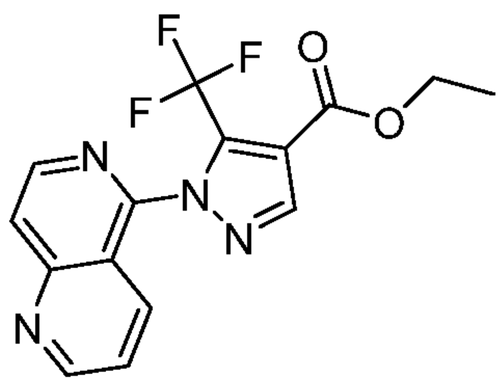
A. 5-Hydrazinyl-1,6-naphthyridine, **35a**



, **35a**

A solution of 5-chloro-1,6-naphthyridine (150 mg, 0.91 mmol) was added into hydrazine hydrate (3 mL), the mixture was heated to 80 °C and stirred for 16 h. The mixture afforded compound **35a** as a solid, collected by filtration. (100 mg, 42 %). LCMS (ESI) m/z M+1: 161.1.

B. Ethyl 1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **35b**

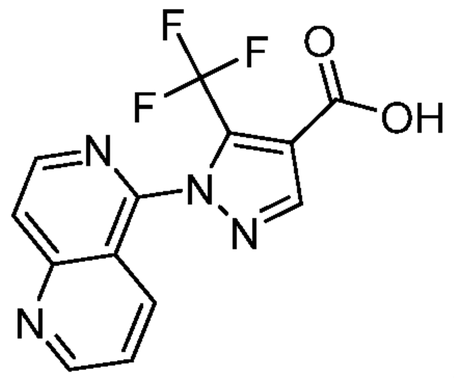


, **35b**

A solution consisting of 5-hydrazinyl-1,6-naphthyridine, **35a** (100 mg, 0.38 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (119.5 mg, 0.50 mmol) in ethanol (5 mL) was stirred at 80 °C for 4 h. The resultant solution was cooled to room

temperature and concentrated to dryness under reduced pressure to afford crude compound **35b**. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford compound **35b** as a yellow solid (100 mg, 85.5 %). LCMS (ESI) m/z M+1: 337.1.

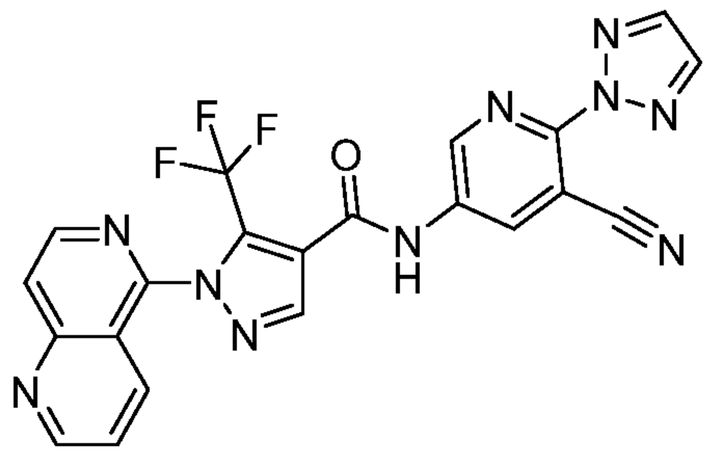
C. 1-(1,6-Naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **35c**



, **35c**

To a solution of ethyl 1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **35b** (90 mg, 0.27 mmol) in water (1 mL) and ethanol (1mL) was added NaOH (12.85 mg, 0.32 mmol) at room temperature. The mixture was stirred for 3 h. 2N HCl (aq) was added to the mixture until the solution was adjusted to pH 2. The solvent was removed under reduced pressure to afford crude compound **35c** as a white solid (82.5 mg, 100 %). LCMS (ESI) m/z M+1: 308.8.

D. *N*-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 100**

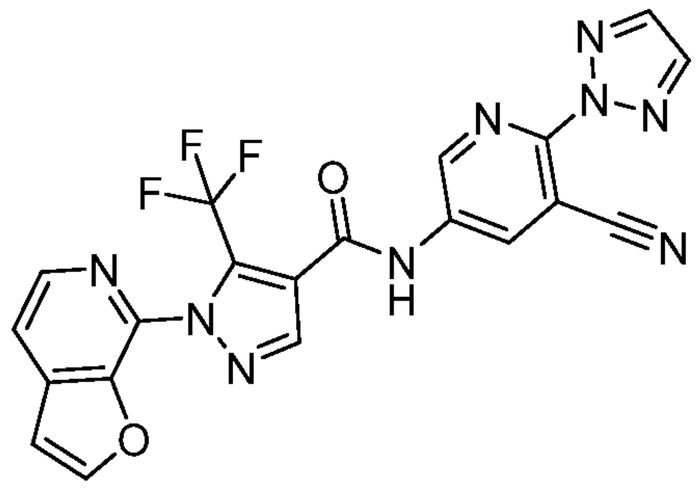


Phosphoryl trichloride (49.4 mg, 0.32 mmol) was added to a mixture of 1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **35c** (82 mg, 0.27 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, 7**b** (59.4 mg, 0.32 mmol), and pyridine (107 μL, 1.33 mmol) in dichloromethane at room temperature. The reaction was

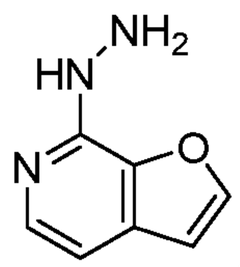
stirred at room temperature for 2 h. Sat. aqueous NH_4Cl (aq) (10mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic extracts were washed with water (5 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to ethyl acetate/ methanol =90:10). The solvent was removed under reduced pressure to afford compound **100** as a white solid (56.4 mg, 43 %). LCMS (ESI) m/z M+1: 447.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 (dd, J=8.60, 4.19 Hz, 1 H), 8.03 (s, 2 H), 8.15 (s, 1 H), 8.16 - 8.22 (m, 2 H), 8.27 (s, 1 H), 8.73 (d, J=5.73 Hz, 1 H), 8.83 (d, J=2.65 Hz, 1 H), 8.96 (d, J=2.65 Hz, 1 H), 9.21 (dd, J=4.30, 1.65 Hz, 1 H).

Example 36

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-*c*]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 99**



A. 7-Hydrazinylfuro[2,3-*c*]pyridine, **36a**

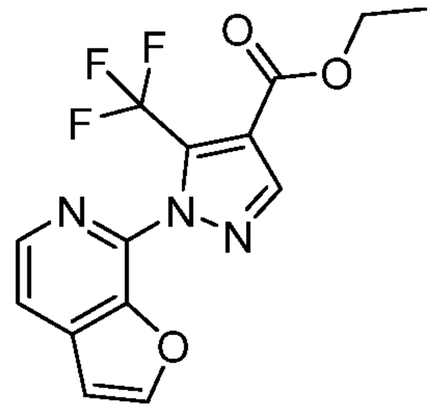


, **36a**

7-Chlorofuro[2,3-*c*]pyridine (300 mg, 1.95 mmol) was dissolved in ethanol (5 mL), hydrazine hydrate (345 mg, 5.86 mmol) was added, and the reaction mixture was stirred at 110 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude compound **36a** as a yellow solid. Compound **36a** was purified by flash column

chromatography over silica gel (dichloromethane/MeOH from 100/0 to 80/20) to afford compound **36a** as a yellow solid (250 mg, 83.9 %). LCMS (ESI) m/z M+1: 150.1.

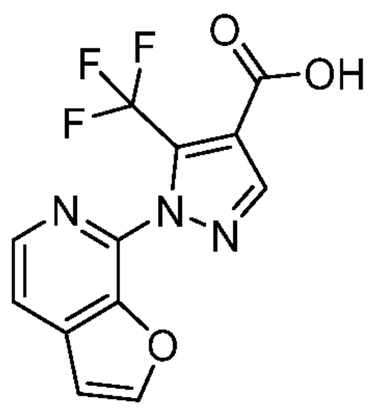
B. Ethyl 1-(furo[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **36b**



, **36b**

7-Hydrazinylfuro[2,3-*c*]pyridine, **36a** (250 mg, 1.64 mmol) was dissolved in ethanol (10 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (788 mg, 3.28 mmol) was added and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford a crude yellow oil. The oil was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 80/20) to afford compound **36b** as a yellow oil (360 mg, 68 %). LCMS (ESI) m/z M+1: 325.9.

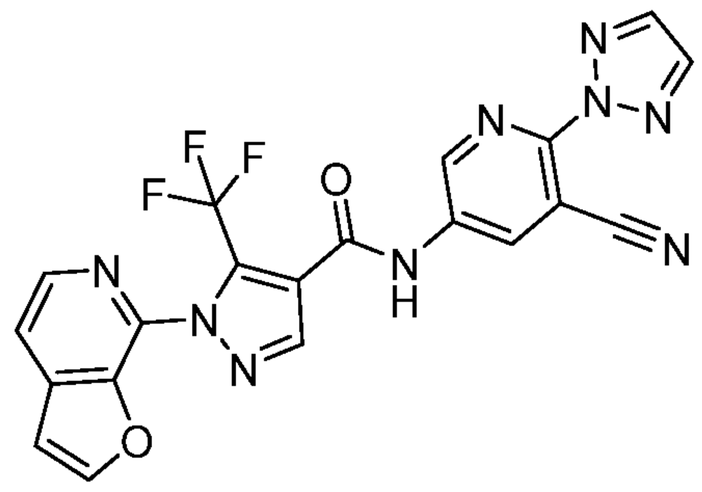
C. 1-(Furo[2,3-*c*]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **36c**



, **36c**

Concentrated HCl (4.7 mL) was added to ethyl 1-(furo[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **36b** (170 mg, 0.52 mmol) and the reaction mixture was stirred at 130 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford compound **36c** as a yellow solid (160 mg, 98 %), which was used in the following reaction without further purification. LCMS (ESI) m/z M+1: 297.9.

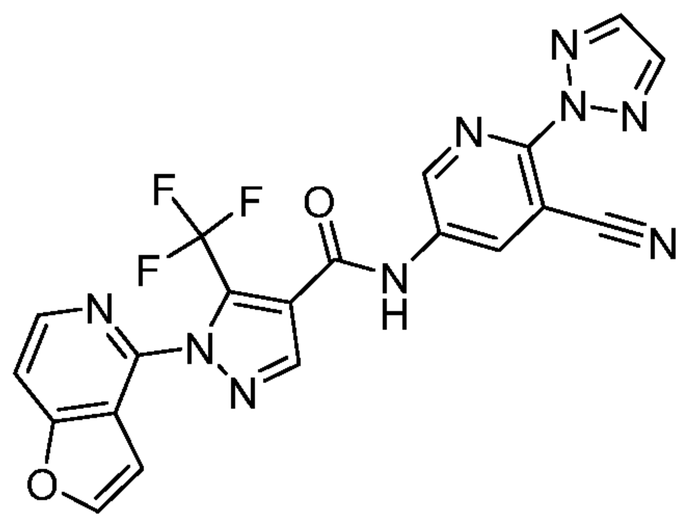
D. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-*c*]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 99**



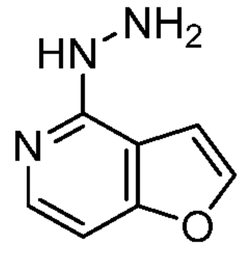
1-(Furo[2,3-*c*]pyridin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **36c** (160 mg, 0.51 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (63.8 mg, 0.34 mmol), and pyridine (122 mg, 1.54 mmol) were dissolved in dichloromethane (3 mL), and phosphoryl trichloride (78.8 mg, 0.51 mmol) was added. The mixture was stirred at 25 °C for 16 h. Sat. aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to afford crude compound **99** as a yellow oil. The oil was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (65%/35% to 40%/60 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **99** as a yellow solid (65 mg, 41 %). LCMS (ESI) m/z M+1: 465.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.41 (s, 1H), 9.06 (d, J=2.4 Hz, 1H), 8.83 (d, J=2.4 Hz, 1H), 8.53 (s, 1H), 8.48 (d, J=5.7 Hz, 1H), 8.32 (d, J=2.4 Hz, 1H), 8.29 (s, 2H), 7.95 (dd, J=0.9, 5.7 Hz, 1H), 7.13 (dd, J=0.9, 2.2 Hz, 1H).

Example 37

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 94**



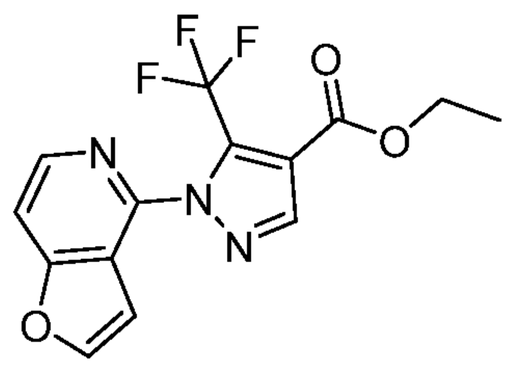
A. 4-Hydrazinylfuro[3,2-c]pyridine, **37a**



, **37a**

A mixture of 4-chlorofuro[3,2-c]pyridine (200 mg, 1.30 mmol) in hydrazine (6.52 g, 130 mmol) was stirred at 80 °C for 12 h. The reaction mixture was extracted with dichloromethane (30 mL x 2). The organic layer partitioned and concentrated to afford compound **37a** as a yellow solid (0.15 g, 77 %).

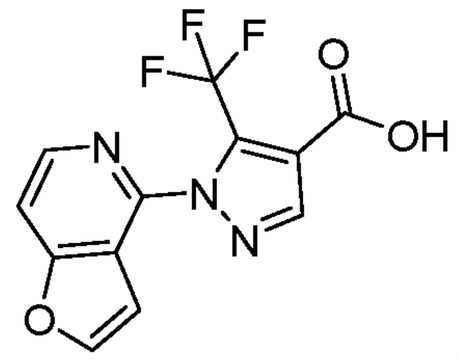
B. Ethyl 1-(furo[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **37b**



, **37b**

A solution consisting of 4-hydrazinylfuro[3,2-c]pyridine, **37a** (150 mg, 1.01 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (314 mg, 1.31 mmol) in ethanol (5 mL) was stirred at 80 °C for 3 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford the crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford crude compound **37b** as a yellow solid (170 mg, 51 %). LCMS (ESI) m/z M+1: 325.9.

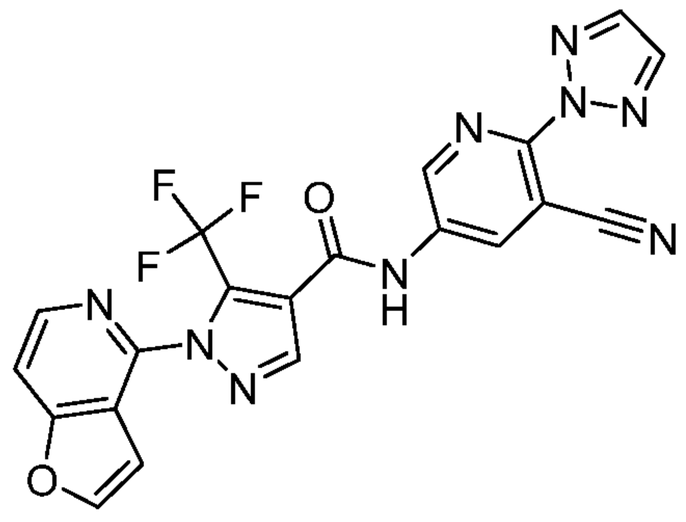
C. 1-(Furo[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **37c**



, **37c**

A mixture of ethyl 1-(furo[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **37b** (170 mg, 0.52 mmol) in concentrated HCl (4.4 mL) was stirred at 110 °C for 5 h. The solvent was removed under reduced pressure to afford compound **37c** as a yellow solid (155 mg, 100 %). LCMS (ESI) m/z M+1: 297.9.

D. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 94**

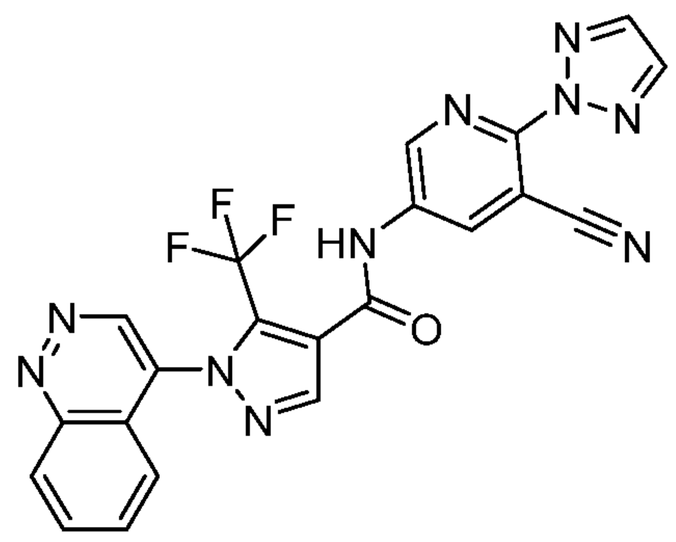


Phosphoryl trichloride (61.6 μL, 0.67 mmol) was added to the mixture of 1-(furo[3,2-*c*]pyridin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **37c** (100 mg, 0.34 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (75.2 mg, 0.40 mmol), and pyridine (135 μL, 1.68 mmol) in dichloromethane at 0 °C. The reaction was stirred at room temperature for 2 h. Sat. aqueous NH_4Cl (aq) (10 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL). The organic extracts were washed with water (5 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (65%/35% to 35%/65 %). The pure

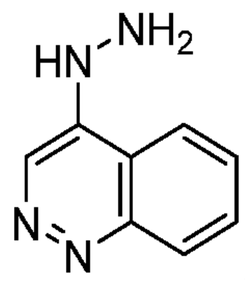
fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **94** as a white solid (73.6 mg, 46 %). LCMS (ESI) m/z M+1: 447.0; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 7.13 (d, J=1.32 Hz, 1 H), 7.94 - 7.99 (m, 1 H), 8.30 (s, 2 H), 8.33 (d, J=2.21 Hz, 1 H), 8.49 (d, J=5.73 Hz, 1 H), 8.55 (s, 1 H), 8.85 (d, J=2.43 Hz, 1 H), 9.07 (d, J=2.43 Hz, 1 H), 11.45 (s, 1 H).

Example 38

1-(Cinnolin-4-yl)-*N*-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 93**



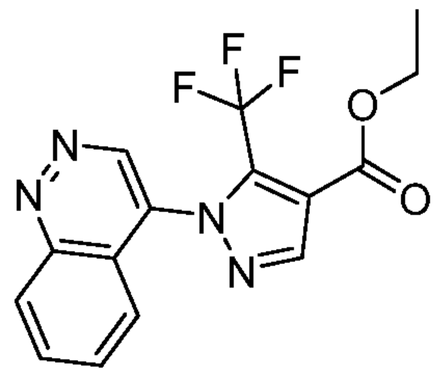
A. 4-Hydrazinylcinnoline, **38a**



, **38a**

A vial with stirbar was charged with 4-chlorocinnoline (212 mg, 1.288 mmol) and hydrazine (0.4 mL, 1.021 g/mL, 12.745 mmol), and the mixture was evacuated and flushed with argon (4x). Within 1-2 min at room temperature, the reaction mixture became a homogeneous amber solution and spontaneously warmed, becoming an orange paste. The reaction was then heated at 110 °C for 5 min. The reaction was allowed to cool to room temperature, water (8 mL) was added to the resulting paste, and the mixture was filtered. The filter cake was washed with water (4 mL x 2) and dried under reduced pressure to afford compound **38a** as a yellow powder (142.1 mg, 69 %).

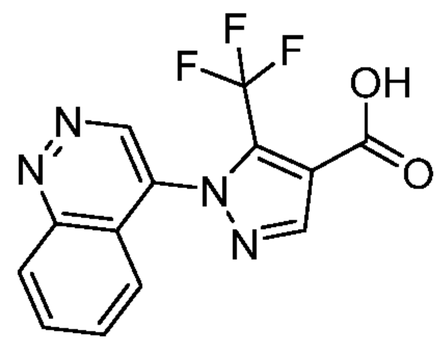
B. Ethyl 1-(cinnolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **38b**



, **38b**

A solution consisting of 4-hydrazinylcinnoline, **38a** (100 mg, 0.51 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (244 mg, 1.02 mmol) in ethanol (5 mL) was stirred at 80 °C for 3 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford crude compound **38b**. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford crude compound **38b** as a yellow solid (90 mg, 53 %). LCMS (ESI) m/z M+1:336.9. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.42 (t, J=7.17 Hz, 3 H), 4.43 (q, J=7.28 Hz, 2 H), 7.54 (d, J=8.60 Hz, 1 H), 7.87 (t, J=7.61 Hz, 1 H), 7.99 (td, J=7.72, 1.10 Hz, 1 H), 8.33 (s, 1 H), 8.74 (d, J=8.60 Hz, 1 H), 9.33 (s, 1 H).

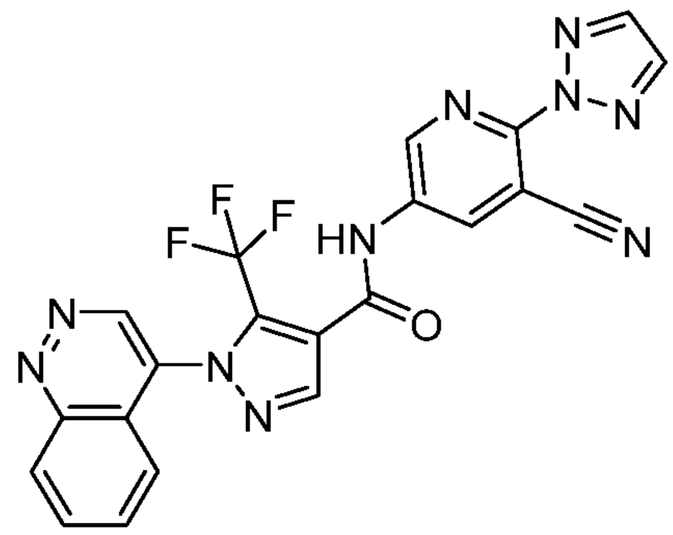
C. 1-(Cinnolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **38c**



, **38c**

A mixture of ethyl 1-(cinnolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **38b** (90 mg, 0.27 mmol) in concentrated HCl (2.23 mL) was stirred at 110 °C for 5 h. The solvent was removed under reduced pressure to give compound **38c** as a yellow solid (82 mg, 100 %). LCMS (ESI) m/z M+1:308.9.

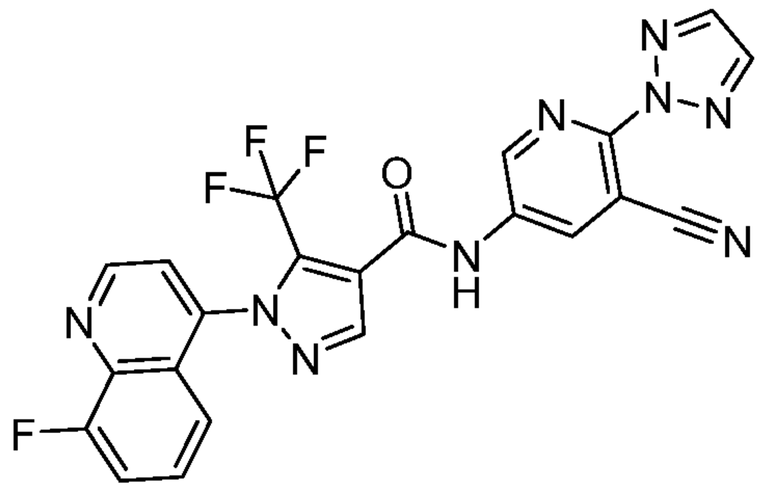
D. 1-(Cinnolin-4-yl)-*N*-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 93**



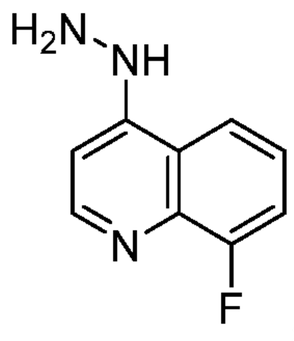
Phosphoryl trichloride (163.2 mg, 1.01 mmol) was added to a mixture of 1-(cinnolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **38c** (82 mg, 0.27 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (59.4 mg, 0.32 mmol), and pyridine (126 mg, 1.60 mmol) in dichloromethane at 0 °C. The reaction was stirred at room temperature for 2 h. Sat. NH_4Cl (aq) (10 mL) was added to the mixture. The mixture was extracted with dichloromethane (30 mL x 2). The organic extracts were washed with water (5 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and the filtrated concentrated under reduced pressure. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (62%/38% to 32%/68 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **93** as a pale yellow solid (20 mg, 16 %). LCMS (ESI) m/z M+1: 477.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 (d, J=8.38 Hz, 1 H), 8.01 - 8.10 (m, 1 H), 8.15 (t, J=7.50 Hz, 1 H), 8.29 (s, 2 H), 8.71 (s, 1 H), 8.74 (d, J=8.60 Hz, 1 H), 8.87 (d, J=2.65 Hz, 1 H), 9.09 (d, J=2.65 Hz, 1 H), 9.77 (s, 1 H), 11.37 (s, 1 H).

Example 39

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 92**



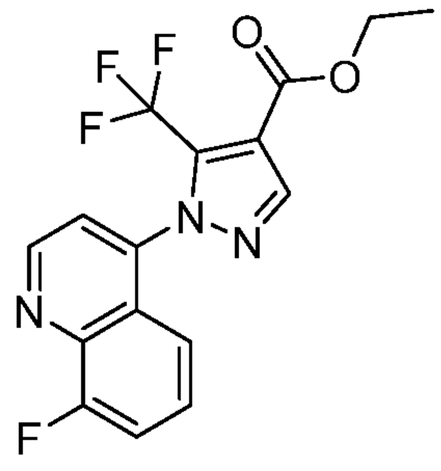
A. 8-Fluoro-4-hydrazinylquinoline, **39a**



, **39a**

4-Chloro-8-fluoroquinoline (300 mg, 1.65 mmol) was dissolved in ethanol (5 mL), hydrazine hydrate (292 mg, 5.0 mmol) was added and the reaction was stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford crude compound **39a** as a yellow solid. The solid was purified by flash column chromatography over silica gel (dichloromethane/MeOH from 100/0 to 80/20) to afford compound **39a** as a yellow solid (350 mg, 82 %). LCMS (ESI) m/z M+1: 178.1.

B. Ethyl 1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **39b**

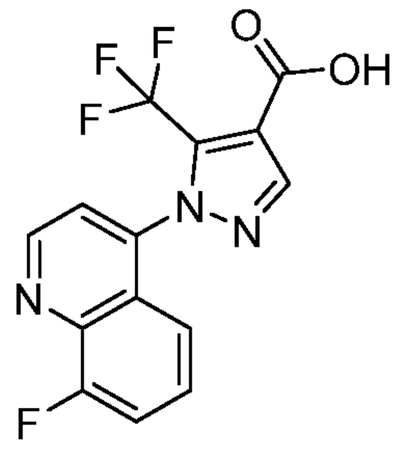


, **39b**

A solution consisting of 8-fluoro-4-hydrazinylquinoline, **39a** (350 mg, 1.35 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (648 mg, 2.70 mmol) in ethanol (10 mL) was stirred at 80 °C for 16 h. The resultant solution was cooled to room

temperature and concentrated to dryness under reduced pressure to afford a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 80:20). The solvent was removed under reduced pressure to afford compound **39b** as a yellow solid (780 mg, 61 %).

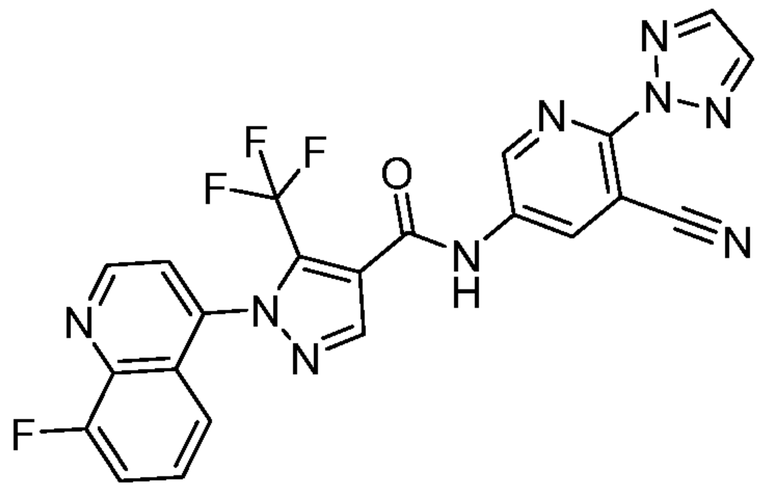
C. 1-(8-Fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **39c**



, **39c**

A mixture of ethyl 1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **39b** (150 mg, 0.43 mmol) in concentrated HCl (10 mL) was stirred at 130 °C for 4 h. The solvent was concentrated under reduced pressure to afford compound **39c** as a yellow solid (140 mg, 100 %). LCMS (ESI) m/z M+1: 325.9.

D. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 92**

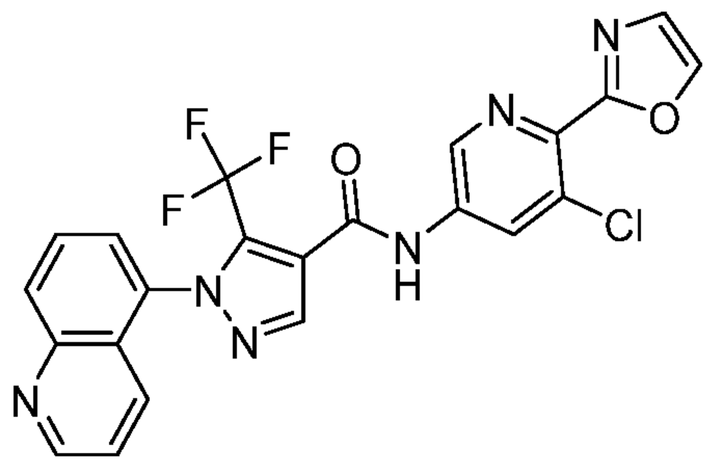


Phosphoryl trichloride (81.2 mg, 0.53 mmol) was added to a mixture of 1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **39c** (150 mg, 0.46 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile, 7**b** (65.7 mg, 0.35 mmol), and pyridine (126 mg, 1.60 mmol) in dichloromethane (3 mL) at 0 °C. The reaction was stirred at room temperature for 2 h. Sat. NH_4Cl (aq) (10 mL) was added to the mixture. The

mixture was extracted with dichloromethane (30 mL x 2). The organic layer was washed with water (5 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resultant residue was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (57%/43% to 27%/73 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **92** as a yellow solid (54 mg, 31 %). LCMS (ESI) m/z M+1: 493.9; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.41 (s, 1H), 9.21 (d, J=4.4 Hz, 1H), 9.10 (d, J=2.2 Hz, 1H), 8.87 (d, J=2.4 Hz, 1H), 8.68 (s, 1H), 8.29 (s, 2H), 8.01 (d, J=4.4 Hz, 1H), 7.82 - 7.67 (m, 2H), 7.14 (d, J=8.4 Hz, 1H).

Example 40

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 91**

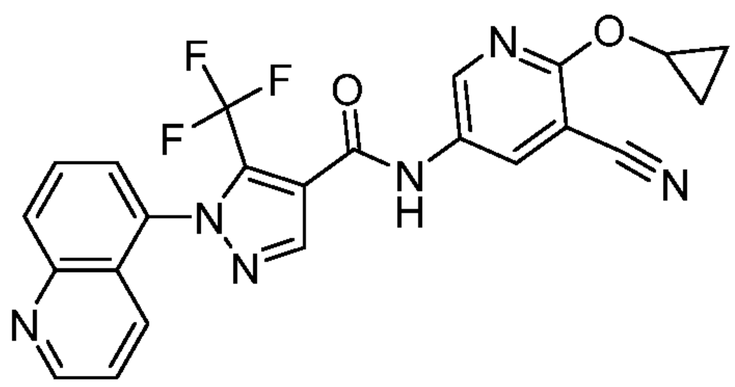


Phosphoryl trichloride (38.5 mg, 0.25 mmol) was added to a mixture of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (51.4 mg, 0.17 mmol), 5-chloro-6-(oxazol-2-yl)pyridin-3-amine, **6b** (60 mg, 0.25 mmol), and pyridine (60 mg, 0.75 mmol) in dichloromethane (3 mL) at 0 °C. The reaction was stirred at room temperature for 16 h. Sat. $NaHCO_3$ (aq) (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (20 mL x 2). The organic layer was washed with water (5 mL), dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resultant residue was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (64%/36% to 34%/66 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **91** as a yellow solid (40 mg, 49 %). LCMS (ESI) m/z M+1: 484.9; ^{1}H NMR (400 MHz, DMSO-

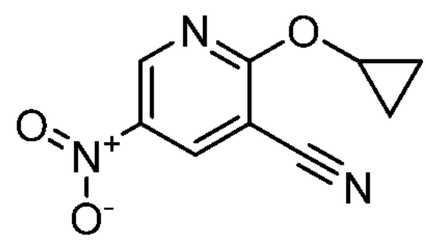
d6) δ ppm 11.40 (s, 1H), 9.11 (dd, J=2.1, 3.6 Hz, 1H), 9.01 (d, J=1.5 Hz, 1H), 8.66 (s, 1H), 8.59 (d, J=2.2 Hz, 1H), 8.37 (d, J=8.4 Hz, 1H), 8.32 (s, 1H), 8.05 - 7.94 (m, 2H), 7.79 - 7.71 (m, 2H), 7.49 (s, 1H).

Example 41

N-(5-cyano-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 88**



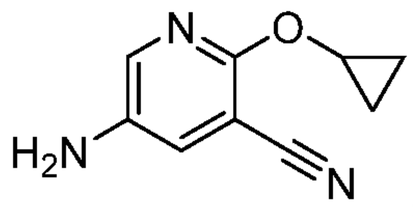
A. 2-Cyclopropoxy-5-nitronicotinonitrile, **41a**



, **41a**

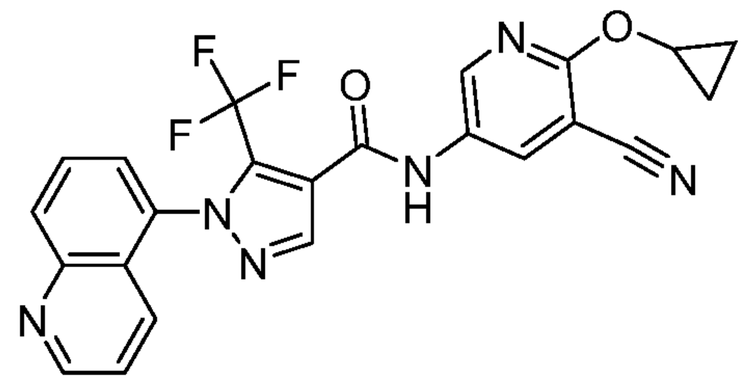
2-Chloro-5-nitronicotinonitrile (300 mg, 1.64 mmol) and cyclopropanol (380 mg, 6.54 mmol) were added to potassium carbonate (339 mg, 2.45 mmol), and the mixture was stirred at room temperature overnight. The mixture was concentrated to dryness and dissolved in ethyl acetate (5 mL). Water (10 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate concentrated to dryness to give crude compound **41a**. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 60/40) to afford compound **41a** as a yellow solid (310 mg, 92 %). ^{1}H NMR (400 MHz, DMSO- *d6*) δ ppm 0.85 - 0.90 (m, 4 H), 4.52 - 4.58 (m, 1 H), 9.18 (d, J=2.76 Hz, 1 H) ,9.35 (d, J=2.76 Hz, 1 H).

B. 5-Amino-2-cyclopropoxynicotinonitrile, **41b**


, **41b**

Fe (0) (422 mg, 7.56 mmol) and NH_4Cl (404 mg, 7.56 mmol) was added to a solution of 2-cyclopropoxy-5-nitronicotinonitrile, **41a** (310 mg, 1.51 mmol) in THF (10 mL), methanol (10 mL) and water (10 mL). The reaction mixture was stirred at 65 °C for 2 h. The mixture was filtered. Sat. aqueous $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7-8. The mixture was extracted with ethyl acetate (10 mL x 3). The organic extracts were dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to afford compound **41b** as a yellow solid (280 mg, 87 %). LCMS (ESI) m/z M+1: 175.8.

C. *N*-(5-Cyano-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 88**

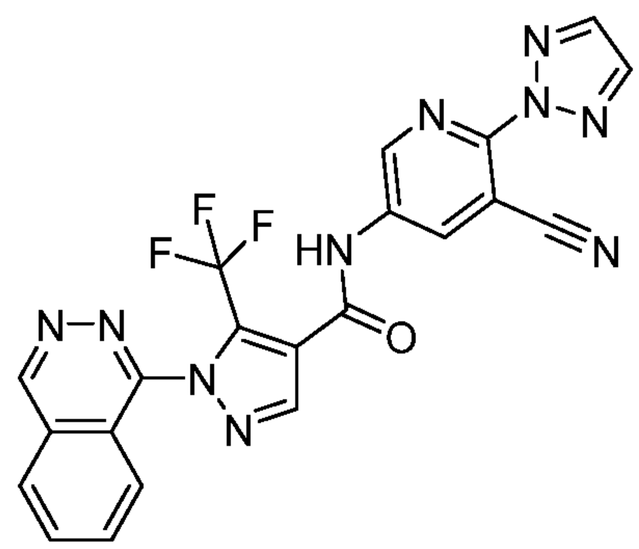


2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (186 mg, 0.49 mmol) was added to a solution of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (100 mg, 0.325 mmol), 5-amino-2-cyclopropoxynicotinonitrile, **41b** (97.1 mg, 0.46 mmol) and triethylamine (142 µL, 0.81 mmol) in DMF (2 mL). The reaction mixture was stirred at room temperature for 1 h. Water (5 mL) was added to the mixture. The aqueous portion was extracted with dichloromethane (5 mL x 3). The separated organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to afford a crude product. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (74%/26% to 44%/56 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **88** as a white solid (90 mg, 43 %).

LCMS (ESI) m/z M+1: 465.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.75 - 0.80 (m, 2 H), 0.81 - 0.87 (m, 2 H), 4.39 (tt, J=6.12, 3.14 Hz, 1 H), 7.63 - 7.73 (m, 2 H), 7.91 - 7.95 (m, 1 H), 7.96 - 8.02 (m, 1 H), 8.34 (d, J=8.38 Hz, 1 H), 8.52 - 8.58 (m, 2 H), 8.75 (d, J=2.43 Hz, 1 H), 9.08 (dd, J=4.08, 1.65 Hz, 1 H), 11.01 (br s, 1 H).

Example 42

N-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 102**

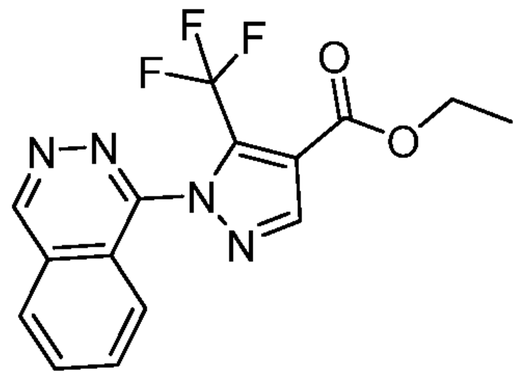


A. 1-Hydrazinylphthalazine, **42a**

, **42a**

A mixture of 1-chlorophthalazine (350 mg, 2.13 mmol) in hydrazine (5.32 g, 106.3 mmol) was stirred at 80 °C for 4 h. The mixture was extracted with dichloromethane (50 mL x 2). The organic layer was concentrated under reduced pressure to afford a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 0:100) to afford crude compound **42a** as a yellow solid (0.25 g, 73.3 %).

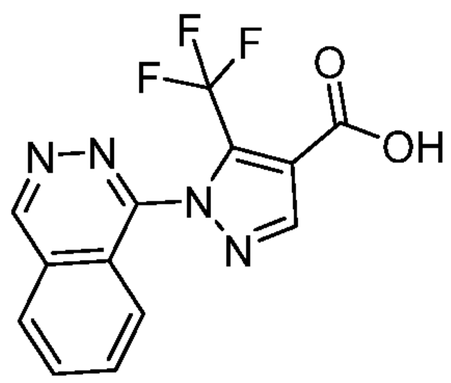
B. Ethyl 1-(phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **42b**



, **42b**

A solution consisting of 1-hydrazinylphthalazine, **42a** (250 mg, 1.56 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (750 mg, 3.12 mmol) in ethanol (5 mL) was stirred at 80 °C for 3 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford crude compound **42b** as a yellow solid (160 mg, 27.4 %). LCMS (ESI) m/z M+1: 336.9.

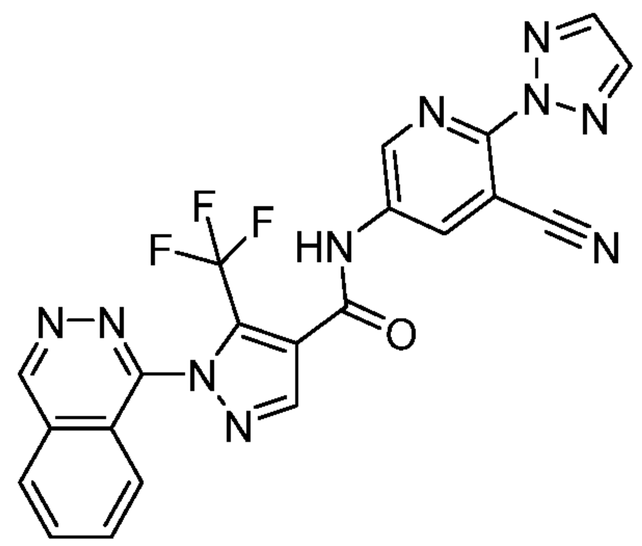
C. 1-(Phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **42c**



, **42c**

A mixture of ethyl 1-(phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **42b** (160 mg, 0.43 mmol) in concentrated HCl (3.5 mL) was stirred at 110 °C for 5 h. The solvent was removed under reduced pressure to afford compound **42c** as a yellow solid (140 mg, 100 %). LCMS (ESI) m/z M+1: 308.9.

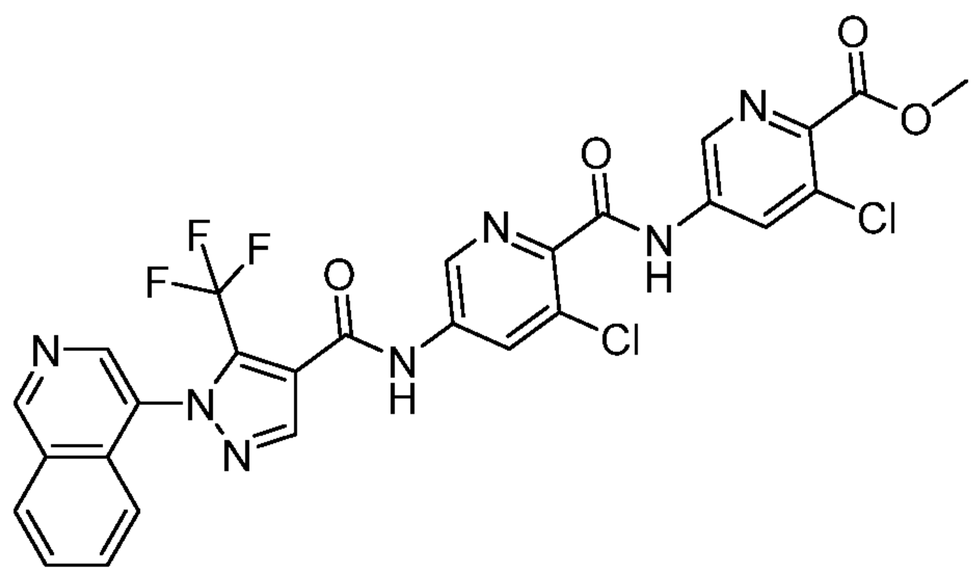
D. *N*-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 102**

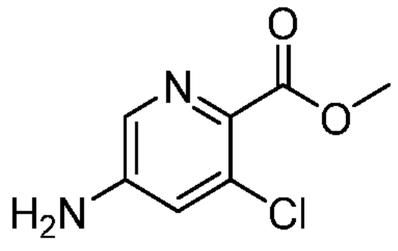


Phosphoryl trichloride (218.2 mg, 1.42 mmol) was added to the mixture of 1-(phthalazin-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **42c** (130 mg, 0.36 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile**,** 7**b** (79.5 mg, 0.43 mmol), pyridine (170 mg, 2.14 mmol) in dichloromethane (10 mL) at 0 °C. The reaction was stirred at room temperature for 2 h. Water (20 mL) was added to the mixture. The mixture was extracted with dichloromethane (20 mL x 2). The organic portion was concentrated under reduced pressure to afford a crude product. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (65%/35% to 35%/65 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **102** as a white solid (15 mg, 9 %). LCMS (ESI) m/z M+1: 477.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.81 (d, J=8.38 Hz, 1 H), 8.14 - 8.25 (m, 2 H), 8.44 (d, J=7.72 Hz, 1 H), 8.73 (s, 1 H), 8.89 (d, J=2.43 Hz, 1 H), 9.12 (d, J=2.43 Hz, 1 H), 9.98 (s, 1 H), 11.45 (s, 1 H).

Example 43

Methyl 3-chloro-5-(3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamido)picolinamido)picolinate, **Cpd 44**

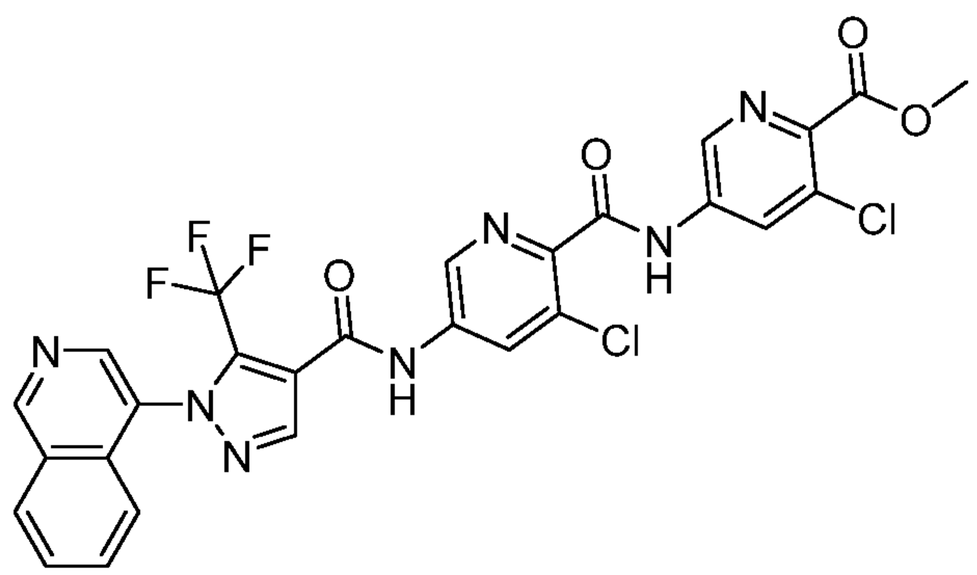




, **43a**

A mixture of 6-bromo-5-chloropyridin-3-amine (500 mg, 2.41 mmol), 1,1-bis(diphenylphosphino)ferrocene (134 mg, 0.24 mmol) and triethylamine (732 mg, 7.23 mmol) in MeOH (3 mL) and toluene (15 mL) was heated at 70 °C under a CO (35 psi) atmosphere with dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (catalyst, 197 mg, 0.24 mmol), and the mixture was stirred overnight. After uptake of CO (1 equiv), the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 50/50) to afford compound **43a** as a red solid (300 mg, 67 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.96 (s, 3 H), 4.14 - 4.24 (m, 2 H), 7.03 (d, J=2.26 Hz, 1 H), 8.03 (d, J=2.51 Hz, 1 H).

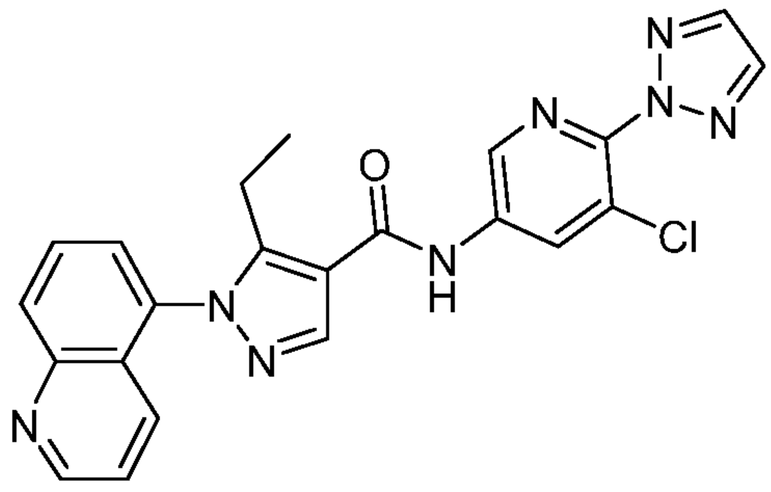
B. Methyl 3-chloro-5-(3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamido)picolinate, **Cpd 44**



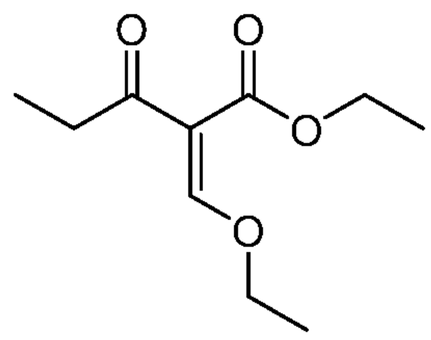
Phosphoryl trichloride (29.8 mg, 0.32 mmol) was added dropwise to a solution of 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (50 mg, 0.16 mmol), methyl 5-amino-3-chloropicolinate, **43a** (38.8 mg, 0.21 mmol) and pyridine (64.7 mg, 0.80 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 1 h. Water (5 mL) was added to the mixture. The aqueous portion was extracted with dichloromethane (5 mL x 3). The separated organic extracts were dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford a crude product. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (55%/45% to 25%/75 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **44** as a white solid (22 mg, 21 %). LCMS (ESI) m/z M+1: 629.8; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.90 (s, 3 H), 7.30 (d, J=8.38 Hz, 1 H), 7.84 - 8.00 (m, 2 H), 8.39 (d, J=8.16 Hz, 1 H), 8.58 (dd, J=10.69, 1.87 Hz, 2 H), 8.68 (s, 1 H), 8.81 (s, 1 H), 9.01 (dd, J=10.03, 1.87 Hz, 2 H), 9.64 (s, 1 H), 11.36 (d, J=19.40 Hz, 2 H).

Example 44

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 17**



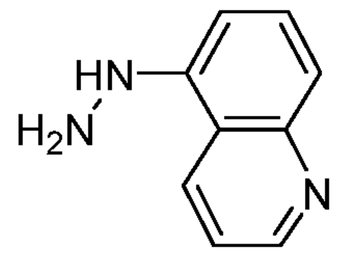
A. 3-(Ethoxymethylene)-1-methoxyhexane-2,4-dione, **44a**



, **44a**

A solution consisting of ethyl 3-oxopentanoate (1.0 g, 6.9 mmol), triethoxymethane (3.1 g, 21 mmol), and acetic anhydride (20 mL) was stirred at 135 °C for 16 h before cooling to room temperature. The resultant mixture was concentrated to dryness under reduced pressure to afford crude compound **44a** (1.8 g, crude), which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 - 7.54 (m, 1H), 4.33 - 4.15 (m, 4H), 2.70 (dd, *J* = 7.6, 13.2 Hz, 2H), 1.41 - 1.26 (m, 6H), 1.13 - 1.05 (m, 3H).

B. 5-Hydrazinylquinoline, **44b**

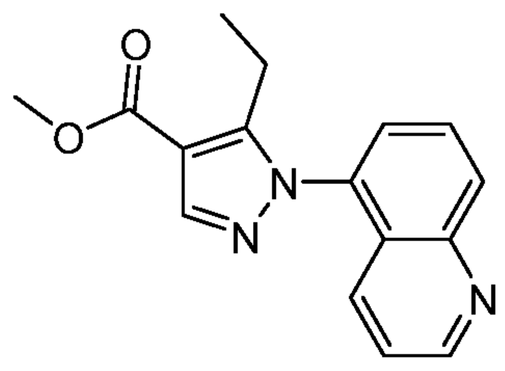


, **44b**

A solution consisting of 5-aminoquinoline (1.0 g, 6.9 mmol) and concentrated hydrochloric acid (5 mL) was stirred at 0 °C (ice/water) for 10 min. A solution consisting of sodium nitrite (0.57 g, 8.3 mmol) and water (0.5 mL) was added to the cold reaction mixture over 10 min and stirred at 0 °C (ice/water) for 1 h. *L*-ascorbic acid (1.3 g, 7.3 mmol) was added to the reaction mixture over 10 min. The resultant mixture was warmed

to room temperature and stirred for 50 min. The reaction mixture was then heated at 80 °C for 20 min and water (4 mL) was added. The suspension was again cooled to 0 °C (ice/water) and stirred for 2 h. A solid was collected by filtration and washed with methanol to afford compound **44b** (870 mg, 79 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.01 (br. s., 1H), 9.28 - 9.13 (m, 2H), 8.06 - 7.86 (m, 3H), 7.33 - 7.20 (m, 1H).

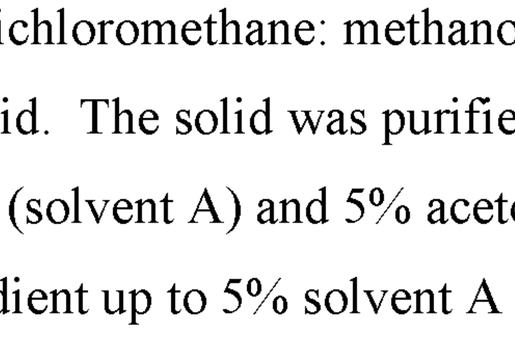
C. Ethyl 5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **44c**



, **44c**

A solution consisting of 3-(ethoxymethylene)-1-methoxyhexane-2,4-dione, **44a** (755 mg, 3.77 mmol), 5-hydrazinylquinoline, **44b** (500 mg, 3.14 mmol), and ethanol (15 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The resultant solution was concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (dichloromethane: methanol = 10:1) to afford compound **44c** (700 mg, 75 %) as a brown solid. The solid was purified by reverse phase HPLC (95% water containing 0.038% TFA (solvent A) and 5% acetonitrile containing 0.02% TFA (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 - 9.11 (m, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 8.06 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.83 - 7.78 (m, 1H), 7.77 - 7.71 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.78 - 2.68 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H).

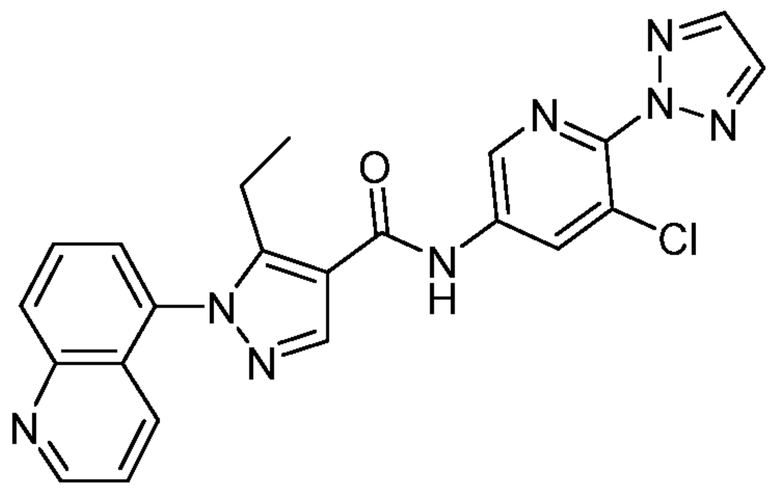
D. 5-Ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **44d**



, **44d**

A solution consisting of lithium hydroxide hydrate (298 mg, 7.11 mmol) and water (5 mL) was added to a solution consisting of ethyl 5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **44c** (700 mg, 2.37 mmol) and ethanol (10 mL). The resultant solution was stirred at room temperature for 16 h. The resultant solution was concentrated to dryness under reduced pressure to afford a crude product, which was poured into water (3 mL) and acidified with 3N HCl to pH 5. A precipitate was removed by filtration, the filter cake was washed with water (3 mL), and then dried under reduced pressure to afford compound **44d** (400 mg, 63 %) as a brown solid. LCMS (ESI): R_T = 0.54 min, mass calcd. for $C_{15}H_{13}N_3O_2$ 267.10, m/z found 268.0 $[M+H]^+$. Purification by reverse phase HPLC (95% water containing 0.038% TFA (solvent A) and 5% acetonitrile containing 0.02% TFA (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B) afforded compound **44d**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.55 (br. s., 1H), 9.02 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 8.8 Hz, 1H), 8.10 (s, 1H), 7.97 - 7.91 (m, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.63 - 7.53 (m, 2H), 2.77 - 2.65 (m, 2H), 0.88 (t, J = 7.6 Hz, 3H).

E. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 17**

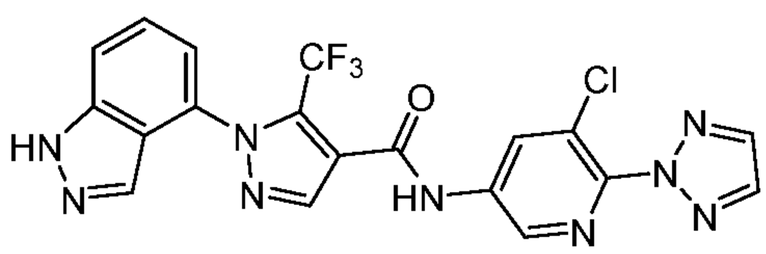


$POCl_3$ (172 mg, 1.12 mmol) was added dropwise to a solution consisting of 5-ethyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **44d** (250 mg, 0.935 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (201 mg, 1.03 mmol), and pyridine (5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h. To the resultant mixture was added sat. aqueous $NaHCO_3$ (10 mL) and the mixture was extracted with ethyl acetate (15 mL x 3). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to dryness under reduced pressure to give a crude product. The

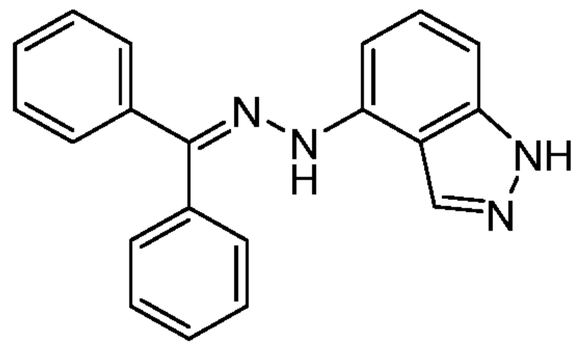
crude material was purified by reverse phase HPLC (40% to 50% (v/v) CH_3CN and water with 0.05% NH_3) to afford compound **17** (100 mg). Compound **17** was further purified by reverse phase HPLC (30% to 60% (v/v) CH_3CN and water with 10 mM NH_4HCO_3) to afford pure compound **17**, which was suspended in water (10 mL), frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **17** (56.50 mg, 13 %). LCMS (ESI): R_T = 4.51 min, mass calcd. for $C_{22}H_{17}ClN_8O$ 444.12, m/z found 445.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.78 (d, *J* = 2.4 Hz, 1H), 8.54 (d, *J* = 2.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.96 (s, 2H), 7.89 - 7.83 (m, 1H), 7.65 - 7.57 (m, 2H), 7.46 (dd, *J* = 4.4, 8.4 Hz, 1H), 2.88 (br.s., 2H), 1.07 (t, *J* = 7.6 Hz, 3H).

Example 45

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1*H*-indazol-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 68**



A. 4-(2-(Diphenylmethylene)hydrazinyl)-1*H*-indazole, **45a**

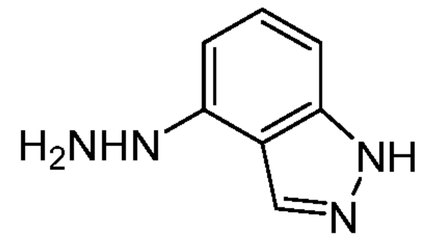


, **45a**

A mixture consisting of 4-bromo-1*H*-indazole (1.50 g, 0.760 mmol), (diphenylmethylene)hydrazine (1.49 g, 7.61 mmol), *t*-BuONa (2.19 g, 22.8 mmol), $Pd_2(dba)_3$ (697 mg, 0.760 mmol), Xantphos (440 mg, 0.760 mmol), and 1,4-dioxane (20 mL) was stirred at 110 °C for 24 h under a N_2 atmosphere. The mixture was cooled to room temperature, filtered and the filtrate was concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (petroleum ether: ethyl acetate =

1:2) to afford compound **45a** (1 g, 42 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.37 (br s, 1H), 8.52 (s, 1H), 7.95 (s, 1H), 7.67 - 7.56 (m, 5H), 7.42 - 7.33 (m, 5H), 7.25 - 7.21 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H).

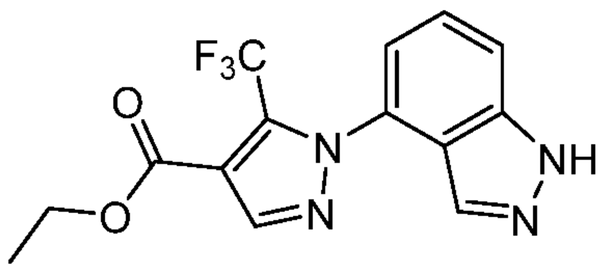
B. 4-Hydrazinyl-1*H*-indazole, **45b**



, **45b**

A mixture consisting of 4-(2-(diphenylmethylene)hydrazinyl)-1*H*-indazole, **45a** (800 mg, 2.56 mmol), conc. HCl (10 mL), and ethanol (5 mL) was stirred at room temperature for 16 h. The ethanol was removed under reduced pressure and the aqueous phase was extracted with ethyl acetate (20 mL x 2). The extracts were concentrated to dryness under reduced pressure to afford compound **45b** (450 mg, 95 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.50 (br s, 3H), 8.17 (s, 1H), 7.28 - 7.20 (m, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.55 (d, *J* = 7.3 Hz, 1H).

C. Ethyl 1-(1*H*-indazol-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **45c**

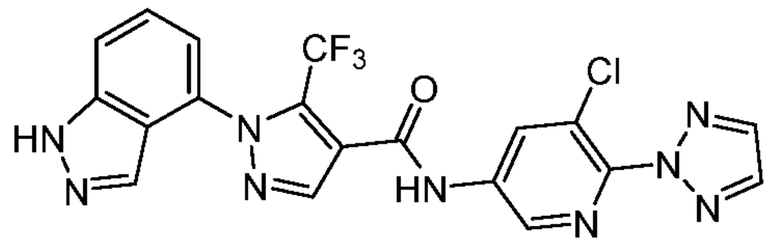


, **45c**

A mixture consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, cpd **1f** (39.0 mg, 0.160 mmol), 4-hydrazinyl-1*H*-indazole, **45b** (30.0 mg, 0.160 mmol), triethylamine (18.0 mg, 0.180 mmol), and ethanol (3 mL) was stirred at 80 °C for 16 h. The mixture was cooled to room temperature and concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (petroleum ether: ethyl acetate = 2:1) to afford impure compound **45c** (550 mg). The post-chromatographic product (550 mg) was further purified by preparative HPLC (32% to 62% (v/v) CH_3CN and water with 0.05% NH_3) to afford compound **45c**, which was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **45c** (260

mg, 33 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.01 (br s, 1H), 8.24 (s, 1H), 7.96 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.50 - 7.46 (m, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

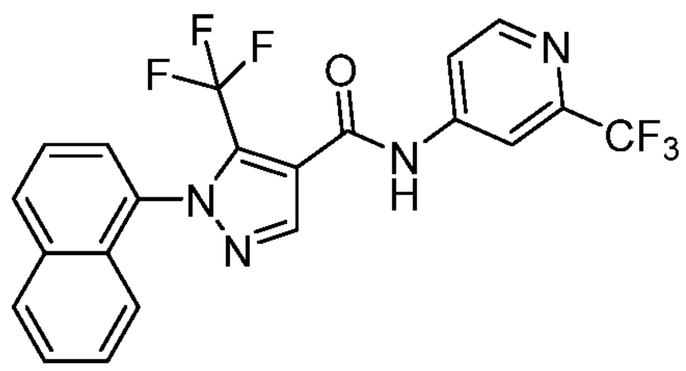
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1*H*-indazol-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 68**



A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (79.6 mg, 0.410 mmol) and THF (1 mL) was added dropwise to a solution of *t*-BuOK (1.02 mL, 1.02 mmol, 1 M in THF) at 0 °C. Then a solution consisting of ethyl 1-(1*H*-indazol-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **45c** (20.0 mg, 0.0600 mmol), and THF (1 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 16 h before quenching with water and extracting with ethyl acetate (50 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a residue, which was purified by reverse phase HPLC (26% to 56% (v/v) CH_3CN and water with 0.05% NH_3) to afford pure compound **68**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **68** (70 mg, 44 %). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 13.63 (br s, 1H), 11.29 (br s, 1H), 8.86 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H), 8.54 (s, 1H), 8.20 (s, 2H), 7.88 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.60 - 7.51 (m, 1H), 7.32 (d, *J* = 7.6 Hz, 1H).

Example 46

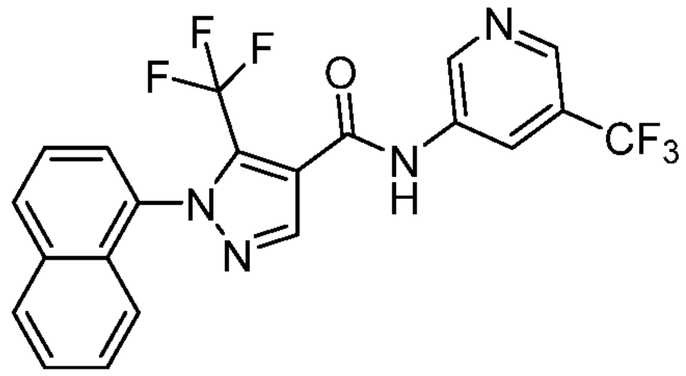
1-(Naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 3**



$POCl_3$ (90.1 mg, 0.588 mmol) was added dropwise to a solution consisting of 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **2b** (150 mg, 0.490 mmol), 2-(trifluoromethyl)pyridin-4-amine (87.3 mg, 0.539 mmol) and pyridine (3 mL). The mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated to dryness under reduced pressure to give a crude product, which was purified by preparative high performance liquid chromatography using Kromasil 150 x 25 mm x 10 μm (55% to 55% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **3**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to afford compound **3** (76.90 mg, 35 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.28 (br.s., 1H), 8.72 (d, J = 6.0 Hz, 1H), 8.56 (s, 1H), 8.25 (d, J = 6.4 Hz, 2H), 8.15 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 4.8 Hz, 1H), 7.83 - 7.76 (m, 1H), 7.75 - 7.60 (m, 3H), 7.12 (d, J = 8.0 Hz, 1H).

Example 47

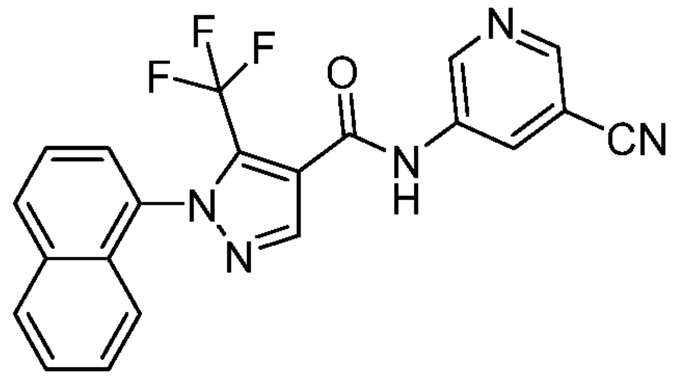
1-(Naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(5-(trifluoromethyl)pyridin-3-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 4**



$POCl_3$ (120 mg, 0.784 mmol) was added dropwise to a solution consisting of 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **2b** (200 mg, 0.653 mmol), 5-(trifluoromethyl)pyridin-3-amine (116 mg, 0.718 mmol) and pyridine (3 mL). The mixture was stirred at 0 °C for 1 h. The resultant mixture was concentrated to dryness under reduced pressure to give a crude product, which was purified by reverse phase HPLC (54% to 84% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **4**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **4** (81.70 mg, 28 %). LCMS (ESI): R_T = 4.32 min, mass calcd. for $C_{21}H_{12}F_6N_4O$ 450.337, m/z found 451.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.15 (br.s., 1H), 9.14 (s, 1H), 8.77 (s, 1H), 8.62 (s, 1H), 8.55 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.75 - 7.61 (m, 3H), 7.12 (d, J = 8.0 Hz, 1H).

Example 48

N-(5-Cyanopyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 5**

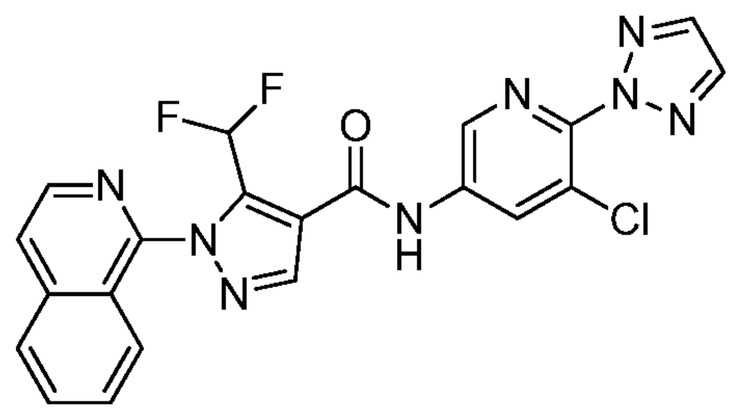


$POCl_3$ (22.9 mg, 0.149 mmol) was added dropwise to a solution consisting of 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **48b** (200 mg, 0.653 mmol), 5-aminonicotinonitrile (85.6 mg, 0.718 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resulting mixture was washed with water (20 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by reverse phase HPLC (46% to 76% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **5** (74.90 mg, 28 %). LCMS (ESI): R_T = 5.12 min, mass calcd. for $C_{21}H_{12}F_3N_5O$ 407.348, m/z found 408.1$[M+H]^+$. ^1H NMR (400 MHz,

DMSO-d_6) δ ppm 11.15 (s, 1H), 9.12 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H), 8.65 (t, J = 2.0 Hz, 1H), 8.55 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.17 - 8.12 (m, 1H), 7.81 - 7.76 (m, 1H), 7.75 - 7.61 (m, 3H), 7.13 (d, J = 8.4 Hz, 1H).

Example 49

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(difluoromethyl)-1-(isoquinolin-1-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 56**

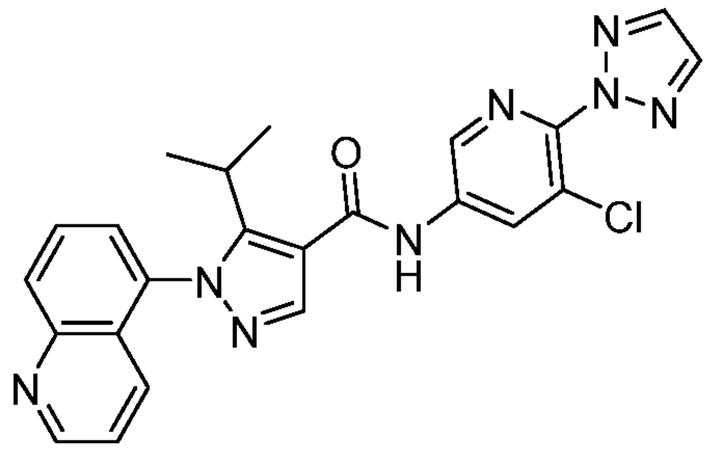


A 4 mL vial with stirbar was charged with 1-hydrazinylisoquinoline, **10a** (44.9 mg, 0.282 mmol), THF (0.56 mL, 0.5 M, 0.28 mmol), ethyl 2-(ethoxymethylene)-4,4-difluoro-3-oxobutanoate/THF (0.56 mL, 0.5 M, 0.28 mmol), and the resulting amber homogeneous solution was stirred at room temperature (capped) for 10 min, followed by stirring at 70 °C for 1 h. The reaction was then cooled to room temperature and treated with calcium sulfate (184 mg, 1.352 mmol) and stirred (capped) for 10 min. The reaction was then cooled to room temperature, treated with 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (55.7 mg, 0.284 mmol) and 1.01 M KOtBu/THF (0.42 mL, 0.424 mmol), and the resulting dark reaction was stirred at room temperature for 3 h. The mixture was partitioned with 5 M NH_4Cl (1 mL) and ethyl acetate (1 mL). The organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated to provide a clear red/ amber oil (119 mg). This oil was purified by flash column chromatography on a 12 g Silicycle HP column (50 - 100% EtOAc in heptane over 10 CVs, then isocratic) to provide impure compound **56** (43 mg) as a beige solid. This was crystallized from MeOH (1 mL) to provide, after washing the crystals with MeOH (2 × 0.5 mL), compound as an off-white powder (31.3 mg, 24 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.72-8.75 (m, 1H), 8.55-8.57 (m, 1H), 8.51 (d, J=5.56 Hz,

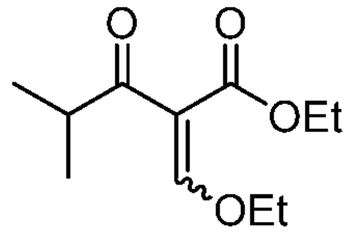
1H), 8.39-8.44 (m, 1H), 8.34 (s, 1H), 7.97-8.02 (m, 2H), 7.96 (s, 2H), 7.88-7.91 (m, 1H), 7.80-7.87 (m, 1H), 7.67-7.73 (m, 1H), 7.40 (t, *J*=53.1 Hz, 1H); MS m/e 467.1 (M+H).

Example 50

N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 26**



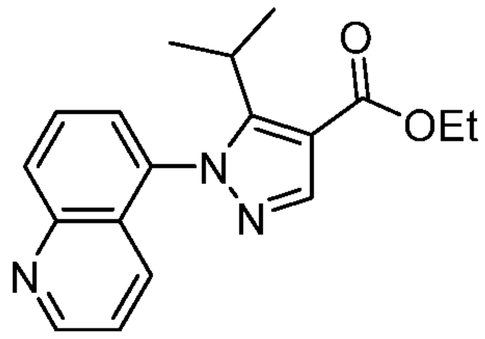
A. Ethyl 2-(ethoxymethylene)-4-methyl-3-oxopentanoate, **50a**



, **50a**

A solution consisting of ethyl 4-methyl-3-oxopentanoate (500 mg, 3.16 mmol), triethoxymethane (1.41 mg, 9.48 mmol) and Ac_2O (5 mL) was stirred at 130 °C for 16 h before cooling to room temperature and concentrating to dryness under reduced pressure to afford compound **50a** (550 mg, crude), which was used in the following reaction without further purification.

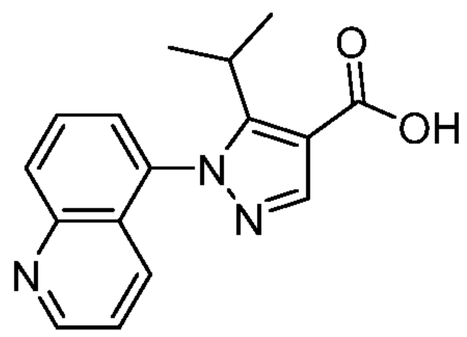
B. Ethyl 5-isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **50b**



, **50b**

A solution consisting of ethyl 2-(ethoxymethylene)-4-methyl-3-oxopentanoate, **50a** (550 mg, 2.57 mmol), 5-hydrazinylquinoline, **13a** (408 mg, 2.57 mmol) and ethanol (5 mL) was stirred at 80 °C for 16 h before cooling to room temperature and concentrating to dryness under reduced pressure to give a crude product, which was purified by FCC (dichloromethane: methanol = 100:0 to 90:10) to afford compound **50b** (450 mg, 57 %). LCMS (ESI): R_T = 0.75 min, mass calcd. for $C_{18}H_{19}N_3O_2$ 309.362, m/z found 310.0 $[M+H]^+$. The compound was further purified by reverse phase HPLC (95% water containing 0.038% TFA (solvent A) and 5% acetonitrile containing 0.02% TFA (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B).

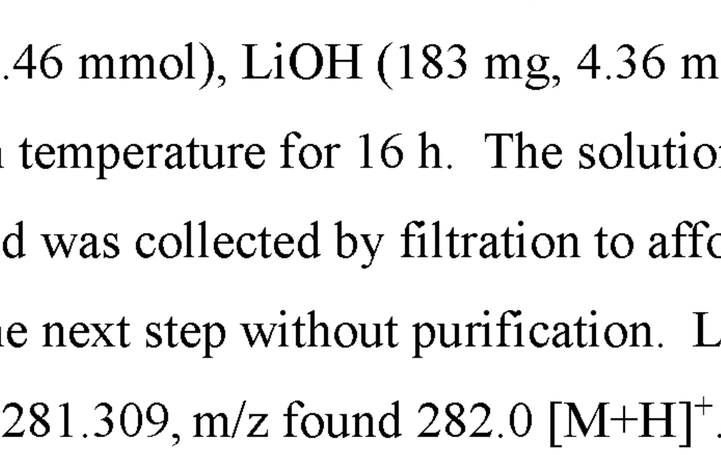
C. 5-Isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **50c**



, **50c**

A solution consisting of ethyl 5-isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **50b** (450 mg, 1.46 mmol), LiOH (183 mg, 4.36 mmol) and water: EtOH (6 mL, 1:2) was stirred at room temperature for 16 h. The solution was neutralized to pH 7 with 4 M aq. HCl, and a solid was collected by filtration to afford compound **50c** (280 mg, crude), which was used in the next step without purification. LCMS (ESI): R_T = 0.62 min, mass calcd. for $C_{16}H_{15}N_3O_2$ 281.309, m/z found 282.0 $[M+H]^+$.

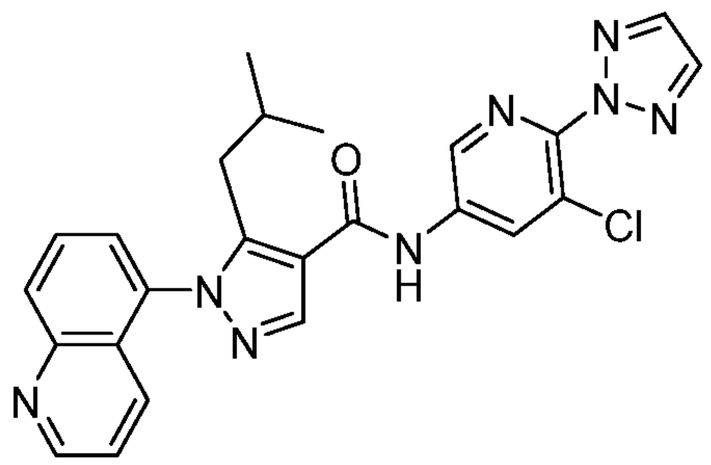
D. *N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 26**



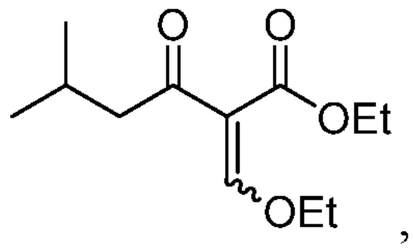
$POCl_3$ (183 mg, 1.19 mmol) was added dropwise to a solution consisting of 5-isopropyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **50c** (280 mg, 0.995 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (389 mg, 1.99 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resultant mixture was poured into sat. aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to give a crude product, which was purified by reverse phase HPLC (40% to 70% (v/v) ACN and H_2O with 0.05% NH_3) to afford pure compound **26**. Compound **26** was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **26** (48.60 mg, 10 %). LCMS (ESI): R_T = 4.79 min, mass calcd. for $C_{23}H_{19}ClN_8O$ 458.903, m/z found 459.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.70 (s, 1H), 9.04 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.91 (d, *J* = 2.8 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 1H), 8.48 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 8.18 (s, 2H), 7.99 - 7.95 (m, 1H), 7.83 - 7.82 (m, 1H), 7.64 (dd, *J* = 4.4, 8.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 3.10 - 3.00 (m, 1H), 1.28 - 1.13 (m, 6H).

Example 51

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 16**

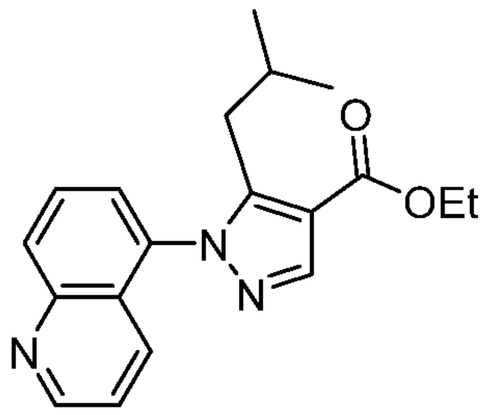


A. Ethyl 2-(ethoxymethylene)-5-methyl-3-oxohexanoate, **51a**


, **51a**

A solution consisting of ethyl 5-methyl-3-oxohexanoate (500 mg, 2.90 mmol), triethoxymethane (1.29 mg, 8.71 mmol) and Ac_2O (5 mL) was stirred at 130 °C for 16 h. The reaction was cooled to room temperature and concentrated to dryness under reduced pressure to afford crude compound **51a** (580 mg, 88 %), which was used in the following step without purification.

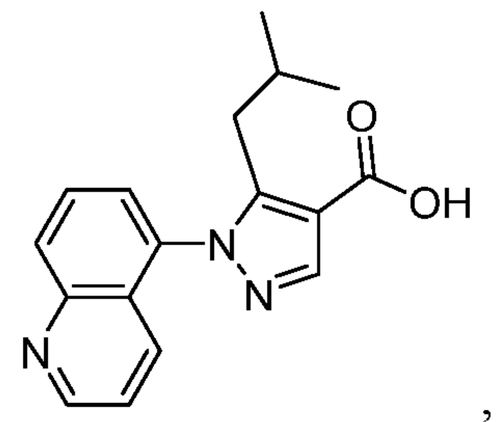
B. Ethyl 5-isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **51b**



, **51b**

A solution consisting of ethyl 2-(ethoxymethylene)-5-methyl-3-oxohexanoate, **51a** (430 mg, 1.89 mmol), 5-hydrazinylquinoline, **13a** (300 mg, 1.89 mmol) and ethanol (10 mL) was refluxed at 80 °C for 16 h before cooling to room temperature and concentrating to dryness under reduced pressure to afford crude compound **51b**, which was purified by FCC (dichloromethane: methanol = 100:0 to 95:5) to afford compound **51b** (330 mg, 54 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 - 9.15 (m, 1H), 8.49 - 8.41 (m, 1H), 8.20 (s, 1H), 8.14 - 8.06 (m, 1H), 7.97 (d, J = 6.8 Hz, 2H), 7.85 - 7.77 (m, 1H), 4.29 (d, J = 6.8 Hz, 2H), 2.74 (d, J = 7.2 Hz, 2H), 1.61 - 1.48 (m, 1H), 1.31 (t, J = 6.8 Hz, 3H), 0.70 - 0.50 (m, 6H).

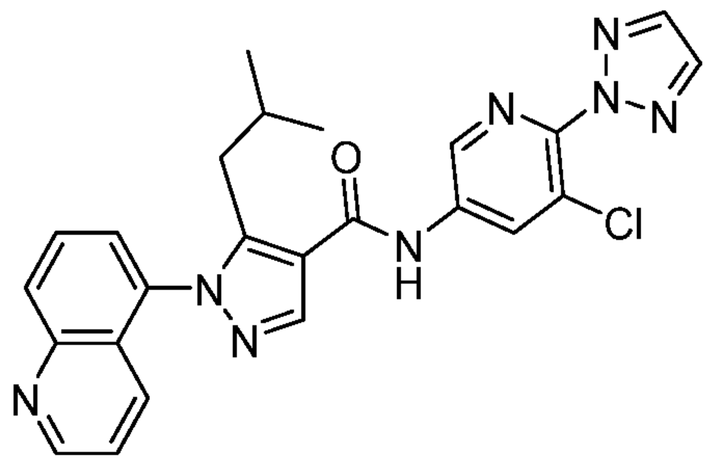
C. 5-Isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **51c**



, **51c**

A solution consisting of ethyl 5-isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **51b** (200 mg, 0.618 mmol), LiOH (77.9 mg, 1.86 mmol) and water: EtOH (6 mL, 1:2) was stirred at room temperature for 16 h. The reaction mixture was neutralized to pH 7 with 4 N aq. HCl, extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to dryness under reduced pressure to give crude compound **51c** (160 mg), which was used in the following reaction without further purification.

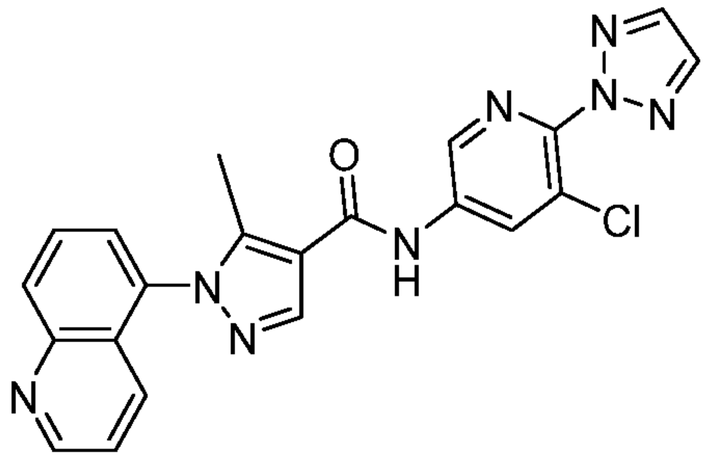
D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 16**



$POCl_3$ (74.8 mg, 0.488 mmol) was added dropwise to a solution consisting of 5-isobutyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **51c** (140 mg, 0.474 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (87.4 mg, 0.447 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resultant mixture was washed with water (20 mL), extracted with ethyl acetate (10 mL x 3), dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to give a crude product, which was purified by reverse phase HPLC (40% to 70% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **16**. Compound **16** was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to give compound **16** (24.30 mg, 11 %). LCMS (ESI): R_T = 3.66 min, mass calcd. for $C_{24}H_{21}ClN_8O$ 472.93, m/z found 473.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.63 (br.s., 1H), 9.05 - 9.02 (m, 1H), 8.91 - 8.89 (m, 1H), 8.72 - 8.71 (m, 1H), 8.55 (s, 1H), 8.30 - 8.26 (m, 1H), 8.19 (s, 2H), 7.99 - 7.93 (m, 1H), 7.85 - 7.81 (m, 1H), 7.69 - 7.61 (m, 2H), 2.85 - 2.78 (m, 2H), 1.66 - 1.57 (m, 1H), 0.62 (d, *J* = 6.0 Hz, 6H).

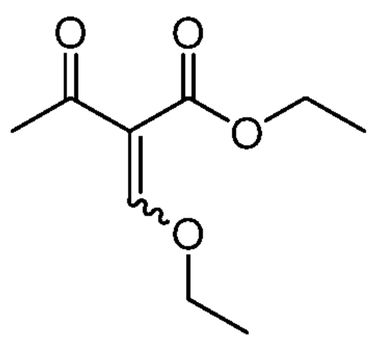
Example 52

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 39**



, **Cpd 39**

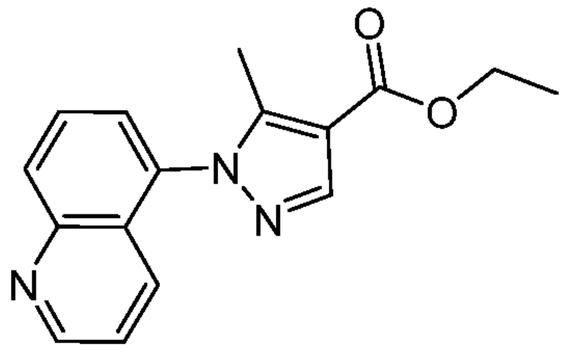
A. Ethyl 2-(ethoxymethylene)-3-oxobutanoate, **52a**



, **52a**

A solution consisting of ethyl 3-oxobutanoate (10.0 g, 76.8 mmol), triethylorthoformate (38.3 g, 230 mmol), and acetic anhydride (100 mL) was stirred at 135 °C for 18 h. The mixture was concentrated to dryness under reduced pressure to give compound **52a** (21 g, crude), which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64, 7.61 (s, 1H), 4.30 - 4.18 (m, 4H), 2.32, 3.38 (s, 3H), 1.40 - 1.27 (m, 6H).

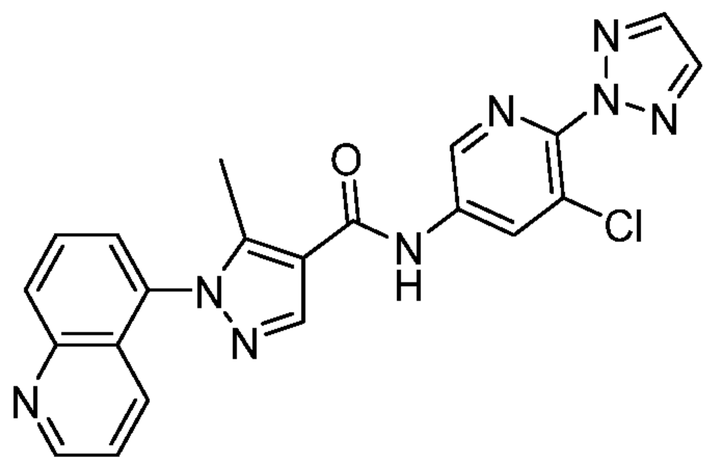
B. Ethyl 5-methyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **52b**



, **52b**

A mixture consisting of ethyl 2-(ethoxymethylene)-3-oxobutanoate, **52a** (1.50 g, 8.06 mmol), 5-hydrazinylquinoline, **13a** (1.28 g, 8.06 mmol), triethylamine (0.89 g, 8.86 mmol), and ethanol (15 mL) was stirred at 80 °C for 16 h. The mixture was concentrated to dryness under reduced pressure to give a crude residue, which was purified by FCC (petroleum ether: ethyl acetate = 2:1 to 1:2) to afford compound **52b** (520 mg, 23 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 – 8.97 (m, 1H), 8.32 – 8.27 (m, 1H), 8.16 (s, 1H), 7.83 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.44 (dd, *J* = 4.0, 8.4 Hz, 1H), 7.27 (s, 1H), 4.40 – 4.34 (m, 2H), 2.38 (s, 3H), 1.43 – 1.39 (m, 3H).

C. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)298rimethy-3-yl)-5-methyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 39**

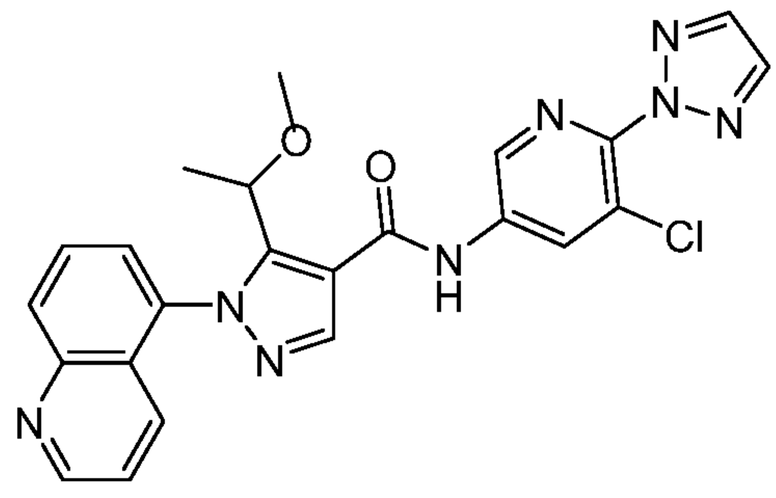


A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (194 mg, 0.990 mmol) and THF (2 mL) was added dropwise to a solution of *t*-BuOK (3.3 mL, 3.3 mmol, 1 M in THF) at 0 °C. A solution consisting of ethyl 5-methyl-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **52b** (186 mg, 0.660 mmol) and THF (2 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 16 h before quenching with water and extracting with ethyl acetate (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give crude compound **39**, which was purified by reverse phase chromatography (33% to 43% (v/v) CH_3CN and water with 0.05% NH_3) to afford pure compound **39**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **39** (61.3 mg, 22 %). LCMS (ESI): R_T = 4.16 min, mass calcd. for $C_{21}H_{15}ClN_8O$ 430.850, m/z

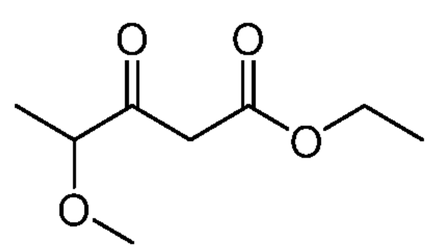
found 431.0 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.77 (d, *J* = 2.4 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.95 (s, 2H), 7.89 – 7.83 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.47 (dd, *J* = 4.4, 8.4 Hz, 1H), 2.47 (s, 3H).

Example 53

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(1-methoxyethyl)-1- (quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 35**



A. Ethyl 4-methoxy-3-oxopentanoate, **53a**

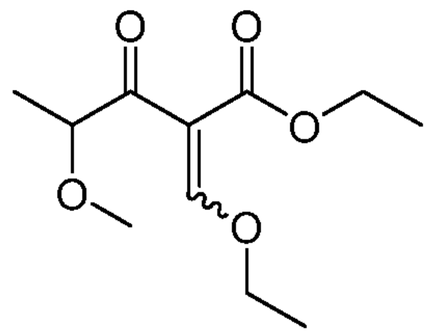


, **53a**

Bis(1*H*-imidazol-1-yl)methanone (8.57 g, 52.8 mmol) was added to a solution consisting of 2-methoxypropanoic acid (5.00 g, 48.0 mmol), and THF (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. In a separate flask, isopropylmagnesium chloride (110 mL, 144 mmol, 1.3 M in THF) was added dropwise to a solution consisting of 3-ethoxy-3-oxopropanoic acid (9.52 g, 72.0 mmol), and THF (90 mL) at 0 °C. The mixture was stirred at room temperature for 3 h. This solution was added dropwise to the acyl imidazole solution at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with aqueous citric acid (25 mL, 10 wt.%) and extracted with ethyl acetate (100 mL x 3). The combined organic extracts were washed with sat. aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered,

and concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (petroleum ether: ethyl acetate = 10 :1) to afford compound **53a** (3.6 g, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.21 – 4.19 (m, 2H), 3.86 – 3.79 (m, 1H), 3.39 – 3.38 (m, 3H), 3.36 (s, 2H), 1.29 – 1.26 (m, 6H).

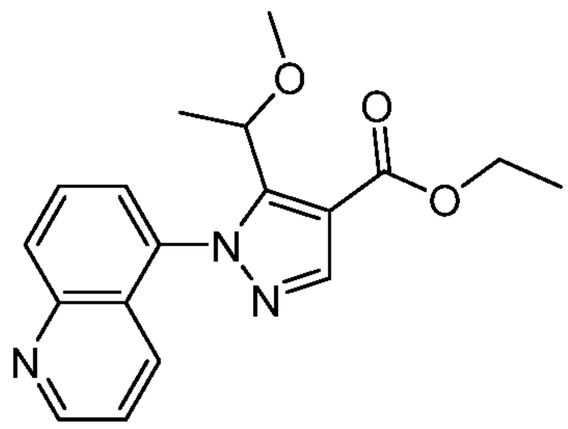
B. Ethyl 2-(ethoxymethylene)-4-methoxy-3-oxopentanoate, **53b**



, **53b**

A solution consisting of ethyl 4-methoxy-3-oxopentanoate, **53a** (3.60 g, 20.6 mmol), triethylorthoformate (9.19 g, 1.72 mmol), and acetic anhydride (30 mL) was stirred at 135 °C for 18 h. The mixture was cooled to room temperature and concentrated to dryness under reduced pressure to give compound **53b** (5.4 g), which was used in the following reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70(s, 0.5H), 7.58 (s, 0.5H), 4.30 – 4.21 (m, 4H), 3.60 (q, J = 7.2 Hz, 1H), 3.35, 3.32 (s, 3H), 1.38 – 1.29 (m, 9H).

C. Ethyl 5-(1-methoxyethyl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **53c**

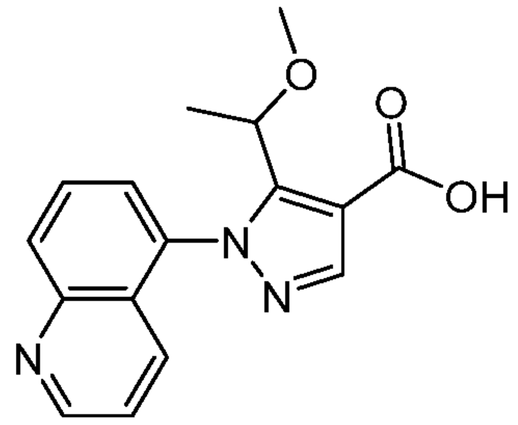


, **53c**

A mixture consisting of ethyl 2-(ethoxymethylene)-4-methoxy-3-oxopentanoate, **53b** (600 mg, 2.61 mmol), 5-hydrazinylquinoline, **13a** (414 mg, 2.61 mmol), triethylamine (290 mg, 2.87 mmol), and ethanol (12 mL) was stirred at 80 °C for 16 h. The mixture was cooled to room temperature and concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (dichloromethane: methanol = 10:1) to afford

compound **53c** (300 mg, 35 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.00 – 8.93 (m, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.17 (s, 1H), 7.80 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.65 (br d, *J* = 7.2 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.41 (dd, *J* = 4.0, 8.4 Hz, 1H), 5.29 – 5.14 (m, 1H), 4.44 – 4.32 (m, 2H), 3.33 – 2.91 (m, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.36 – 1.27 (m, 3H).

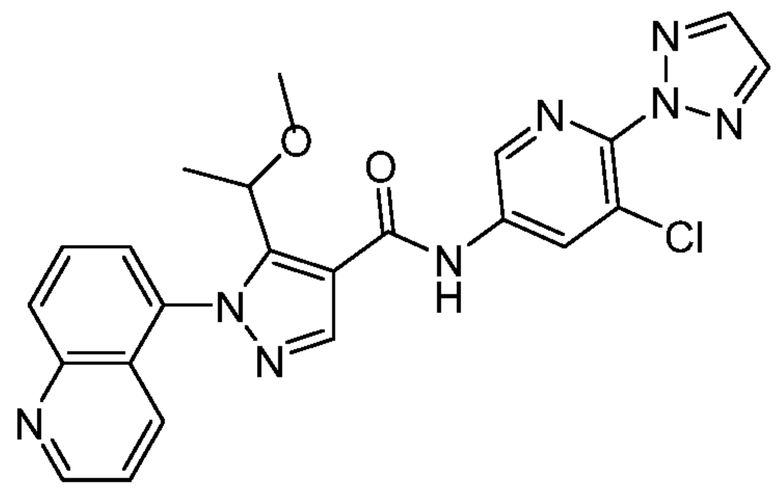
D. 5-(1-Methoxyethyl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **53d**



, **53d**

A mixture consisting of ethyl 5-(1-methoxyethyl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **53c** (265 mg, 0.840 mmol), aq. NaOH (2.44 mL, 2.44 mmol, 1 M), and ethanol (3 mL) was stirred at room temperature for 16 h. The mixture was neutralized with 1 M HCl and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford compound **53d** (120 mg, 50 %). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.97 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 1H), 7.93 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.80 (d, *J* = 6.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 4.4, 8.4 Hz, 1H), 5.36 - 5.24 (m, 1H), 3.32 (s, 3H), 1.37 - 1.29 (m, 3H).

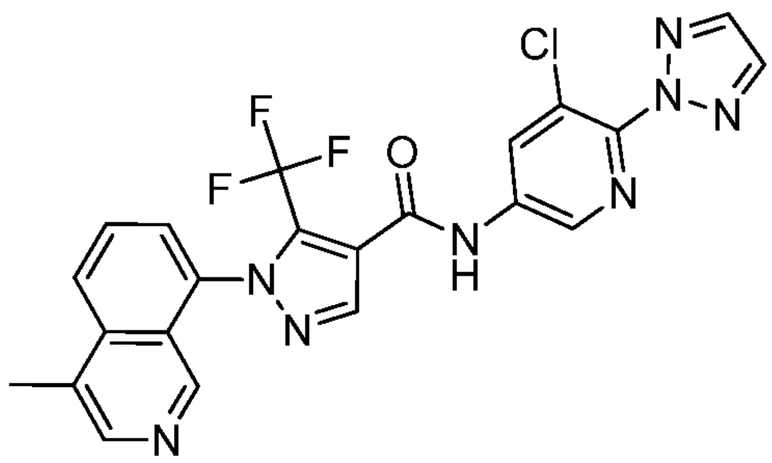
E. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(1-methoxyethyl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 35**



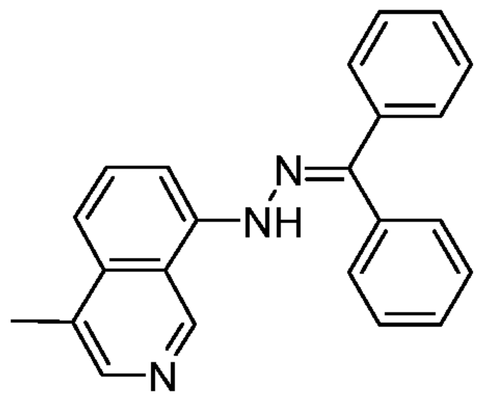
$POCl_3$ (0.1 mL) was added to a mixture consisting of 5-(1-methoxyethyl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylic acid, **53d** (120 mg, 0.40 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (78.95 mg, 0.40 mmol), and pyridine (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h before quenching with aq. $NaHCO_3$. The mixture was extracted with ethyl acetate (50 mL x 3), and the combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford a residue, which was purified by reverse phase HPLC (16% to 46% (v/v) CH_3CN and water with 0.05% NH_4HCO_3) to afford pure compound **35**. Compound **35** was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **35** (29.1 mg, 15 %). LCMS (ESI): R_T = 4.61 min, mass calcd. for $C_{23}H_{19}ClN_8O_2$ 474.902, m/z found 475.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.72(s, 0.5H), 10.68(s, 0.5H), 9.08 - 9.01 (m, 1H), 8.79 - 8.78 (m, 1H), 8.50 (dd, *J* = 2.0, 7.6 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 0.5H), 8.37 (s, 0.5H), 7.94 (s, 2H), 7.92 - 7.84 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 0.5H), 7.67 (d, *J* = 7.2 Hz, 0.5H), 7.55 - 7.46 (m, 2H), 4.41 (q, *J* = 6.4 Hz, 0.5H), 4.30 (q, *J* = 6.4 Hz, 0.6H), 3.54 (s, 1.4H), 3.25 (s, 1.7H), 1.68 (d, *J* = 6.8 Hz, 1.6H), 1.42 (d, *J* = 6.8 Hz, 1.4H).

Example 54

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 33**



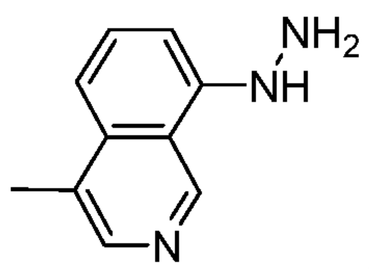
A. 8-(2-(Diphenylmethylene)hydrazinyl)-4-methylisoquinoline, **54a**



, **54a**

Palladium diacetate (30.3 mg, 0.135 mmol) and Binap (84.1 mg, 0.135 mmol) were added to a solution consisting of 8-bromo-4-methylisoquinoline (300 mg, 1.35 mmol), (diphenylmethylene)hydrazine (265 mg, 1.35 mmol), sodium *tert*-butoxide (389 mg, 4.05 mmol), and 1,4-dioxane (5 mL). The mixture was heated at 100 °C for 16 h before cooling to room temperature. The resultant mixture was filtered, and the filtrate concentrated under reduced pressure to give crude compound **54a**, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to afford compound **54a** (250 mg, 55 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 9.41 (s, 1H), 8.40 (s, 1H), 8.14 - 8.08 (m, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.70 - 7.63 (m, 4H), 7.59 - 7.55 (m, 2H), 7.54 - 7.50 (m, 2H), 7.44 - 7.42 (m, 3H), 2.67 (s, 3H).

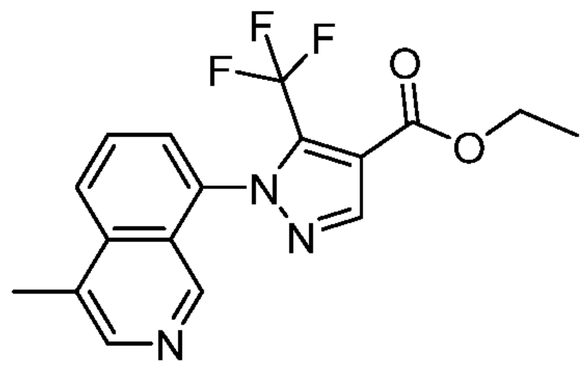
B. 8-Hydrazinyl-4-methylisoquinoline, **54b**



, **54b**

A solution consisting of 8-(2-(diphenylmethylene)hydrazinyl)-4-methylisoquinoline, **54a** (250 mg, 0.741 mmol), conc. HCl (4 mL) and EtOH (2 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with water (10 mL), and washed with dichloromethane (20 mL). The mixture was concentrated under reduced pressure to give crude compound **54b** (180 mg, crude), which was used in the following reaction without further purification.

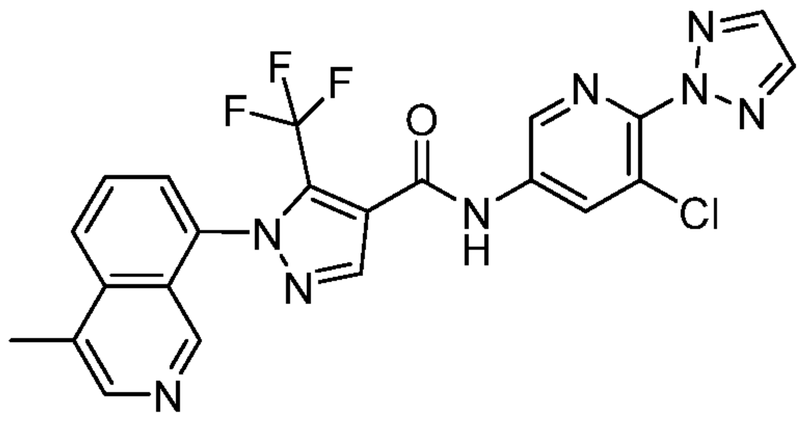
C. Ethyl 1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **54c**



, **54c**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (150 mg, 0.650 mmol), 8-hydrazinyl-4-methylisoquinoline, **54b** (160 mg, 0.650 mmol), triethylamine (132 mg, 1.30 mmol), and ethanol (5 mL) was stirred at 80 °C for 16 h before cooling to room temperature and concentrating to dryness under reduced pressure to afford crude compound **54c**, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to give compound **54c** (110 mg, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.54 (s, 1H), 8.27 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.82 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.69 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

D. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 33**

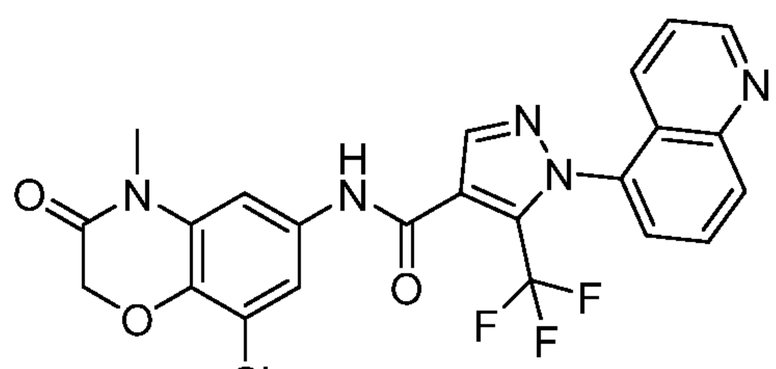


A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (56.0 mg, 0.286 mmol) and THF (1 mL) were added to potassium *tert*-butoxide (0.8 mL, 0.8 mmol, 1 M in THF) at 0 °C, then a solution consisting of ethyl 1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **54c** (100 mg, 0.286 mmol) and THF (1 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The

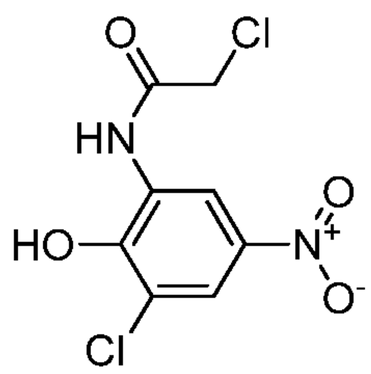
reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative high performance liquid chromatography using Phenomenex Gemini 150 x 25 mm x 5 μm (45% to 75% (v/v) ACN and water with 0.05% NH_3) to afford pure compound **33**. The product was suspended in water (10 mL), the mixture frozen using dry ice/acetone, and then lyophilized to dryness to afford compound **33** (31.50 mg, 22 %). LCMS (ESI): R_T = 4.46 min, mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.848, m/z found 499.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J = 2.4 Hz, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.58 (s, 1H), 8.55 (s, 1H), 8.45 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.19 (s, 2H), 8.06 - 7.96 (m, 2H), 2.71 (s, 3H).

Example 55

N-(8-Chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 95**



A. 2-Chloro-*N*-(3-chloro-2-hydroxy-5-nitrophenyl)acetamide, **55a**

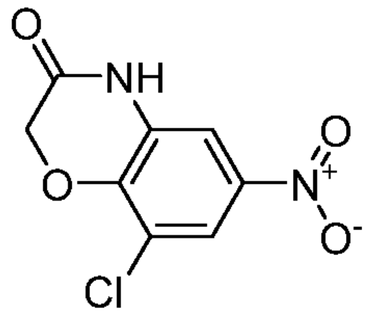


, **55a**

Chloroacetyl chloride (1.98 g, 17.5 mmol) was added to a solution of 2-amino-6-chloro-4-nitrophenol (3.0 g, 15.9 mmol), triethylamine (3.2 g, 31.8 mmol) in dichloromethane (30 mL). The mixture was stirred at rt for 3 h. Water (50 mL) and dichloromethane (50 mL) were added to the mixture. The organic layer was partitioned and washed with brine (50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated

under reduced pressure to afford compound **55a** as a yellow oil (4.0 g, 94.9 %), which was used in the following reaction without further purification.

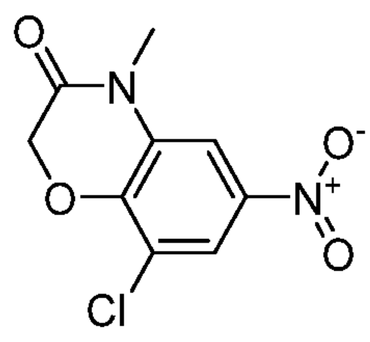
B. 8-Chloro-6-nitro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55b**



, **55b**

Sodium methoxide (896.8 mg, 16.6 mmol) was added to a solution of 2-chloro-*N*-(3-chloro-2-hydroxy-5-nitrophenyl)acetamide, **55a** (4.0 g, 15.1 mmol) in methanol (40 mL). The mixture was stirred at 80 °C for 16 h. Water (150 mL) and dichloromethane (100 mL) were added to the mixture. The organic layer was partitioned, washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford compound **55b** as a yellow oil. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/ ethyl acetate=1:1) to afford compound **55b** as a yellow solid (2.5 g, 73 %). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 4.84 (s, 2 H), 7.72 (d, J=2.65 Hz, 1 H), 7.98 (d, J=2.65 Hz, 1 H).

C. 8-Chloro-4-methyl-6-nitro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55c**

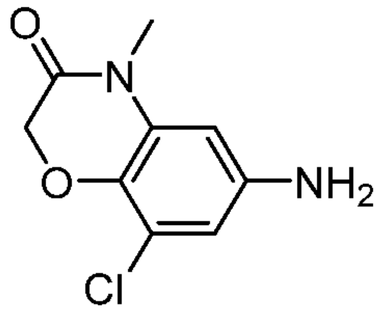


, **55c**

Iodomethane (931 mg, 6.56 mmol) was added to a mixture of 8-chloro-6-nitro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55b** (500 mg, 2.19 mmol) and potassium carbonate (1.51 g, 10.94 mmol) in DMF (5 mL). The mixture was stirred at 25 °C for 18 h. The solvent was concentrated under reduced pressure. A crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=10:1 to petroleum ether/

ethyl acetate=1:1) to afford compound **55c** as a white solid (0.3 g, 56.5 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.44 (s, 3 H), 4.85 (s, 2 H), 7.78 (d, J=2.51 Hz, 1 H), 8.04 (d, J=2.51 Hz, 1 H).

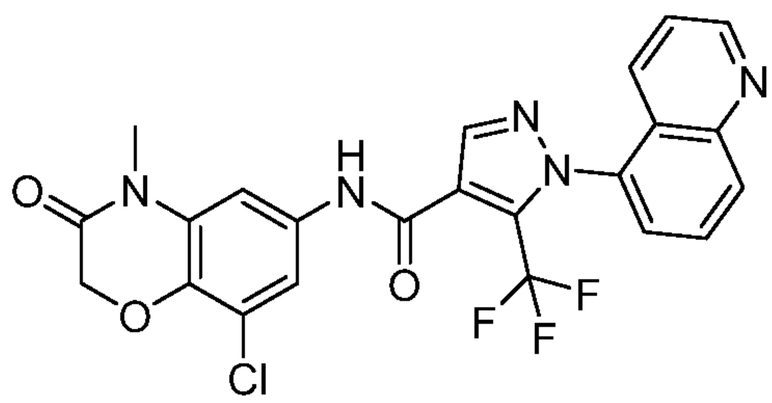
D. 6-Amino-8-chloro-4-methyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55d**



, **55d**

Zinc (804 mg, 12.37 mmol) was added to a solution of 8-chloro-4-methyl-6-nitro-2H-benzo[b][1,4]oxazin-3(4*H*)-one, **55c** (300 mg, 1.24 mmol) in aqueous NH_4Cl (2 mL) and methanol (2 mL). The mixture was stirred at rt for 16 h. To the suspension was added aqueous $NaHCO_3$ to adjust the pH to 9-10, and the mixture was filtered though a pad of diatomaceous earth. The filter cake was washed with dichloromethane (30 mL x 3). The combined filtrates were washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford compound **55d** as a brown solid. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=2:1 to petroleum ether/ ethyl acetate=0:1) to afford compound **55d** as a yellow solid (200 mg, 76.1 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.31 (s, 3 H), 4.61 (s, 2 H), 6.23 (d, J=2.43 Hz, 1 H), 6.42 (d, J=2.43 Hz, 1 H).

E. *N*-(8-Chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 95**

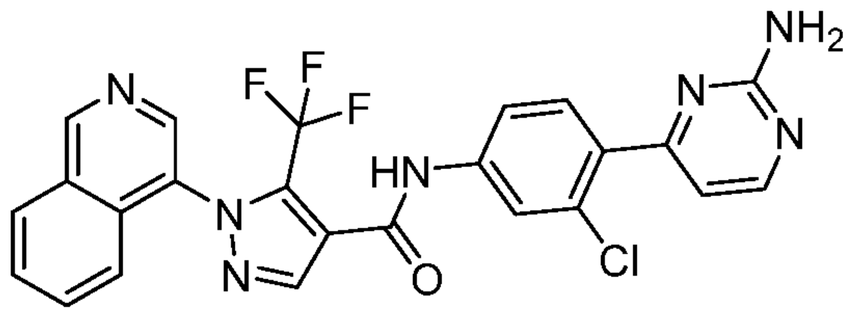


1-(Quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (120 mg, 0.39 mmol), 6-amino-8-chloro-4-methyl-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55d** (100

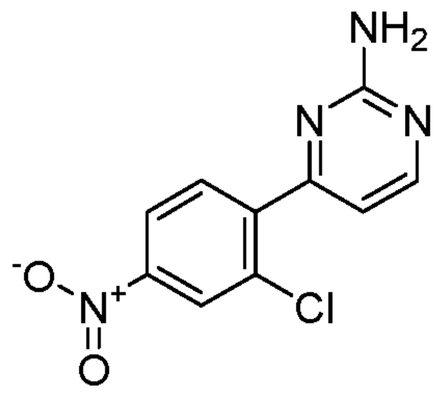
mg, 0.47 mmol), and HATU (223 mg, 0.59 mmol) were dissolved in DIPEA (253 mg, 1.96 mmol) and DMF (2 mL). The mixture was stirred at 25 °C for 3 h. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford compound **95** as a crude brown oil. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (70%/30% to 40%/60 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **95** as a pale white solid (139 mg, 71 %). LCMS (ESI): m/z 501.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.27 (s, 3 H), 4.77 (s, 2 H), 7.47 (s, 1 H), 7.57 - 7.63 (m, 1 H), 7.64 - 7.70 (m, 2 H), 7.87 - 7.92 (m, 1 H), 7.93 - 7.99 (m, 1 H), 8.31 (d, J=8.60 Hz, 1 H), 8.50 (s, 1 H), 9.04 (d, J=2.65 Hz, 1 H), 10.74 (s, 1 H).

Example 56

N-(4-(2-Aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 58**



A. 4-(2-Chloro-4-nitrophenyl)pyrimidin-2-amine, **56a**

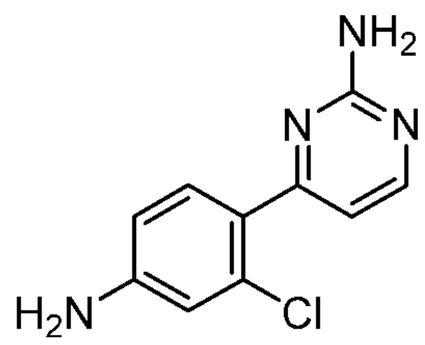


, **56a**

A mixture of 2-(2-chloro-4-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (250 mg, 0.882 mmol), 2-amino-4-chloropyrimidine (126 mg, 0.97 mmol) and cesium carbonate (862 mg, 2.65 mmol) in dioxane/water (4:1) was stirred at rt. $Pd(PPh_3)_2Cl_2$ was

added under N_2 at rt. The reaction mixture was stirred at 80 °C overnight. The mixture was filtered though a pad of diatomaceous earth and the filter cake was washed with ethyl acetate (50 mL). The filtrate was washed with water (10 mL). The organic layer was separated and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 0/100) to afford compound **56a** as a yellow solid (155 mg, 70 %). LCMS (ESI): m/z 250.9 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 5.17 (br s, 2 H), 6.99 (d, J=5.07 Hz, 1 H), 7.78 (d, J=8.38 Hz, 1 H), 8.21 (dd, J=8.49, 2.09 Hz, 1 H), 8.36 (d, J=2.20 Hz, 1 H), 8.43 (d, J=5.07 Hz, 1 H).

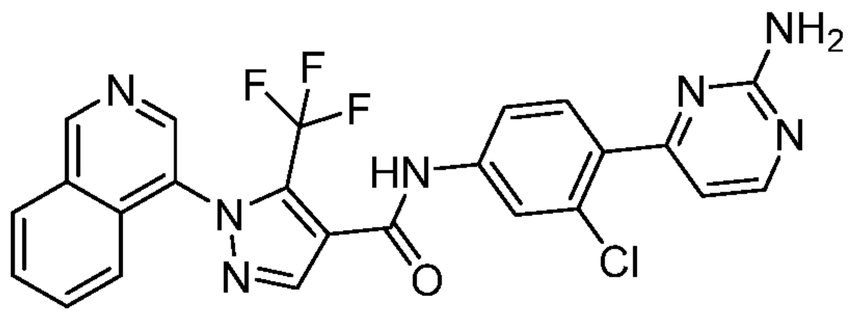
B. 4-(4-Amino-2-chlorophenyl)pyrimidin-2-amine, **56b**



, **56b**

4-(2-Chloro-4-nitrophenyl)pyrimidin-2-amine, **56a** (132 mg, 0.53 mmol), Fe(0) (294 mg, 5.27 mmol) , and NH_4Cl (282, 5.27 mmol) were added to a mixture of THF (5 mL) and water (1 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with ethyl acetate (20 mL x 3). The combined filtrates were concentrated to dryness to give crude compound **56b** as a yellow solid. The crude compound was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 50/50 to 0/100) to afford compound **56b** as a yellow solid (85 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.76 - 3.88 (m, 2 H), 4.98 (br s, 2 H), 6.57 (dd, J=8.27, 2.32 Hz, 1 H), 6.68 (d, J=2.21 Hz, 1 H), 6.96 (d, J=5.07 Hz, 1 H), 7.41 (d, J=8.38 Hz, 1 H), 8.22 (d, J=5.29 Hz, 1 H).

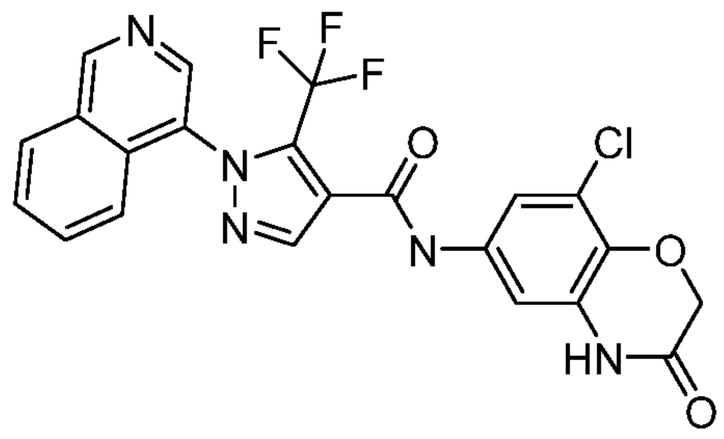
C. *N*-(4-(2-Aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 58**



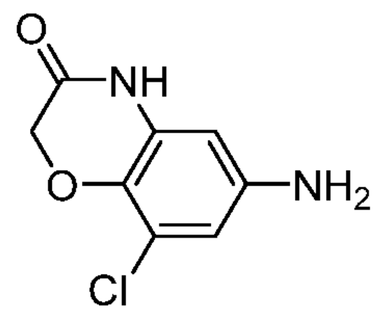
4-(4-Amino-2-chlorophenyl)pyrimidin-2-amine, **56b** (80 mg, 0.36 mmol), 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (111 mg, 0.36 mmol), and HATU (207 mg, 0.54 mmol) were dissolved in triethylamine (234 mg, 1.81 mmol) and DMF (2 mL). The mixture was stirred at 25 °C for 3 h. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford crude compound **58** as a yellow oil. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (82%/18% to 52%/48 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **58** as a pale white solid (20.1 mg, 11 %). LCMS (ESI): m/z 510.0 $(M+H)^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 7.46 (d, J=6.61 Hz, 1 H), 7.57 (d, J=8.60 Hz, 1 H), 7.83 - 7.89 (m, 2 H), 8.02 - 8.07 (m, 1 H), 8.12 - 8.19 (m, 2 H), 8.39 (d, J=6.62 Hz, 1 H), 8.46 (s, 1 H), 8.55 (d, J=8.38 Hz, 1 H), 8.91 (s, 1 H), 9.83 (s, 1 H).

Example 57

N-(8-Chloro-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 87**



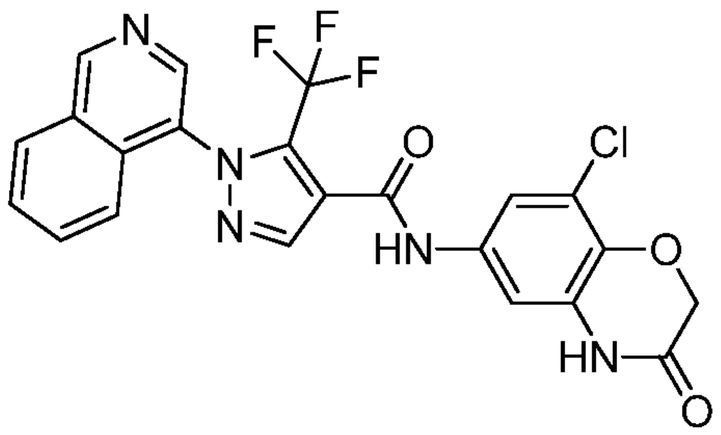
A. 6-Amino-8-chloro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **57a**



, **57a**

Zinc (0) (426.5 mg, 6.56 mmol) was added to a solution of 8-chloro-6-nitro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **55b** (150 mg, 0.66 mmol) in aqueous NH_4Cl (2 mL) and MeOH (2 mL). The mixture was stirred at rt for 16 h. To the suspension was added aqueous $NaHCO_3$ to adjust the pH to 9-10, and the mixture was filtered though a pad of diatomaceous earth. The filter cake was washed with dichloromethane (30 mL x 3). The combined filtrates were washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford compound **57a** as a brown solid. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=2:1 to petroleum ether/ ethyl acetate=0:1) to afford compound **57a** as a yellow solid (90 mg, 69.1 %). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.57 (br s, 2 H), 4.61 (s, 2 H), 6.05 (d, J=2.43 Hz, 1 H), 6.39 (d, J=2.43 Hz, 1 H), 7.90 - 8.05 (m, 1 H).

B. *N*-(8-Chloro-3-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 87**

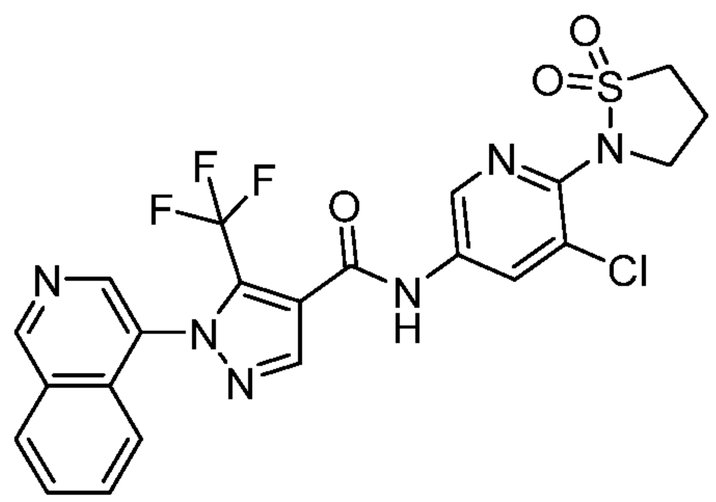


1-(Isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (100 mg, 0.29 mmol), 6-amino-8-chloro-2*H*-benzo[b][1,4]oxazin-3(4*H*)-one, **57a** (57.1 mg, 0.29 mmol), HATU (164.1 mg, 0.43 mmol) and DIEA (185.9 mg, 1.44 mmol) were dissolved in DMF (2 mL). The mixture was stirred at 25 °C for 3 h. Sat. aqueous NH_4Cl (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The

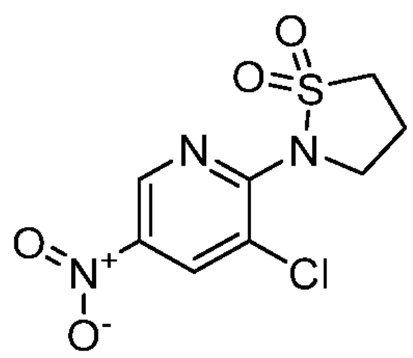
combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford crude compound **87** as a yellow oil. The crude product was purified by reverse phase HPLC (A: water (0.05% HCl), B: MeCN; then: A/B (95%/5% to 65%/35 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **87** as a pale white solid (54 mg, 38 %). LCMS (ESI): m/z 487.9 $(M+H)^+$. ^1H NMR (400 MHz, METHANOL-d_4) δ ppm 4.68 (s, 2 H), 7.36 (d, J=2.21 Hz, 1 H), 7.43 (d, J=2.43 Hz, 1 H), 7.55 (d, J=8.38 Hz, 1 H), 8.00 - 8.08 (m, 1 H), 8.11 - 8.19 (m, 1 H), 8.37 (s, 1 H), 8.54 (d, J=8.16 Hz, 1 H), 8.90 (s, 1 H), 9.82 (s, 1 H).

Example 58

N-(5-Chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 42**



A. 2-(3-Chloro-5-nitropyridin-2-yl)isothiazolidine 1,1-dioxide, **58a**

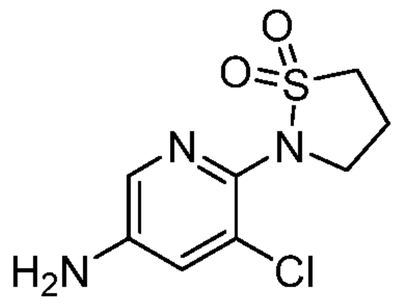


, **58a**

(1*S*,2*S*)-N1,N2-Dimethylcyclohexane-1,2-diamine (46.1 mg, 0.30 mmol) and copper iodide (56.3 mg, 0.30 mmol) were added to a mixture of 2,3-dichloro-5-nitropyridine (571 mg, 2.96 mmol), isothiazolidine 1,1-dioxide (430 mg, 3.55 mmol) and potassium carbonate (817.5 mg, 5.92 mmol) in dioxane (6 mL) under N_2. The reaction

mixture was stirred at 100 °C for 16 h. The mixture was filtered, and the filtrate was extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=50:50) to afford compound **58a** as a white solid (600 mg, 73 %).

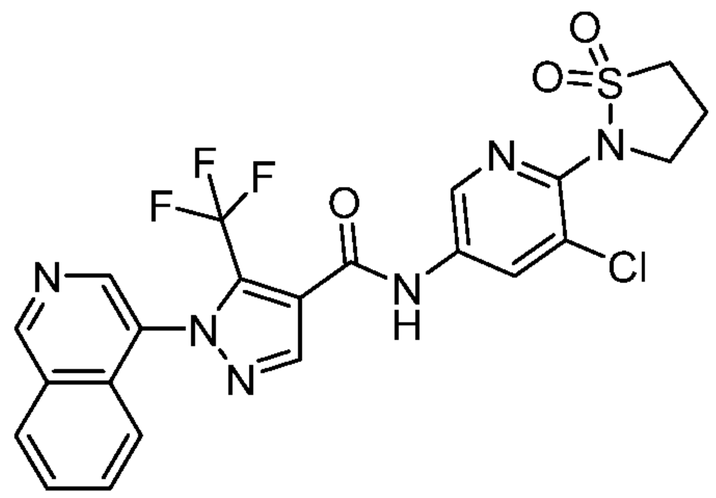
B. 2-(5-Amino-3-chloropyridin-2-yl)isothiazolidine 1,1-dioxide, **58b**



, **58b**

2-(3-Chloro-5-nitropyridin-2-yl)isothiazolidine 1,1-dioxide, **58a** (600 mg, 2.12 mmol), Fe(0) (967 mg, 17.29 mmol) , and NH_4Cl (925 mg, 17.29 mmol) were added to a mixture of THF (6 mL), MeOH (3 mL), and water (1.5 mL). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was filtered though a pad of diatomaceous earth, and the pad was washed with ethyl acetate (20 mL x 3). The combined filtrates were concentrated to dryness to give crude compound **58b** as a yellow oil (530 mg, 99 %).

C. *N*-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 42**

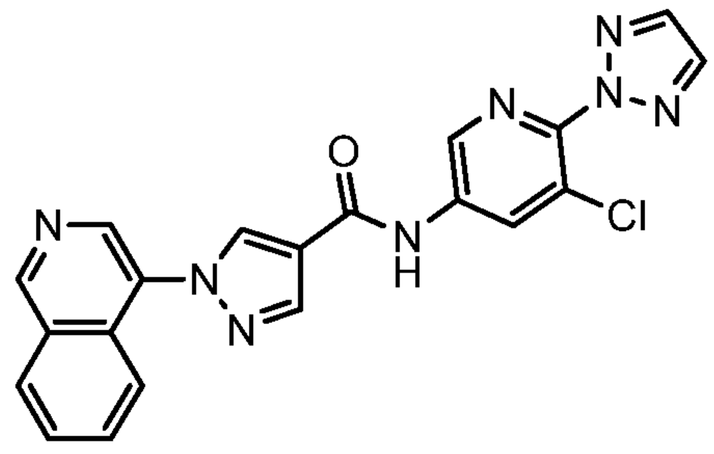


Phosphoryl trichloride (0.052 mL, 0.57 mmol) was added to a solution of 1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **4c** (60 mg, 0.19 mmol), 2-(5-amino-3-chloropyridin-2-yl)isothiazolidine 1,1-dioxide, **58b** (60.6 mg, 0.245 mmol), and pyridine (0.091 mL, 1.13 mmol) in dichloromethane at room temperature. The

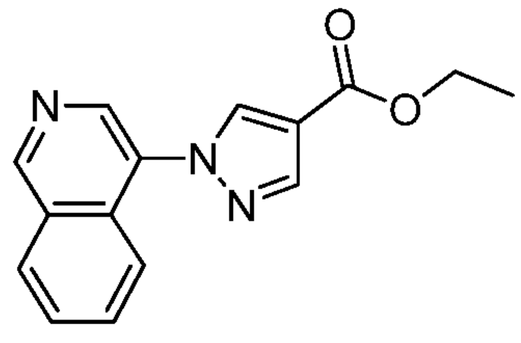
mixture was stirred for 2 h. The mixture was poured into water (10 mL), and the mixture was extracted with dichloromethane (20 mL x 2). The separated organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated under reduced pressure to afford a crude product. The crude product was purified by reverse phase HPLC (0.05% ammonia hydroxide v/v); B: MeCN; then: A/B (65%/35% to 35%/65 %). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **42** as a white solid (35.6 mg, 35 %). LCMS (ESI): m/z 536.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.53 - 2.60 (m, 2 H), 3.19 (br t, J=7.50 Hz, 2 H), 4.05 (br t, J=6.84 Hz, 2 H), 7.29 (br d, J=7.94 Hz, 1 H), 7.73 (dt, J=13.40, 6.64 Hz, 2 H), 7.94 (br s, 1 H), 8.09 (br d, J=8.16 Hz, 1 H), 8.19 (s, 1 H), 8.29 (br s, 1 H), 8.44 (br s, 1 H), 8.55 (s, 1 H), 9.38 (s, 1 H).

Example 59

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-1H-pyrazole-4-carboxamide, **Cpd 76**



A. Ethyl 1-(isoquinolin-4-yl)-1*H*-pyrazole-4-carboxylate, **59a**

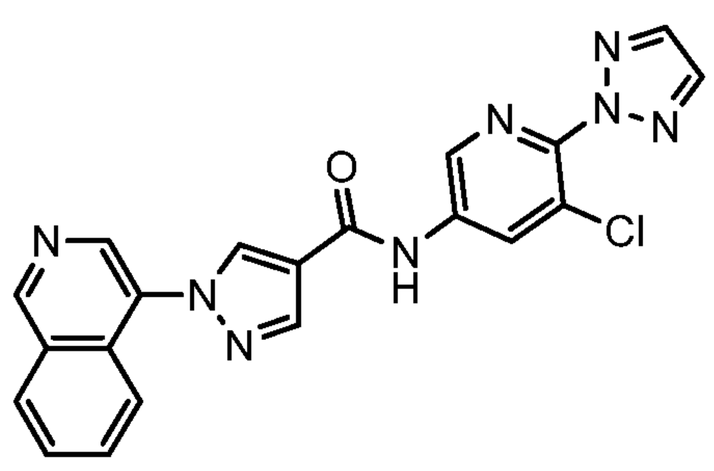


, **59a**

A solution consisting of ethyl 2-formyl-3-oxopropanoate (90.5 mg, 0.628 mmol), 4-hydrazinylisoquinoline, **4a** (100 mg, 0.628 mmol) and 2-propanol (2 mL) was stirred at 80 °C overnight before cooling to room temperature and concentrating to dryness under reduced pressure to give the crude product, which was purified by FCC (petroleum ether:

ethyl acetate = 100:0 to 80:20) to give compound **59a** (140 mg, 84 %). LCMS (ESI): R_T = 0.70 min, mass calcd. for $C_{15}H_{13}N_3O_2$ 267.283, m/z found 268.0 $[M+H]^+$.

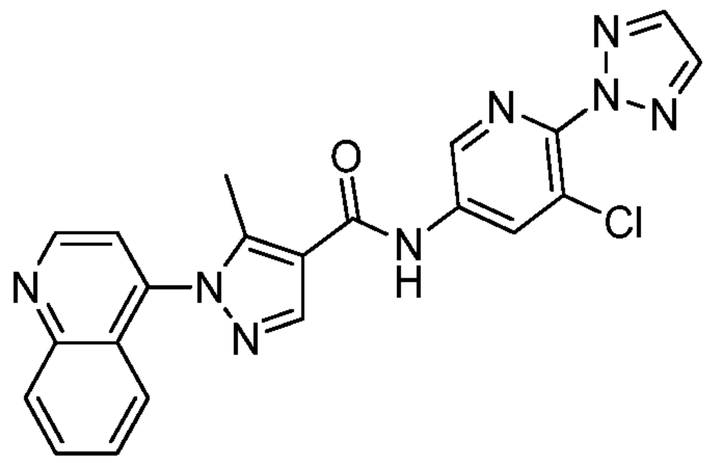
B. N-(5-Chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-1H-pyrazole-4-carboxamide, **Cpd 76**



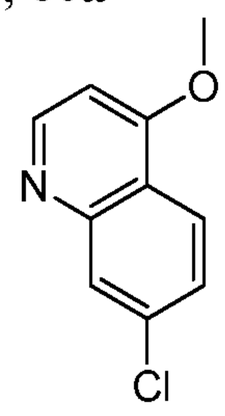
A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (87.8 mg, 0.449 mmol) and THF (1 mL) were added to 1 M potassium *tert*-butoxide in THF (1.35 mL, 1.35 mmol) at 0 °C, then a solution consisting of ethyl 1-(isoquinolin-4-yl)-1*H*-pyrazole-4-carboxylate, **59a** (120 mg, 0.449 mmol) and THF (1 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) ACN and H_2O with 0.05% NH_3). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **76** (69.3 mg, 36 %). LCMS (ESI): R_T = 4.36 min, mass calcd. for $C_{20}H_{13}ClN_8O$ 416.823, m/z found 416.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.74 (br.s., 1H), 9.52 (s, 1H), 9.01 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.76 (s, 1H), 8.70 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.19 (s, 2H), 7.98 - 7.92 (m, 2H), 7.89 - 7.84 (m, 1H).

Example 60

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 64**



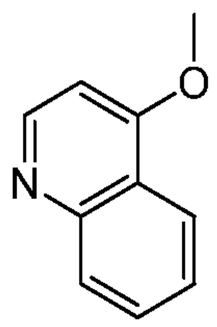
A. 7-Chloro-4-methoxyquinoline, **60a**



, **60a**

4,7-Dichloroquinoline (6.00 g, 30.3 mmol) was added portionwise to a solution consisting of sodium methoxide (1.80 g, 33.3 mmol) and methanol (60 mL) at room temperature. The mixture was stirred at 80 °C for 12 h before quenching with water and extracting with ethyl acetate (200 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (petroleum ether: ethyl acetate = 2:1 to 1:2) to afford compound **60a** (4.1 g, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.73 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 8.8Hz, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.71 (d, *J* = 5.2 Hz, 1H), 4.03 (s, 3H).

B. 4-Methoxyquinoline, **60b**

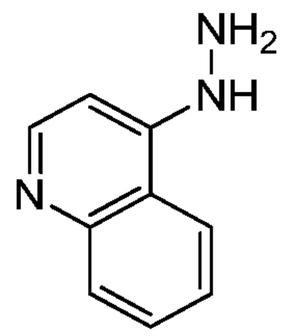


, **60b**

A mixture consisting of 7-chloro-4-methoxyquinoline, **60a** (4.10 g, 21.1 mmol), dry Pd/C (400 mg, 10 wt.%, 0.377 mmol), and methanol (100 mL) was stirred at room-temperature for 16 h under H_2 (15 psi). The mixture was filtered through a pad of

diatomaceous earth and the pad was washed with methanol (50 mL). The filtrate was concentrated to dryness under reduced pressure to give a residue, which was dissolved in aqueous $NaHCO_3$ (80 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 1:3) and further purified by reverse phase HPLC (10% to 40% (v/v) CH_3CN and H_2O with 0.05% NH_3). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **60b** (1.1 g, 33 %). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.2 Hz, 1H), 8.22 - 8.15 (m, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.73 - 7.65 (m, 1H), 7.51 - 7.47 (m, 1H), 6.72 (d, *J* = 5.2 Hz, 1H), 4.03 (s, 3H).

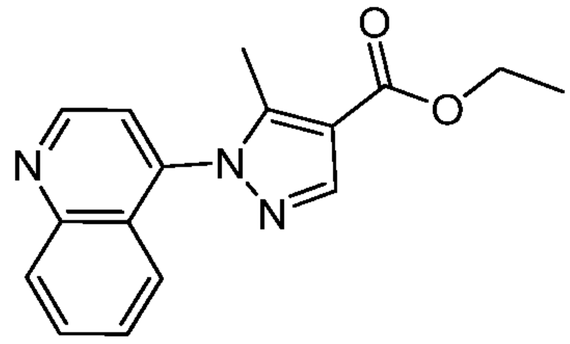
C. 4-Hydrazinylquinoline, **60c**



, **60c**

A mixture consisting of 4-methoxyquinoline, **60b** (1.00 g, 6.28 mmol), hydrazine hydrate (10 mL, 85 wt.%), and ethanol (5 mL) was refluxed for 16 h. Then the ethanol was removed under reduced pressure and the resultant aqueous mixture was filtered to afford compound **60c** (713 mg, 71 %), which was dried under reduced pressure. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.37 (d, *J* = 5.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 5.2 Hz, 1H), 4.37 (br s, 1H).

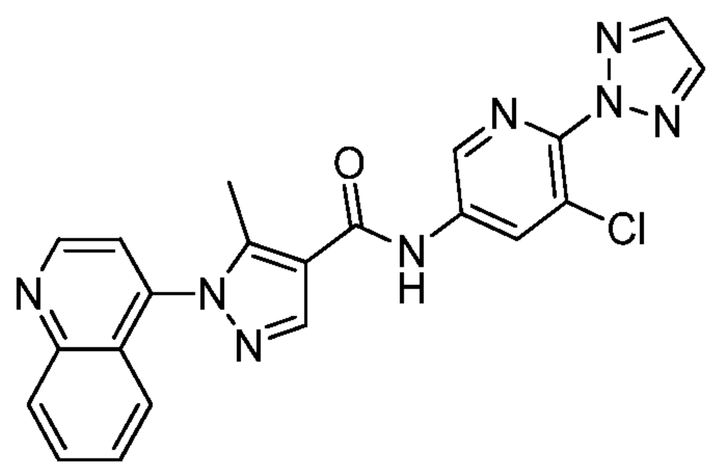
D. Ethyl 5-methyl-1-(quinolin-4-yl)-1H-pyrazole-4-carboxylate, **60d**



, **60d**

A mixture consisting of ethyl 2-(ethoxymethylene)-3-oxobutanoate, **52a** (418 mg, 2.25 mmol), 4-hydrazinylquinoline, **60c** (220 mg, 1.12 mmol), and ethanol (8 mL) was stirred at 80 °C for 16 h. The mixture was cooled to room temperature and concentrated to dryness under reduced pressure to give a residue, which was purified by FCC (petroleum ether: ethyl acetate = 2:1) to afford compound **60d** (320 mg, 51 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.08 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 7.83 - 7.79 (m, 1H), 7.61 - 7.57 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 4.4 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

E. *N*-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 64**

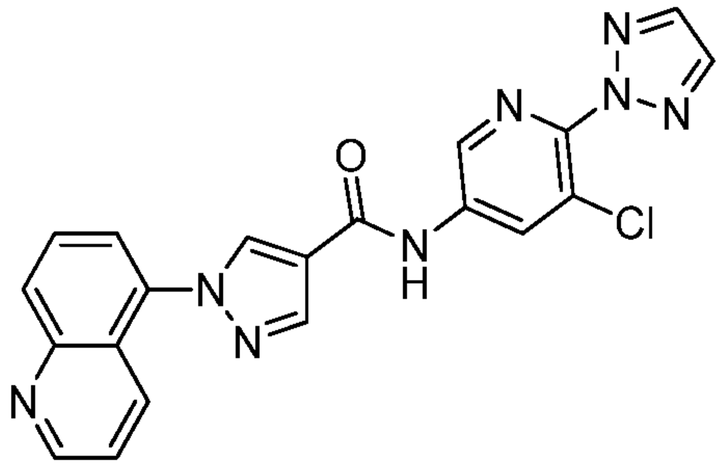


A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (229 mg, 1.17 mmol) and THF (1 mL) was added dropwise to a solution of *t*-BuOK (3.2 mL, 3.2 mmol, 1 M in THF) at 0 °C. Then a solution consisting of ethyl 5-methyl-1-(quinolin-4-yl)-1*H*-pyrazole-4-carboxylate, **60d** (300 mg, 1.07 mmol) and THF (1 mL) was added dropwise. The resultant mixture was warmed to room temperature and stirred for 16 h before quenching with water and extracting with ethyl acetate (50 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a residue, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) CH_3CN and H_2O with 0.05% NH_3). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **64** (153 mg, 33 %). LCMS (ESI): R_T = 4.52 min, mass calcd. for $C_{21}H_{15}ClN_8O$ 430.850, m/z found 431.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 9.14 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 2.4 Hz, 1H), 8.71 (d, *J* = 2.4 Hz, 1H), 8.57 (s, 1H), 8.23 (d,

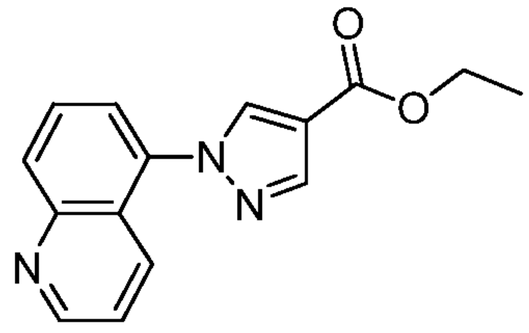
J = 8.4 Hz, 1H), 8.19 (s, 2H), 7.93 - 7.89 (m, 1H), 7.78 (d, J = 4.4 Hz, 1H), 7.73 - 7.69 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 2.45 (s, 3H).

Example 61

N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 60**



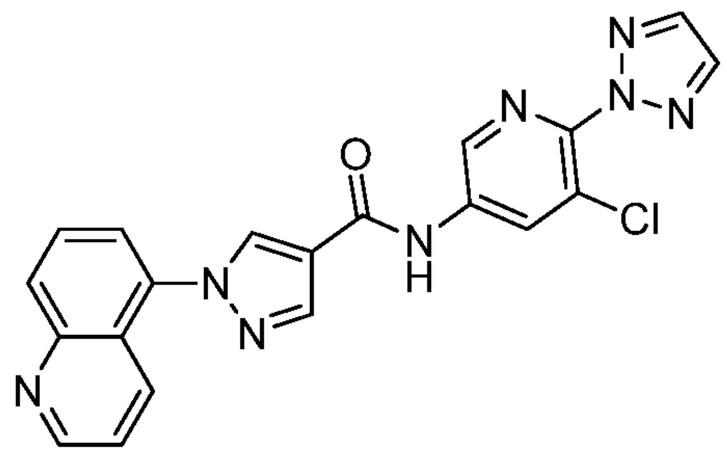
A. Ethyl 1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **61a**



, **61a**

Copper(II) acetate (1.43 g, 7.88 mmol) was added to a mixture consisting of ethyl 1*H*-pyrazole-4-carboxylate (368 mg, 2.63 mmol), quinolin-5-ylboronic acid (500 mg, 2.89 mmol), molecular sieve (4 A, 30 mg), pyridine (624 mg, 7.88 mmol), pyridine 1-oxide (750 mg, 7.88 mmol), and DMF (10 mL). The reaction mixture was stirred under O_2 (1 atm., balloon) at room temperature for 16 h. The suspension was filtered through a pad of diatomaceous earth and the pad was washed with ethyl acetate (100 mL). The filtrate was washed with water (100 mL x 2), dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to give compound **61a** (160 mg, 23 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 4.0 Hz, 1H), 8.32 - 8.22 (m, 4H), 7.82 - 7.78 (m, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.48 (dd, J = 4.4, 8.4 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H).

B. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 60**

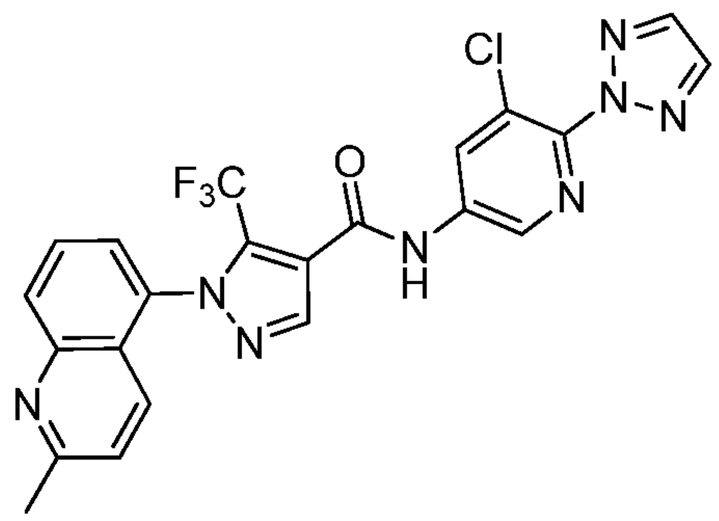


, **Cpd 60**

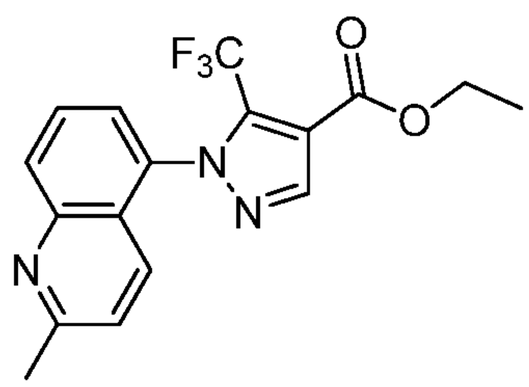
A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (102 mg, 0.524 mmol) and THF (1 mL) were added to 1 M potassium *tert*-butoxide in THF (1.57 mL, 1.57 mmol) at 0 °C, then a solution consisting of ethyl 1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **61a** (140 mg, 0.524 mmol) and THF (1 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) ACN and H_2O with 0.05% NH_3). The pure fractions were concentrated under reduced pressure and lyophilized to dryness to afford compound **60** (104.50 mg, 49 %). LCMS (ESI): R_T = 4.01 min, mass calcd. for $C_{20}H_{13}ClN_8O$ 416.823, m/z found 417.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.96 (s, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 8.50 (s, 1H), 8.33 - 8.28 (m, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 2H), 7.98 - 7.92 (m, 1H), 7.89 - 7.85 (m, 1H), 7.68 (dd, *J* = 4.0, 8.4 Hz, 1H).

Example 61

N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 37**



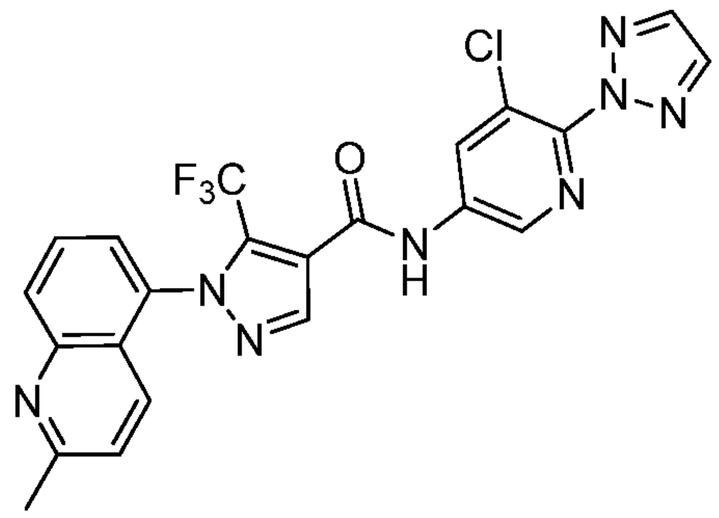
A. Ethyl 1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **61a**



, **61a**

A mixture of 5-chloro-2-methylquinoline (200 mg, 1.12 mmol), hydrazine hydrate (0.111 mL, 98 %, 2.25 mmol), palladium(II)(pi-cinnamyl) chloride dimer (16 mg, 0.030 mmol), *N*-[2-(di-1-adamantylphosphino)phenyl]morpholine (42 mg, 0.090 mmol), sodium *tert*-butoxide (216 mg, 2.25 mmol), and toluene (11 mL, 0.1 M, 1.1 mmol) was bubbled with Argon for 1 min, sealed, and stirred at 100 °C for 2.5 h before cooling to room temperature and treating with ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (270 mg, 1.13 mmol) in one portion under air. The reaction was then sealed under air and stirred at 100 °C for 40 min, then at 90 °C for another 20 h before cooling to room temperature. The mixture was filtered and concentrated under reduced pressure to give a yellow oil, which was purified by FCC (petroleum ether: ethyl acetate = 40: 60) to afford compound **61a** (210 mg, 16 %). LCMS (ESI): R_T = 0.75 min, mass calcd. for $C_{17}H_{14}F_3N_3O_2$ 349.3, m/z found 350.0 $[M+H]^+$.

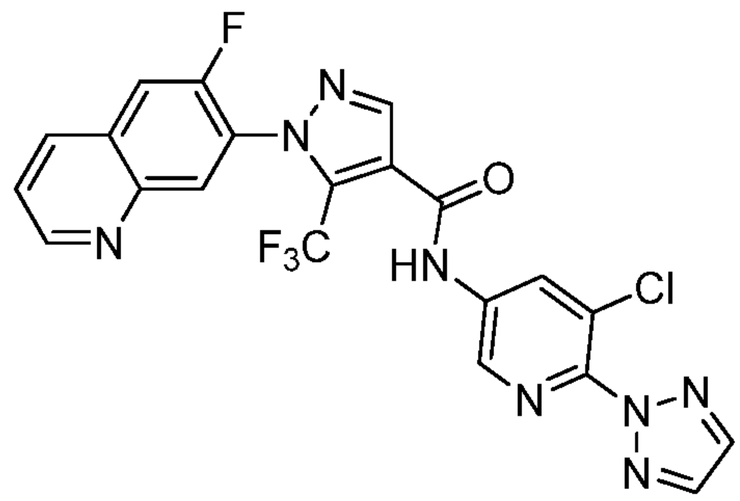
B. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 37**



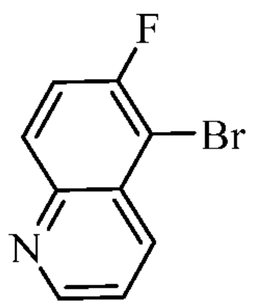
Ethyl 1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **61a** (210 mg, 0.180 mmol) in THF (1 mL) and 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (117 mg, 0.601 mmol) in THF (1 mL) were added into a suspension of potassium *tert*-butoxide (101 mg, 0.902 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at room temperature for 20 h before concentrating under reduced pressure to afford a yellow solid, which was purified by preparative reverse phase HPLC (42% to 72% (v/v) CH_3CN and H_2O with 0.05 % NH_3) from 42% to 72%, v/v) and lyophilized to afford compound **37** (12.0 mg, 13 %). LCMS (ESI): R_T = 4.34 min, mass calcd. for $C_{22}H_{14}ClF_3N_8O$ 498.093, m/z found 499.0 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6) δ 11.30 (br s, 1H), 8.86 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H), 8.58 (s, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 8.20 (s, 2H), 7.92 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.52 - 7.47 (m, 1H), 2.72 (s, 3H).

Example 62

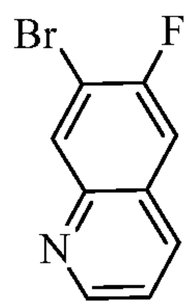
N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 67**



A. 5-Bromo-6-fluoroquinoline, **62a** and 7-Bromo-6-fluoroquinoline, **62a-1**



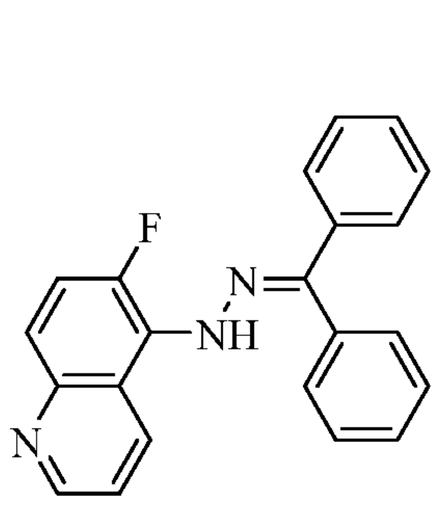
, **62a**



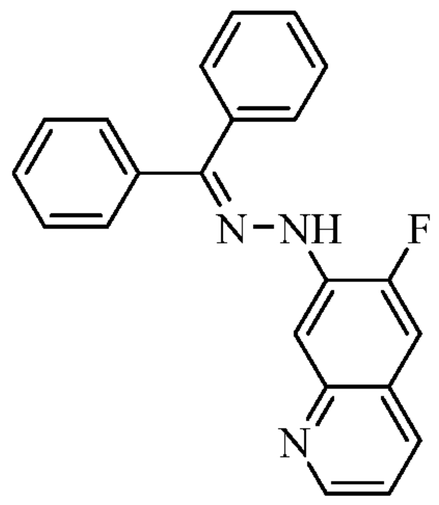
, **62a-1**

Water (11.38 mL) was added to a solution consisting of 3-bromo-4-fluoroaniline (10 g, 53 mmol), sodium 3-nitrobenzenesulfonate (21 g, 95 mmol), and propane-1,2,3-triol (14 g, 0.15 mol). The resultant mixture was carefully treated with concentrated H_2SO_4 (21.1 mL), and then heated to 150 °C with stirring for 2 h before cooling to room temperature. The resultant mixture was carefully neutralized with 5 N sodium hydroxide, filtered through a pad of diatomaceous earth, and the pad was washed with dichloromethane (50 mL). The resultant mixture was extracted with dichloromethane (100 mL x 3) and the combined organic extracts were dried over Na_2SO_4, filtered, and the filtrate concentrated to give a crude product, which was purified by FCC (petroleum ether: ethyl acetate = 3:1) to afford the compounds **62a** and **62a-1** (9.5 g, 80 %). LCMS (ESI): R_T = 0.64, 0.68 min, mass calcd. for C_9H_5BrFN 224.96, m/z found 227.6 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 - 8.87 (m, 2H), 8.55 (d, *J* = 8.8 Hz, 1H), 8.39 (d, *J* = 6.8 Hz, 1H), 8.15 - 8.07 (m, 2H), 7.60 - 7.42 (m, 4H).

B. 5-(2-(Diphenylmethylene)hydrazinyl)-6-fluoroquinoline, **62b** and 7-(2-(Diphenylmethylene)hydrazinyl)-6-fluoroquinoline, **62b-1**



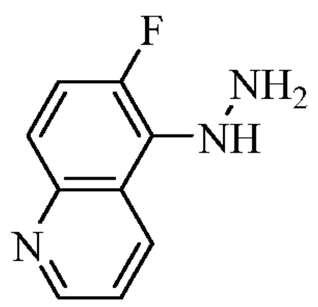
, **62b**



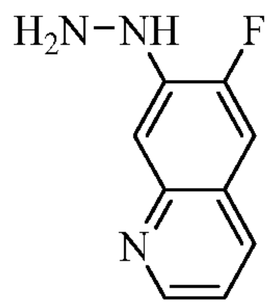
, **62b-1**

A mixture of 5-bromo-6-fluoroquinoline, **62a** and 7-bromo-6-fluoroquinoline, **62a-1** (10 g, 22 mmol), (diphenylmethylene)hydrazine (4.3 g, 22 mmol), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (1.4 g, 2.2 mmol), palladium(II) acetate (0.50 g, 2.2 mmol), *t*-BuONa (6.4 g, 66 mmol), and 1,4-dioxane (150 mL) was stirred at 100 °C for 16 h. The suspension was filtered through a pad of diatomaceous earth and the pad was washed with ethyl acetate (30 mL). The filtrate was concentrated to dryness under reduced pressure to give a crude product, which was added into water (30 mL). The resultant mixture was extracted with ethyl acetate (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 3:1) to afford compounds **62b** and **62b-1** (5 g, 33 %). LCMS (ESI): R_T = 0.68 min, mass calcd. for $C_{22}H_{16}FN_3$ 341.13, m/z found 341.9 $[M+H]^+$.

C. 6-Fluoro-5-hydrazinylquinoline, **62c** and 6-Fluoro-7-hydrazinylquinoline, **62c-1**



, **62c**

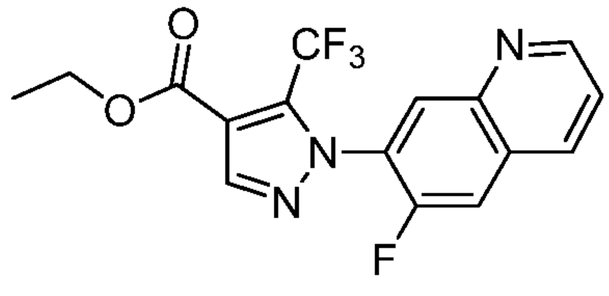


, **62c-1**

Concentrated HCl (10 mL) was added to a solution consisting of 5-(2-(diphenylmethylene)hydrazinyl)-6-fluoroquinoline, **62b** and 7-(2-(diphenylmethylene)hydrazinyl)-6-fluoroquinoline, **62b-1** (5.0 g, 7.3 mmol) and EtOH (3

mL). The resultant solution was stirred at room temperature for 16 h. The resultant mixture was treated with water (30 mL) and extracted with dichloromethane (30 mL x 3). The aqueous phase was basified with 5 M NaOH to pH 12. The suspension was filtered and the collected solids were washed with water (20 mL) and dried under reduced pressure to afford compounds **62c** and **62c-1** (1.2 g, 46 %). LCMS (ESI): R_T = 1.24 min, mass calcd. for $C_9H_8FN_3$ 177.07, m/z found 178.1 $[M+H]^+$.

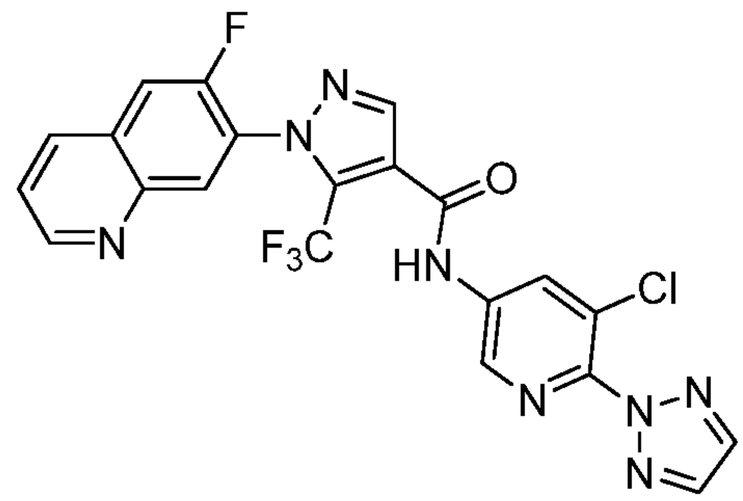
D. Ethyl 1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **62d**



, **62d**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f**(1.79 g, 7.45 mmol), 6-fluoro-5-hydrazinylquinoline and 6-fluoro-7-hydrazinylquinoline, **62c** and **62c-1**(1.10 g, 6.21 mmol), and ethanol (20 mL) was stirred at 80 °C for 16 h before cooling to room temperature. The resultant solution was concentrated to dryness under reduced pressure to afford the crude product. This was purified by FCC (eluent: petroleum ether: ethyl acetate = 3:1) to afford the title compound (1.3 g, 59%). LCMS (ESI): R_T = 3.90 min, mass calcd. for $C_{16}H_{11}F_4N_3O_2$ 353.08, m/z found 353.9 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 4.0 Hz, 1H), 8.30 - 8.18 (m, 3H), 7.65 (d, *J* = 9.7 Hz, 1H), 7.55 (dd, *J* = 4.2, 8.4 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H).

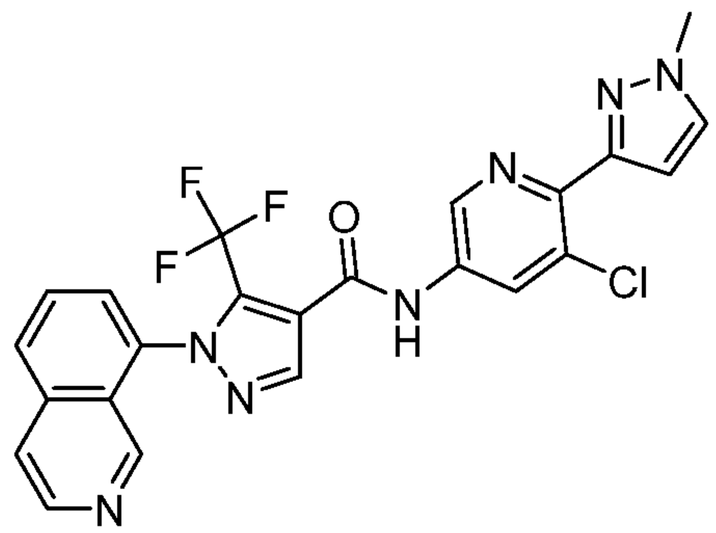
E. *N*-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 67**

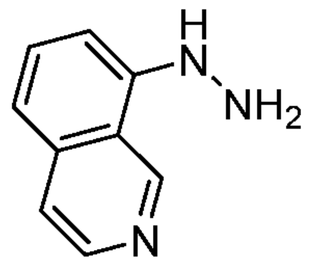


A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (249 mg, 1.27 mmol) and THF (1 mL), and a solution consisting of ethyl 1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **62d** (300 mg, 0.849 mmol) and THF (1 mL) were added to a solution consisting of potassium *tert*-butoxide (2.55 mL, 2.55 mmol, 1 M in THF) at 0 °C. The resultant mixture was stirred at room temperature for 16 h. The resultant mixture was added water (5 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford a crude product, which was purified by preparative reverse phase HPLC (35% to 55% (v/v) CH_3CN and H_2O with 10 mM NH_4HCO_3) and lyophilized to afford compound **67** (70.7 mg, 17 %). LCMS (ESI): R_T = 5.05 min, mass calcd. for $C_{21}H_{11}ClF_4N_8O$ 502.07, m/z found 502.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.81 (br.s., 1H), 9.06 (d, J = 4.0 Hz, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.67 (d, J = 2.4 Hz, 1H), 8.59 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 7.2 Hz, 1H), 8.25 - 8.17 (m, 3H), 7.76 (dd, J = 4.2, 8.4 Hz, 1H).

Example 63

N-(5-Chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 21**

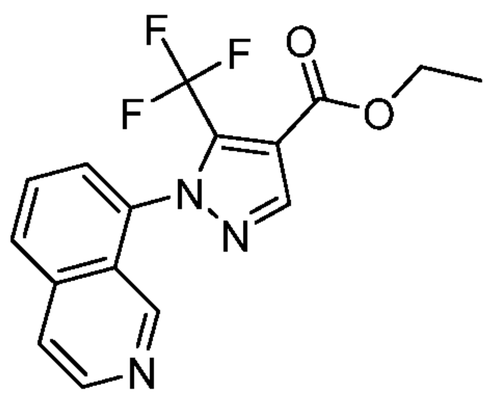




, **63a**

To a stirring solution of isoquinolin-8-amine (4.3 g, 29.8 mmol) in concentrated HCl (43 mL, 215 mmol) at 0 °C was added a solution of sodium nitrite (3.1 g, 44.7 mmol) in water (5 mL) below 0° C. The reaction mixture was stirred at 0 °C for 30 min and a solution of tin chloride (16.8 g, 74.6 mmol) in concentrated HCl (8 mL) was added dropwise. The mixture was stirred at room temperature for 2 h. The mixture was adjusted to pH 12-14 with 20% aqueous sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, filtered, and the filtrate concentrated in under reduced pressure. The resulting crude product was purified by flash chromatography (petroleum ether/ ethyl acetate=100:0 to ethyl acetate/ methnol=90:10) to give compound **63a** (2.83 g, 60 %) as a brown solid.

B. Ethyl 1-(isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **63b**

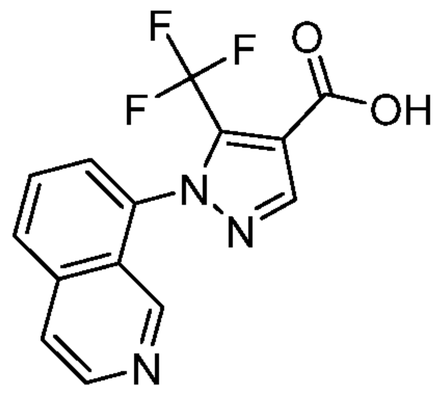


, **63b**

A solution consisting of 8-hydrazinylisoquinoline, **63a** (2.83 g, 17.8 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (5.12 g, 21.3 mmol) in

ethanol (42 mL) was stirred at 80 °C for 16 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford a crude product, which was then purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford compound **63b** as a yellow solid (3.14 g, 53 %). MS m/e 335.9 (M+H).

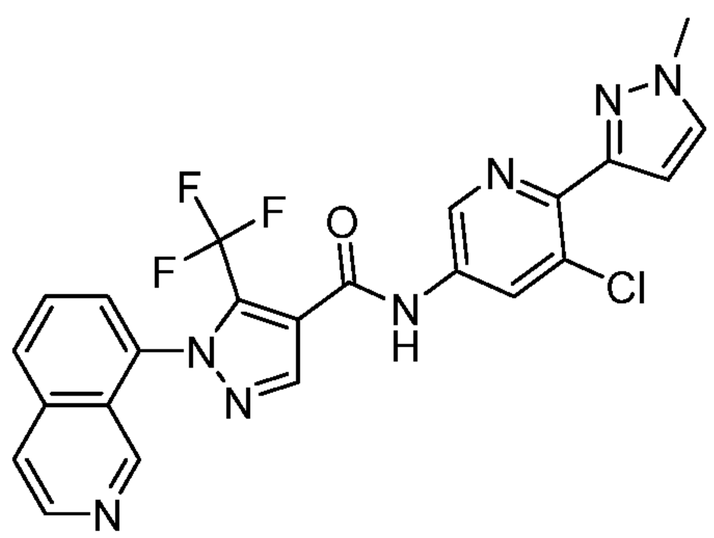
C. 1-(Isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **63c**



, **63c**

NaOH (375 mg, 9.4 mmol) was added to a solution of ethyl 1-(isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **63b** (3.14 g, 9.4 mmol) in methanol (5 mL) and water (15 mL) at room temperature. The mixture was stirred for 4 h. The solvent was concentrated under reduced pressure to afford compound **63c** as a yellow solid (3.093 g 100 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (s, 1H), 8.77 (d, J=5.3 Hz, 1H), 8.53 - 8.37 (m, 3H), 8.23 - 8.16 (m, 1H), 8.11 (d, J=7.1 Hz, 1H).

D. *N*-(5-Chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 21**

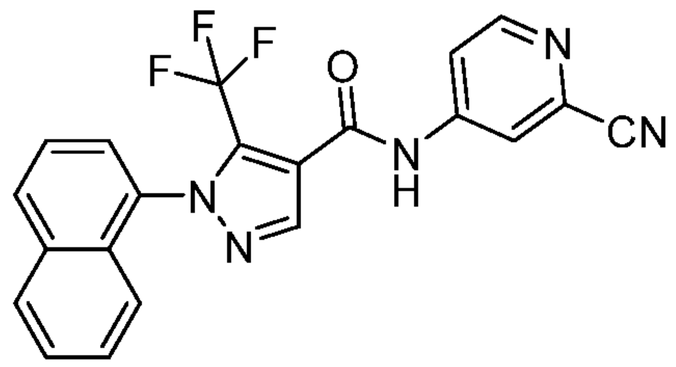


To a solution of 1-(isoquinolin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **63c** (95 mg, 0.29 mmol), 5-chloro-6-(1-methyl-1*H*-pyrazol-3-yl)pyridin-3-amine, **8a**

(60 mg, 0.29 mmol) and pyridine (132.7 mg, 1.7 mmol) in dichloromethane (5 mL) was added $POCl_3$ (102.9 mg, 0.67 mmol) dropwise. The reaction mixture was stirred at 20 °C for 1 h. A solution of saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic phases were washed with brine and dried over Na_2SO_4. The mixture was filtered, and the filtrates concentrated under reduced pressure to afford a crude product as a yellow oil. The crude product was purified by preparative HPLC to afford compound **21** as a white solid (55 mg, 38 %). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 11.02 (s, 1H), 8.82 (d, J=2.2 Hz, 1H), 8.67 (d, J=5.7 Hz, 1H), 8.60 (s, 1H), 8.54 (s, 1H), 8.42 (d, J=2.3 Hz, 1H), 8.29 (d, J=7.4 Hz, 1H), 8.08 - 8.03 (m, 1H), 8.00 - 7.93 (m, 2H), 7.77 (d, J=2.2 Hz, 1H), 6.75 (d, J=2.2 Hz, 1H), 3.92 (s, 3H). MS m/e 498.1 (M+H).

Example 64

N-(2-Cyanopyridin-4-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide**, Cpd 1**

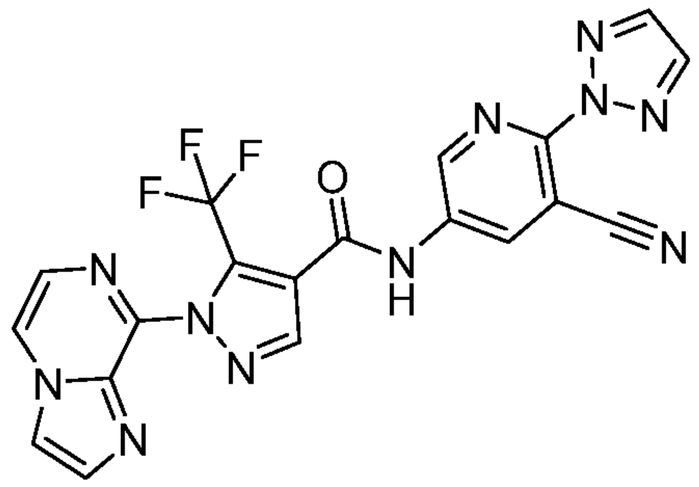


$POCl_3$ (0.3 mL) was added dropwise to a solution consisting of 1-(naphthalen-1-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid **2b** (150 mg, 0.490 mmol), 4-aminopicolinonitrile (64.2 mg, 0.539 mmol) and pyridine (5 mL). The mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative HPLC (40% to 70% (v/v) ACN and H_2O with 0.05% NH_3) to afford compound **1**. Compound **1** was concentrated to dryness under reduced pressure (101.30 mg, 51 %). LCMS (ESI): R_T = 5.45 min, mass calcd. for $C_{21}H_{12}F_3N_5O$ 407.348, m/z found 408.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 11.31 (s, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 8.56 (s, 1H), 8.30 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H),

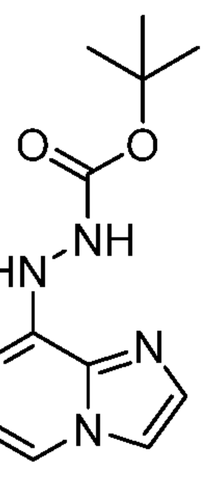
8.15 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.76 - 7.62 (m, 3H), 7.14 (d, J = 8.0 Hz, 1H).

Example 65

N-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 103**



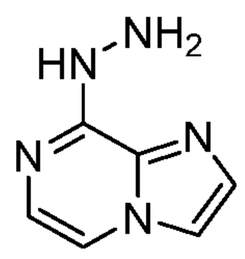
A. *tert*-Butyl 2-(imidazo[1,2-a]pyrazin-8-yl)hydrazine-1-carboxylate, **65a**



, **65a**

8-Chloroimidazo[1,2-a]pyrazine (400 mg, 2.6 mmol) and *tert*-butyl hydrazinecarboxylate (516.4 g, 3.9 mmol) were dissolved in THF (8 mL), sodium hydride (312.5 mg, 7.8 mmol) was added, and the mixture stirred at 30 °C for 16 h. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (10 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates concentrated under reduced pressure to afford a crude product as a black oil. The crude product was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 30/70). The solvent was concentrated under reduced pressure to afford compound **65a** as a yellow solid (220 mg, 28 %). LCMS (ESI): m/z 250.1 $[M+H]^+$.

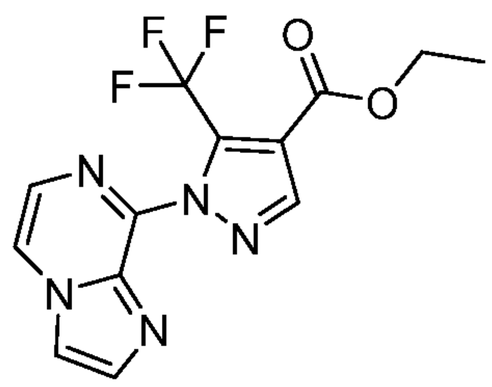
B. 8-Hydrazinylimidazo[1,2-a]pyrazine, **65b**



, **65b**

tert-Butyl 2-(imidazo[1,2-a]pyrazin-8-yl)hydrazine-1-carboxylate, **65a** (220 mg, 0.72 mmol) was suspended in dichloromethane (5 mL) and HCl/dioxane (10 mL) was added. The reaction mixture was stirred at 30 °C for 1 h, then concentrated under reduced pressure to afford compound **65b** as a yellow solid. The solid was used for the next step without further purification.

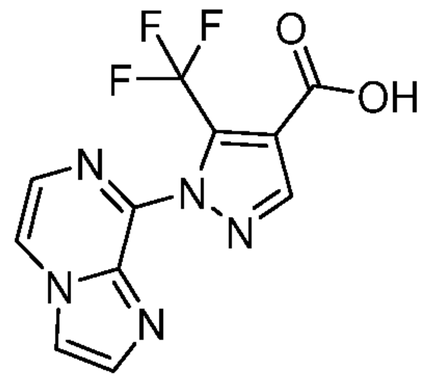
C. Ethyl 1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **65c**



, **65c**

8-Hydrazinylimidazo[1,2-a]pyrazine, **65b** (160 mg, 1.1 mmol) and triethylamine (325.6 mg, 3.2 mmol) were dissolved in ethanol (3 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (515.3 mg, 2.15 mmol) was added and the mixture stirred at 80 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford a crude brown solid. The solid was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 20/80). The solvent was concentrated under reduced pressure to afford compound **65c** as a yellow oil (160 mg, 41 %). LCMS (ESI): m/z 326.0 $[M+H]^+$.

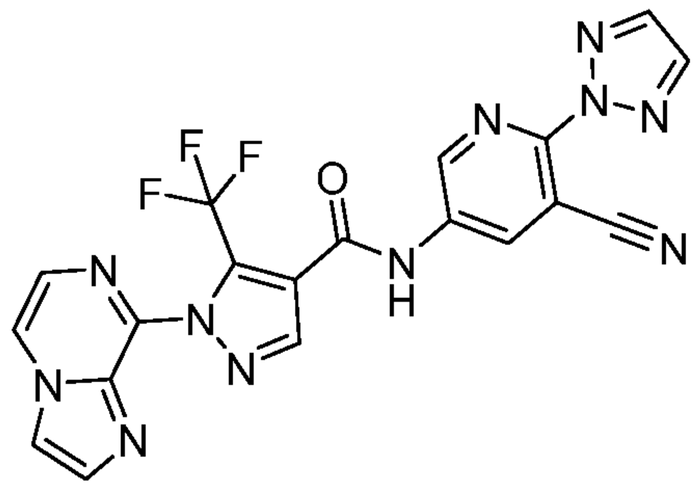
D. 1-(Imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **65d**



, **65d**

Lithium hydroxide monohydrate (183.4 mg, 4.4 mmol) was added to ethyl 1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **65c** (160 mg, 0.44 mmol) and the mixture stirred at 30 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford a crude yellow solid, which was used for the next step without further purification (160 mg).

E. *N*-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide, **Cpd 103**

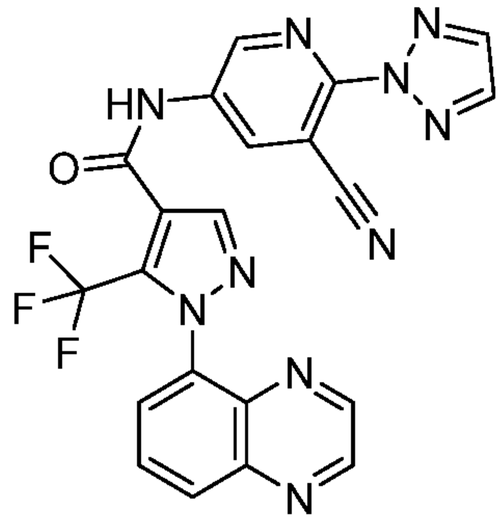


To a solution of 1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **65d** (115 mg, 0.39 mmol), 5-amino-2-(*2H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (47.9 mg, 0.26 mmol) and pyridine (91.5 mg, 1.2 mmol) in dichloromethane (3 mL) was added $POCl_3$ (59.1 mg, 0.39 mmol) dropwise. The reaction mixture was stirred at 20 °C for 16 h. A solution of saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic phases were washed with brine and dried over Na_2SO_4. The mixture was filtered, and the filtrates concentrated under reduced pressure to afford a crude product as a yellow oil. The crude product was purified by preparative HPLC to afford compound **103** as a white solid (5 mg, 4 %). ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm 9.04 (br s,

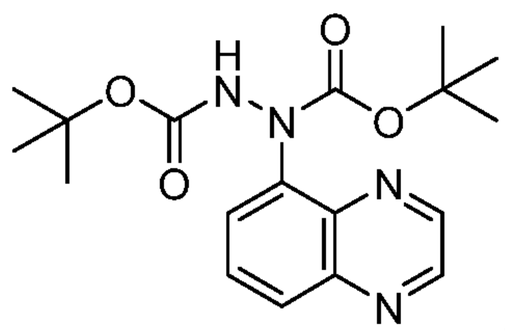
1H), 8.89 (d, J=2.6 Hz, 1H), 8.86 (d, J=4.6 Hz, 1H), 8.50 - 8.43 (m, 2H), 8.19 (d, J=4.6 Hz, 1H), 8.16 (s, 1H), 8.13 (s, 2H). LCMS (ESI): m/z 465.9 $[M+H]^+$.

Example 66

N-(5-Cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinoxalin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamid, **Cpd 105**



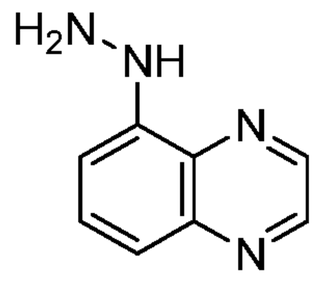
A. Di-*tert*-butyl 1-(quinoxalin-5-yl)hydrazine-1,2-dicarboxylate, **66a**



, **66a**

5-Bromoquinoxaline (300 mg, 1.44 mmol) and di-tert-butyl hydrazine-1,2-dicarboxylate (500 mg, 2.15 mmol) were dissolved in DMF (5 mL). CuI (27.5 mg, 0.14 mmol) and K_3PO_4 (609.3 mg, 2.87 mmol) were added and purged with N_2, cyclohexane-1,3-diamine (32.8 mg, 0.29 mmol) was added and the reaction mixture was stirred at 110 °C for 16 h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (20 mL x 3). The filtrate was concentrated under reduced pressure to afford a crude produce as a brown oil. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=50:50), and the solvents were removed under reduced pressure to afford compound **66a** as a brown oil (0.3 g, 58 %). LCMS (ESI): m/z 383.0 $[M+H]^+$.

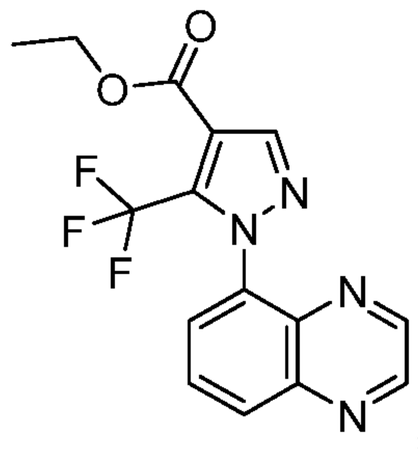
B. 5-Hydrazinylquinoxaline, **66b**



, **66b**

Di-*tert*-butyl 1-(quinoxalin-5-yl)hydrazine-1,2-dicarboxylate, **66a** (300 mg, 0.48 mmol) in HCl in dioxane (10 mL) was mixed at 28 °C for 2 h. The solvent was concentrated under reduced pressure to afford compound **66b**.

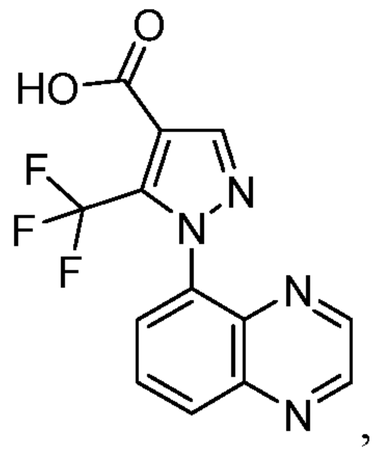
C. Ethyl 1-(quinoxalin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **66c**



, **66c**

5-Hydrazinylquinoxaline, **66b** (200 mg, 1.0 mmol) was dissolved in ethanol (5 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (336.4 mg, 1.53 mmol) was added and the mixture stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure to afford a crude product as a brown solid. The solid was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate from 100/0 to 50/50), and the solvent was concentrated under reduced pressure to afford compound **66c** as a yellow oil (155 mg, 26 %). LCMS (ESI): m/z 336.9 $[M+H]^+$.

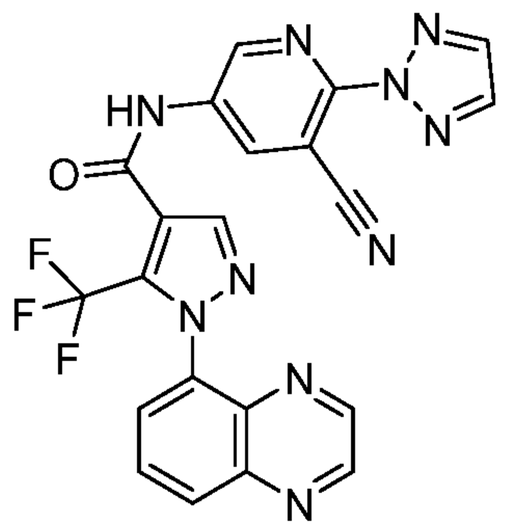
D. 1-(Quinoxalin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **66d**



, **66d**

Lithium hydroxide monohydrate (92 mg, 2.2 mmol) was added to ethyl 1-(quinoxalin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, **66c** (125 mg, 0.37 mmol) and stirred at 30 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford a crude product as a yellow solid. The crude product was used for the next step without further purification (95 mg).

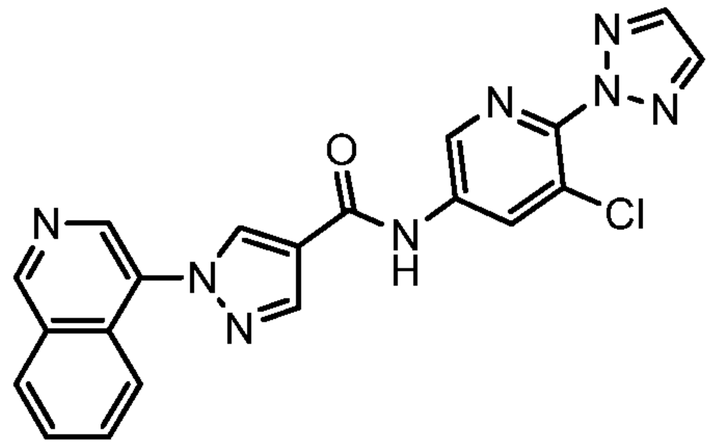
E. *N*-(5-cyano-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinoxalin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamid, **Cpd 105**



To a solution of 1-(quinoxalin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **66d** (56.2 mg, 0.30 mmol), 5-amino-2-(*2H*-1,2,3-triazol-2-yl)nicotinonitrile, **7b** (100 mg, 0.30 mmol) and pyridine (119 mg, 1.5 mmol) in dichloromethane (5 mL) was added $POCl_3$ (92.5 mg, 0.60 mmol) dropwise. The reaction mixture was stirred at 20 °C for 16 h. A solution of saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was extracted with dichloromethane (20 mL x 2). The combined organic phases were washed with brine and dried over Na_2SO_4. The mixture was filtered, and the filtrates concentrated under reduced pressure to afford a crude product as a yellow oil. The crude product was purified by preparative HPLC to afford the compound **105** as a white solid (21 mg, 15 %). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 8.04 - 8.11 (m, 1 H), 8.19 - 8.23 (m, 1 H), 8.29 (s, 2 H), 8.39 (d, J=8.38 Hz, 1 H), 8.56 (s, 1 H), 8.87 (d, J=2.43 Hz, 1 H), 8.97 (d, J=1.54 Hz, 1 H), 9.05 - 9.12 (m, 2 H), 11.29 (s, 1 H). LCMS (ESI): m/z 477.0 $[M+H]^+$.

Example 67

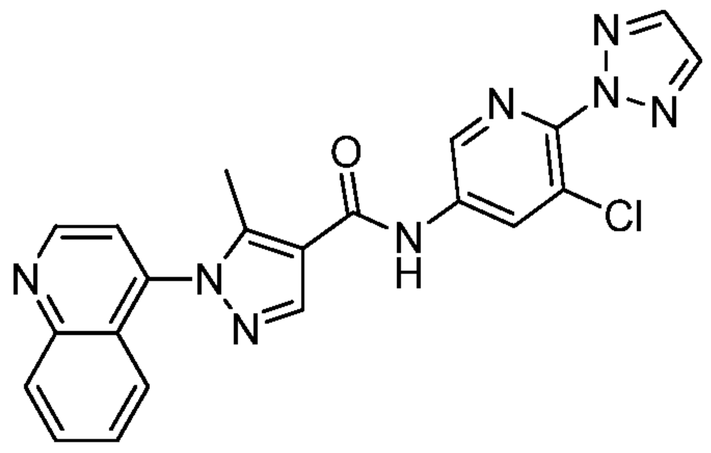
N-(5-Chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-1H-pyrazole-4-carboxamide, **Cpd 76**



A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (87.8 mg, 0.449 mmol) and THF (1 mL) were added to 1 M potassium *tert*-butoxide in THF (1.35 mL, 1.35 mmol) at 0 °C, then a solution consisting of ethyl 1-(isoquinolin-4-yl)-1*H*-pyrazole-4-carboxylate, **59a** (120 mg, 0.449 mmol) and THF (1 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) ACN and H_2O with 0.05% NH_3) and lyophilized to give compound **76** (69.3 mg, 36 %). LCMS (ESI): R_T = 4.36 min, mass calcd. for $C_{20}H_{13}ClN_8O$ 416.823, m/z found 416.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (br.s., 1H), 9.52 (s, 1H), 9.01 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.76 (s, 1H), 8.70 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.19 (s, 2H), 7.98 - 7.92 (m, 2H), 7.89 - 7.84 (m, 1H)

Example 68

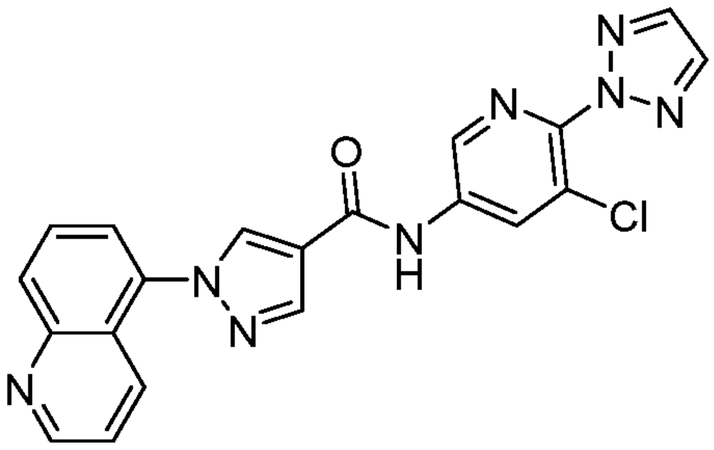
N-(5-Chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-1H-pyrazole-4-carboxamide, **Cpd 64**



A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (229 mg, 1.17 mmol) and THF (1 mL) was added dropwise to a solution of *t*-BuOK (3.2 mL, 3.2 mmol, 1 M in THF) at 0 °C. Then a solution consisting of ethyl 5-methyl-1-(quinolin-4-yl)-1*H*-pyrazole-4-carboxylate, **60d** (300 mg, 1.07 mmol) and THF (1 mL) was added dropwise. The resultant mixture was warmed to room temperature and stirred for 16 h before quenching with water and extracting with ethyl acetate (50 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to give a residue, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) CH_3CN and H_2O with 0.05% NH_3) and lyophilized to afford compound **64** (153 mg, 33 %). LCMS (ESI): R_T = 4.52 min, mass calcd. for $C_{21}H_{15}ClN_8O$ 430.850, m/z found 431.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*$_6$) δ ppm 10.66 (s, 1H), 9.14 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 2.4 Hz, 1H), 8.71 (d, *J* = 2.4 Hz, 1H), 8.57 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 2H), 7.93 - 7.89 (m, 1H), 7.78 (d, *J* = 4.4 Hz, 1H), 7.73 - 7.69 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 2.45 (s, 3H).

Example 69

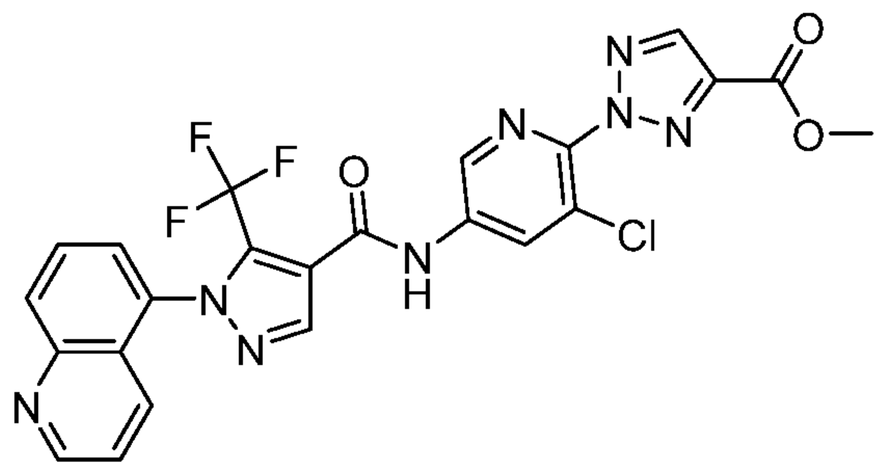
N-(5-Chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxamide, **Cpd 60**



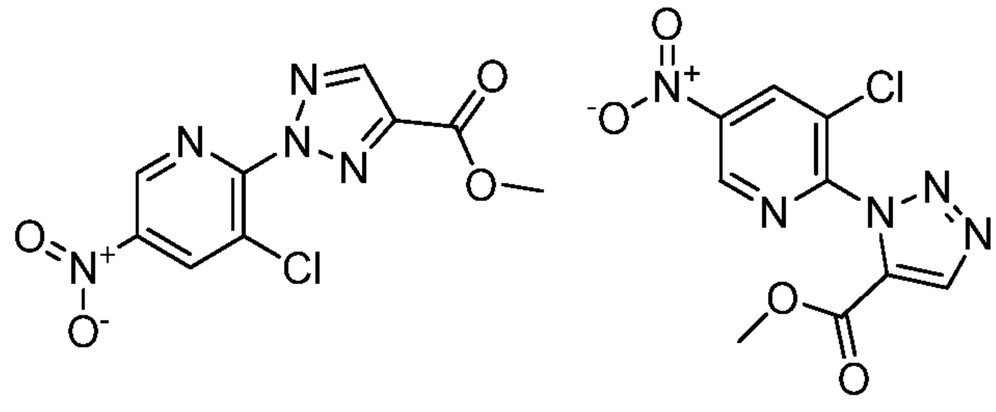
A solution consisting of 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (102 mg, 0.524 mmol) and THF (1 mL) were added to 1 M potassium *tert*-butoxide in THF (1.57 mL, 1.57 mmol) at 0 °C, then a solution consisting of ethyl 1-(quinolin-5-yl)-1*H*-pyrazole-4-carboxylate, **61a** (140 mg, 0.524 mmol) and THF (1 mL) was added. The resultant mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give a crude product, which was purified by preparative reverse phase HPLC (30% to 60% (v/v) ACN and H_2O with 0.05% NH_3) to afford compound **60** (104.50 mg, 49 %). LCMS (ESI): R_T = 4.01 min, mass calcd. for $C_{20}H_{13}ClN_8O$ 416.823, m/z found 417.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.04 (dd, *J* = 1.6, 4.0 Hz, 1H), 8.96 (s, 1H), 8.88 (d, *J* = 2.4 Hz, 1H), 8.70 (d, *J* = 2.4 Hz, 1H), 8.50 (s, 1H), 8.33 - 8.28 (m, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.19 (s, 2H), 7.98 - 7.92 (m, 1H), 7.89 - 7.85 (m, 1H), 7.68 (dd, *J* = 4.0, 8.4 Hz, 1H).

Example 70

Methyl 2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate, **Cpd 108**



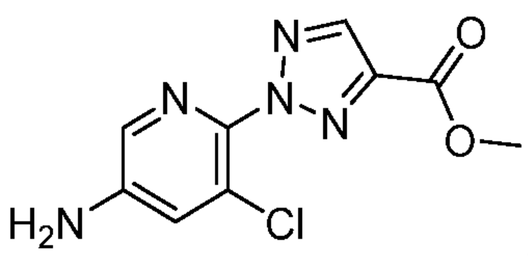
A. Mixture of methyl 1-(3-chloro-5-nitropyridin-2-yl)-1H-1,2,3-triazole-5-carboxylate compound with methyl 2-(3-chloro-5-nitropyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate, **70a**



, **70a**

Potassium carbonate (7249.14 mg, 52.45 mmol) was added to a solution of 2,3-dichloro-5-nitropyridine (7249.14 mg, 17.48 mmol) and methyl 1h-1,2,3-triazole-4-carboxylate (2000 mg, 15.76 mmol) in MeCN (20 mL). The mixture was reacted at 60°C for 12 h. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give the crude product as yellow oil, which was purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=40:60). The pure fractions were collected and the solvent was concentrated under reduced pressure to give the product as yellow solid.

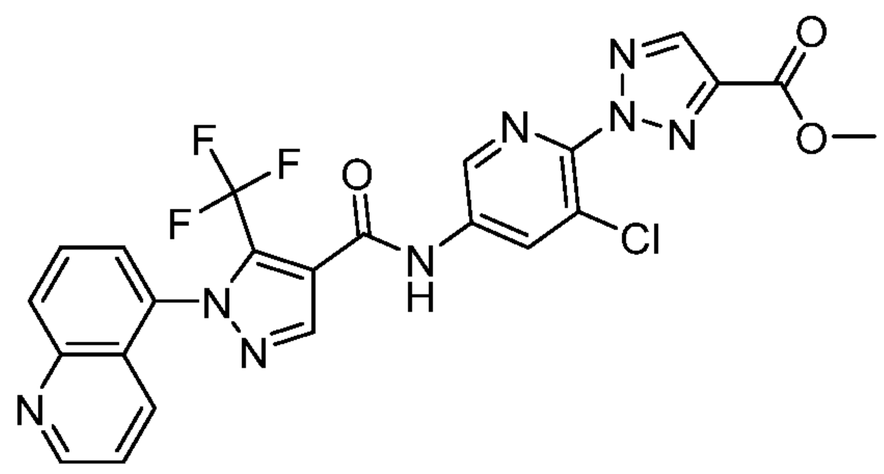
B. Methyl 2-(5-amino-3-chloropyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate, **108b**



, **108b**

Mixture of methyl 1-(3-chloro-5-nitropyridin-2-yl)-1H-1,2,3-triazole-5-carboxylate and methyl 2-(3-chloro-5-nitropyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate (2500 mg, 4.41 mmol) was added to a solution of Fe (1230 mg, 22.04 mmol) and NH_4Cl (1178 mg, 22.04 mmol) in THF (10 mL)/ water (5 mL). The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (50 mL× 2). The combined filtrates were concentrated to dryness to give crude as yellow solid, which was purified by FFS (petroleum ether/ ethyl acetate=50:50 to petroleum ether/ ethyl acetate=0:100). The desired fractions were collected and the solvent was concentrated under reduced pressure. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 3.98 (s, 3 H), 4.17 (br s, 2 H), 7.17 (d, J=2.43 Hz, 1 H), 7.91 (d, J=2.65 Hz, 1 H), 8.30 (s, 1 H).

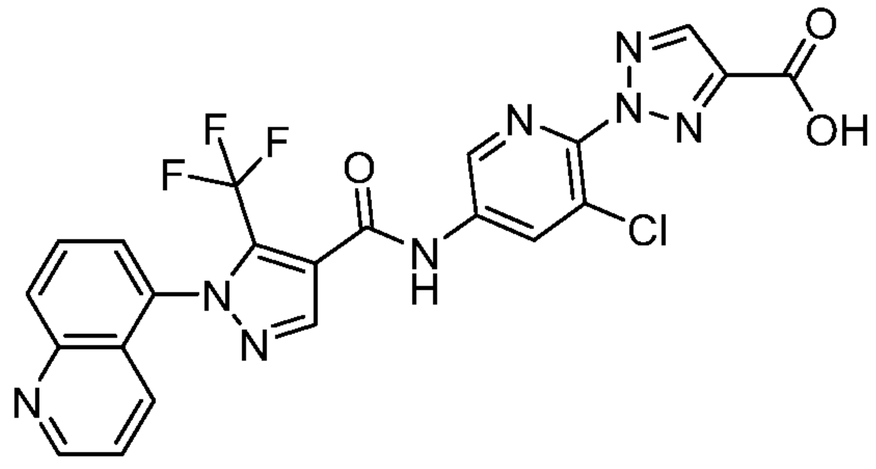
C. Methyl 2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate, **Cpd 108**



1-(Quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (240.87 mg, 0.77 mmol), methyl 2-(5-amino-3-chloropyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate (200 mg, 0.79 mmol), $POCl_3$ (142.24 mg, 0.93 mmol) were dissolved in DCM (8 mL), and pyridine (183.44 mg, 2.32 mmol) was added. The mixture was stirred at 25 °C for 1 h, sat. $NaHCO_3$ (30 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford a brown oil, which was purified by FFS (petroleum ether/ ethyl acetate=50:50 to petroleum ether/ ethyl acetate=0:100). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.90 (s, 3 H), 7.58 - 7.62 (m, 1 H), 7.64 - 7.69 (m, 1 H), 7.90 - 7.99 (m, 2 H), 8.32 (d, J=8.38 Hz, 1 H), 8.59 (s, 1 H), 8.69 (s, 1 H), 8.71 (d, J=2.21 Hz, 1 H), 8.87 (d, J=2.43 Hz, 1 H), 9.05 (dd, J=3.97, 1.54 Hz, 1 H), 11.32 (s, 1 H). LCMS (ESI) m/z M+1: 543.2.

Example 109

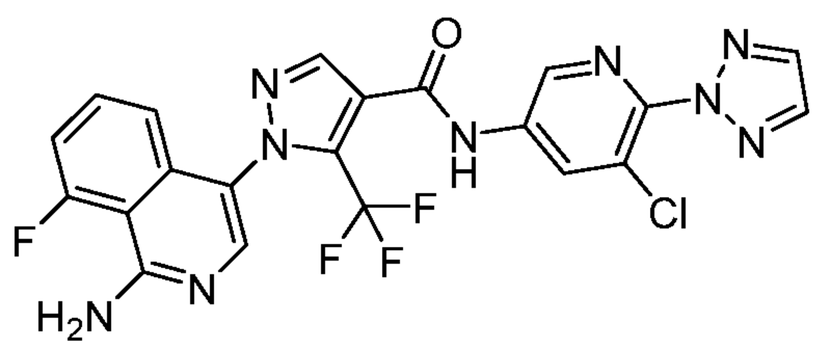
2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid, **Cpd 109**



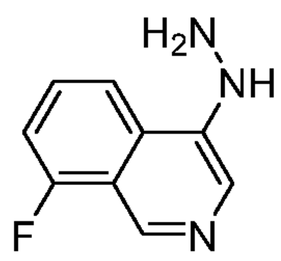
NaOH (63.528 mg, 1.588 mmol) was added to a solution of methyl 2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate, **cpd 108** (445 mg, 0.794 mmol) in EtOH/H_2O=1:1 (5 mL) was reacted at 18 °C for 2 h. The solvent was concentrated under reduced pressure, 1M HCl solution was add to the mixture to adjust the pH to ~5 and solid formed. The solid was collected to afford the product. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.58 - 7.62 (m, 1 H), 7.64 - 7.69 (m, 1 H), 7.90 - 7.99 (m, 2 H), 8.32 (d, J=7.94 Hz, 1 H), 8.58 (d, J=11.47 Hz, 2 H), 8.70 (d, J=2.21 Hz, 1 H), 8.87 (d, J=2.21 Hz, 1 H), 9.05 (dd, J=3.97, 1.54 Hz, 1 H), 11.34 (s, 1 H). LCMS (ESI) m/z M+1: 542.9.

Example 110

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 110**



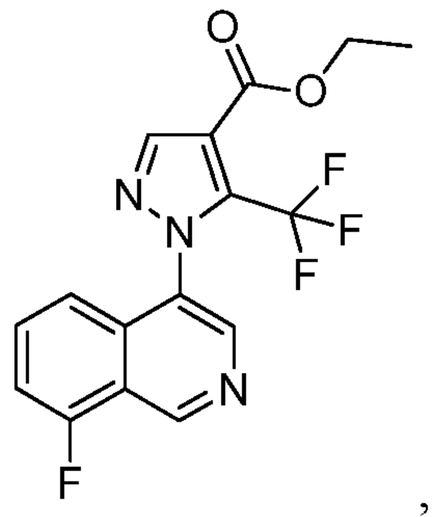
A. 8-Fluoro-4-hydrazinylisoquinoline, **110a**



, **110a**

A mixture of palladium (II) (pi-cinnamyl) (103.14 mg, 0.20 mmol) chloride dimer and N-[2-(di-1-adamantylphosphino) phenyl] morpholine (184.6 mg, 0.40 mmol) in dioxane (20 mL) was evacuated with argon (4x). The resulting clear yellow solution was stirred at room temp under argon for 10 min. 4-Bromo-8-fluoroisoquinoline (900 mg, 3.98 mmol) and tBuONa (765.27 mg, 7.96 mmol) were added to the mixture and purged with argon (4x). The resulting yellow reaction was stirred at room temperature for 5 min and then treated with hydrazine (398.63 mg, 7.96 mmol) via syringe and purged with argon (4x). Then the mixture was stirred at 55 °C under argon for 2 h. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give the crude product as a brown solid.

B. Ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **110b**

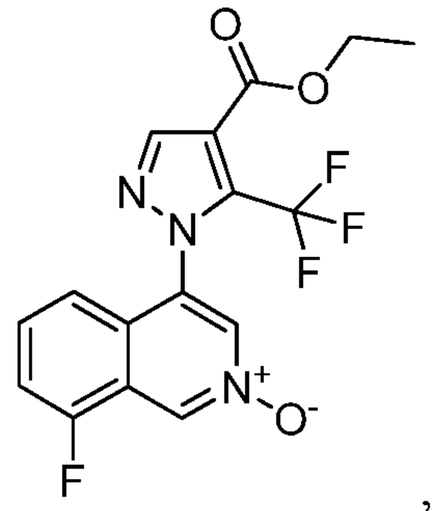


, **110b**

8-Fluoro-4-hydrazinylisoquinoline (700 mg, 3.95 mmol) was added to a solution of ethyl ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1423.34 mg, 5.93 mmol) in EtOH (15 mL) was reacted at 80 °C for 1 h. The mixture was concentrated under reduced pressure, then was purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=80:20). The desired fractions were collected and the solvent

was concentrated under reduced pressure to give the product as brown oil. LCMS (ESI) m/z M+1: 353.9.

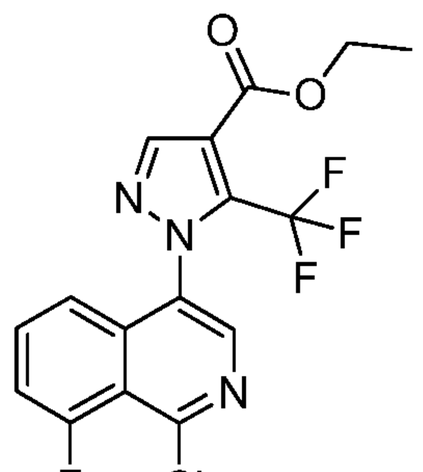
C. 4-(4-(Ethoxycarbonyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-8-fluoroisoquinoline 2-oxide, **110c**



, **110c**

m-CPBA (700 mg, 3.95 mmol) was added to a solution of ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (800 mg, 2.25 mmol) in DCM (10 mL) was reacted at 30 °C for 2 h. The mixture was added to 40 mL sat.Na_2CO_3 solution, extracted with 50 mL CH_2Cl_2, the organic layer was concentrated under reduced pressure and purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=50:50). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as a yellow oil. LCMS (ESI) m/z M+1: 370.0.

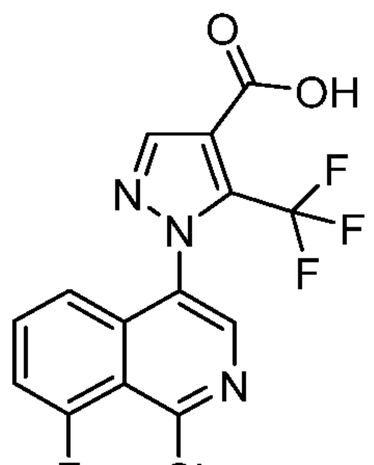
D. Ethyl 1-(1-chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **110d**



, **110d**

$POCl_3$ (5 mL) was added to a solution of 4-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1H-pyrazol- 1-yl)-8-fluoroisoquinoline 2-oxide, (720 mg, 1.95 mmol) in $CHCl_3$ (15 mL) was reacted at 70 °C for 2 h. The mixture was added to 30 mL sat.Na_2CO_3 solution, extracted with 30 mL CH_2Cl_2, the organic layer was concentrated under reduced pressure, then purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=85:15). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as colorless oil. LCMS (ESI) m/z M+1: 388.0.

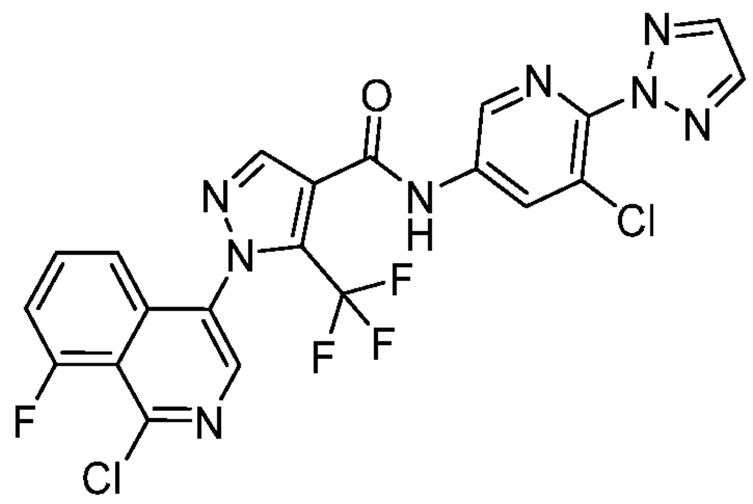
E. 1-(1-Chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **110e**



, **110e**

LiOH (70.415 mg, 2.940 mmol) was added to a solution of ethyl 1-(thieno[2,3-c]pyridin-7-yl)-5- (trifluoromethyl)-1H-pyrazole-4-carboxylate (240 mg, 0.59 mmol) in THF/H_2O=1:1 (10 mL) was reacted at 23 °C for 2 h. The solvent was concentrated under reduced pressure, 1M HCl solution was add to the mixture to adjust the pH to ~5 and EtOAc (30mL x 3) was added to the mixture. The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the product as a brown oil. LCMS (ESI) m/z M+1: 359.9.

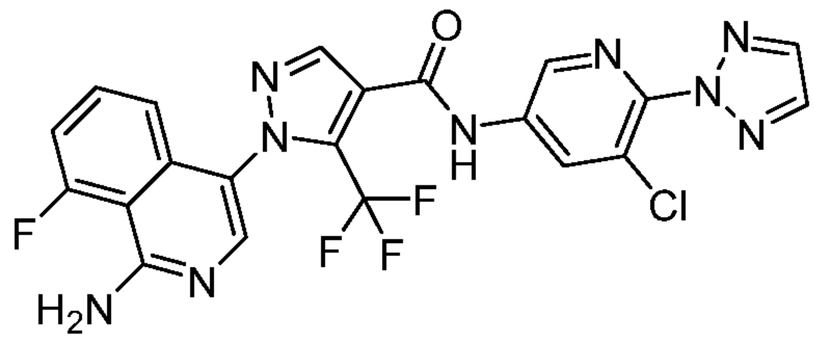
F. N-(5-Chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **110f**



, **110f**

1-(1-Chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (210 mg, 0.22 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (107.93 mg, 0.55 mmol), $POCl_3$ (96.69 mg, 0.63 mmol) were dissolved in DCM (5 mL), and pyridine (124.7 mg, 1.58 mmol) was added. The mixture was stirred at 25 °C for 1 h, sat.$NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the product as a brown oil. LCMS (ESI) m/z M+1: 536.9.

G. 1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 110**

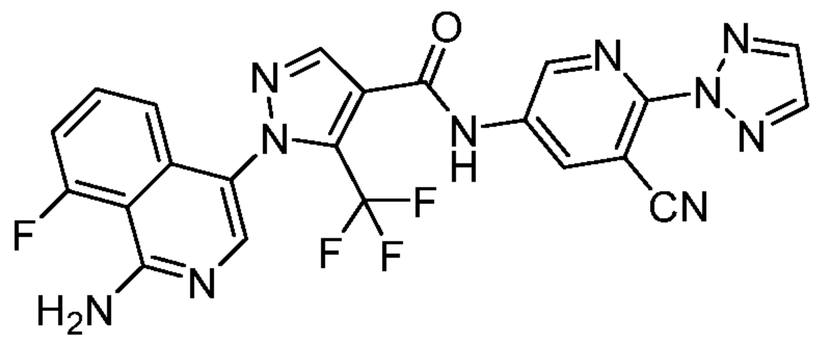


N-(5-Chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (200 mg, 0.18 mmol) in $NH_3.H_2O$ (12 mL) was reacted at 80 °C for 16 h. The solvent was concentrated under reduced pressure the give the crude compound, which was purified by preparative HPLC (77 % to 57 % (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (29 mg, 31.5%). LCMS (ESI) m/z M+1: 518.0. ^1H NMR (400 MHz, DMSO-d6) δ ppm 6.77 (d, J=8.53 Hz, 1 H), 7.56 (dd, J=12.92, 7.91 Hz, 1 H), 7.81 - 7.91 (m, 1 H),

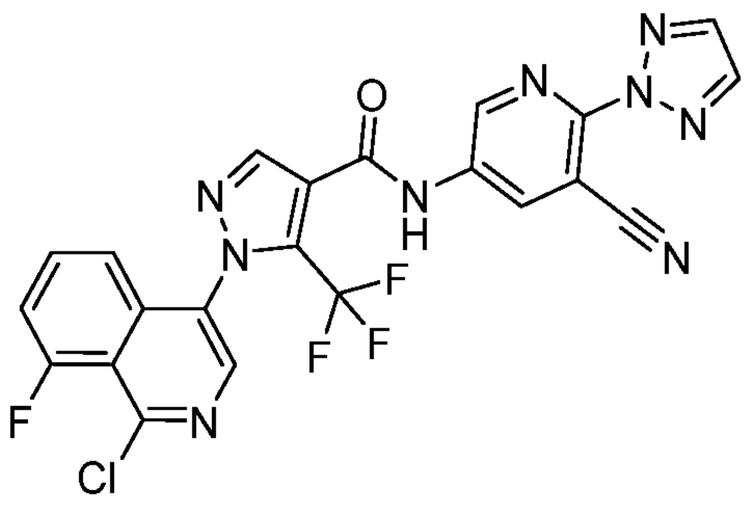
8.20 (s, 2 H), 8.22 (s, 1 H), 8.61 (s, 1 H), 8.70 (d, J=2.01 Hz, 1 H), 8.89 (d, J=2.01 Hz, 1 H), 11.36 (s, 1 H).

Example 111

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 111**



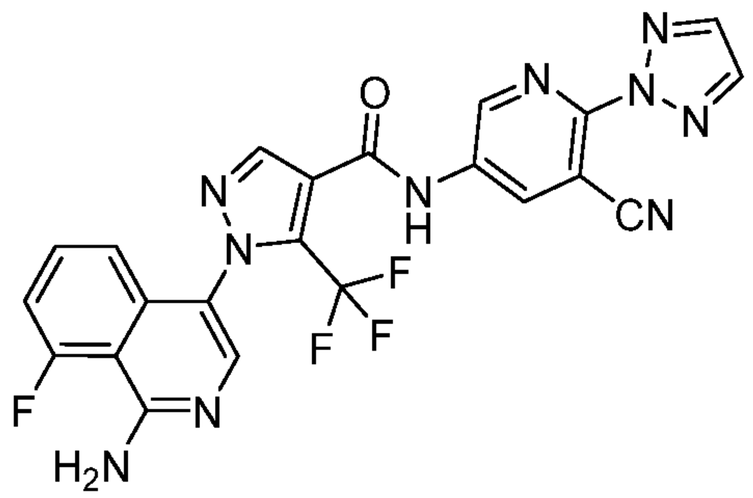
A. 1-(1-chloro-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **111a**



, **111a**

1-(1-chloro-8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **cpd 110e** (230 mg, 0.588 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (109.474 mg, 0.588 mmol), $POCl_3$ (108.195 mg, 0.706 mmol) were dissolved in DCM (5 mL), and pyridine (139.537 mg, 1.764 mmol) was added. The mixture was stirred at 25 °C for 1 h, sat. $NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as brown oil which was purified by FFS (petroleum ether/ ethyl acetate=10:1 to ethyl acetate). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as colorless oil. LCMS (ESI) m/z M+1: 528.1

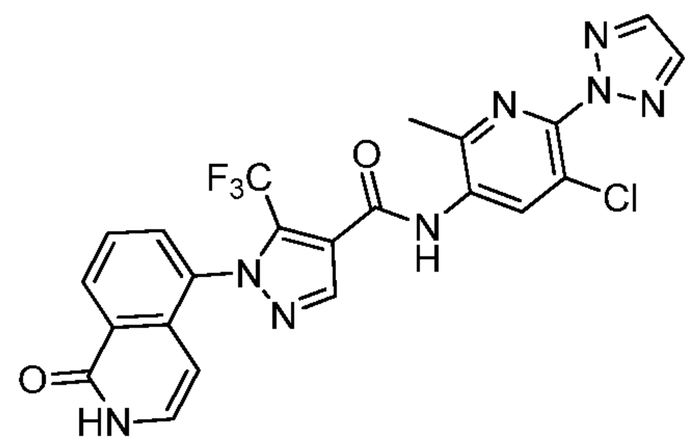
B. 1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 111**



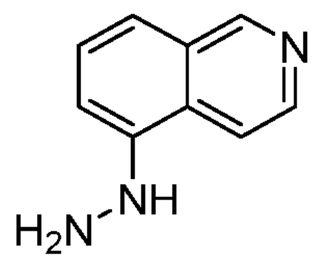
1-(1-Chloro-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (140 mg, 0.262 mmol) in $NH_3.H_2O$ (10 mL) was stirred at 60°C for 2 h. The solvent was concentrated under reduced pressure the give the crude compound, which was purified by preparative HPLC (83 % to 53 % (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (50.0 mg, 37.6%). ^1H NMR (400 MHz, DMSO-d6) δ ppm 6.79 (d, J=8.28 Hz, 1 H), 7.60 (dd, J=12.92, 7.91 Hz, 1 H), 7.90 (td, J=8.16, 5.27 Hz, 1 H), 8.27 (s, 1 H), 8.32 (s, 2 H), 8.64 (s, 1 H), 8.91 (d, J=2.51 Hz, 1 H), 9.15 (d, J=2.26 Hz, 1 H). LCMS (ESI) m/z M+1: 508.9. 11.51 (s, 1 H).

Example 112

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 112**



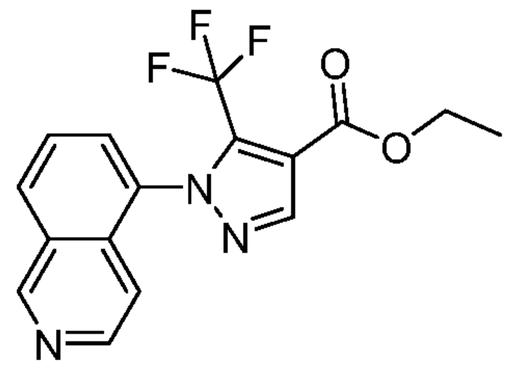
A. 5-hydrazinylisoquinoline, **112a**



, **112a**

To a stirring solution of isoquinolin-5-amine (30 g, 208.1 mmol) in concentrated HCl (300 mL) at 0° C was added a solution of sodium nitrite (21.5 g, 312.1 mmol) in H_2O (85 mL) below 0° C. The reaction mixture was stirred at 0° C for 30 min and a solution of tin(II) chloride dehydrate (117.4 g, 520.2 mmol) dissolved in concentrated HCl (55 mL) was added dropwise. The mixture was stirred at room temperature for 3 h. The mixture was adjusted to pH 12-14 with 20% aqueous sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the title product as a yellow solid (27 g, 81.5% yield).

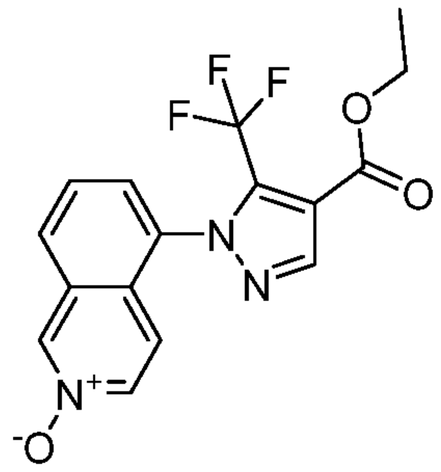
B. Ethyl 1-(isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **112b**



, **112b**

A solution consisting of 5-hydrazinylisoquinoline (27 g, 169.6 mmol) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3- oxobutanoate (40.7 g, 169.6 mmol) in EtOH (300 mL) was stirred at 60 °C for 3 h. The resultant solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford the crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30). The solvent was concentrated to get the title product as yellow solid (22 g, 38.7% yield). LCMS (ESI) m/z M+1: 336.0.

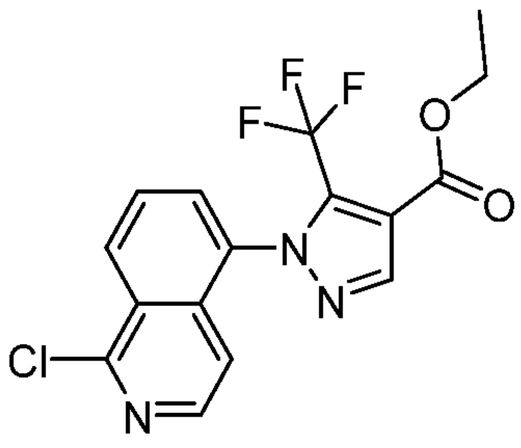
C. 5-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline 2-oxide, **112c**



, **112c**

To a cooled (0 °C) solution of ethyl 1-(isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (3 g, 8.95 mmol) in DCM (40 mL) was added mCPBA (4.63 g, 26.8 mmol) over 10 min. The mixture was warmed to rt and allowed to stir overnight. The solution was washed twice with a half-saturated aqueous solution of sodium bisfulfite (100 mL) to destroy excess oxidant. The mixture was then twice washed with half-saturated aqueous potassium carbonate (100 mL), and brine (100 mL). The extracts were dried over magnesium sulfate, filtered and concentrated to afford a crude oil that was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 20/80). The desired fractions were collected and the solvent was concentrated to dryness under reduced pressure to give title product as yellow solid (2 g, 63.6% yield). LCMS (ESI) m/z M+1: 351.9.

D. Ethyl 1-(1-chloroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **112d**

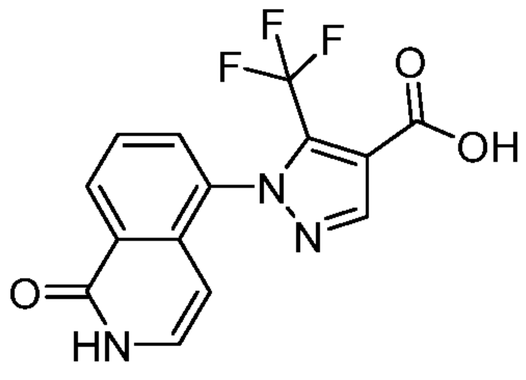


, **112d**

A solution consisting of $POCl_3$ (16.6 g, 108.2 mmol) and 5-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline 2-oxide (19 g, 54.1 mmol) in $CHCl_3$ (40 mL) was stirred at 60 °C for 3 h. The resulting solution was cooled to room temperature and concentrated to dryness under reduced pressure to afford the crude product. The crude

product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30). The solvent was concentrated to get the title product as a yellow solid (12 g, 60.0% yield). LCMS (ESI) m/z M+1: 369.9

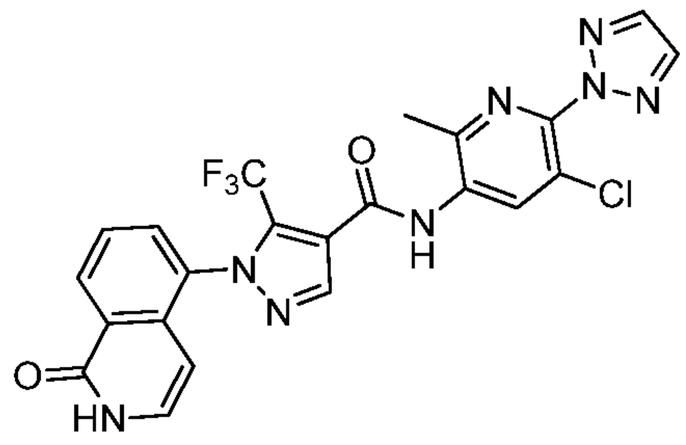
E. 1-(1-Oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **112e**



, **112e**

A mixture of ethyl 1-(1-chloroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (12 g, 32.546 mmol) in concentrated HCl (20 mL) was stirred at 120 °C for 3 h. The solvent concentrated under reduced pressure to give the product as a yellow solid (11 g, 83% yield). LCMS (ESI) m/z M+H: 324.1.

F. N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 112**

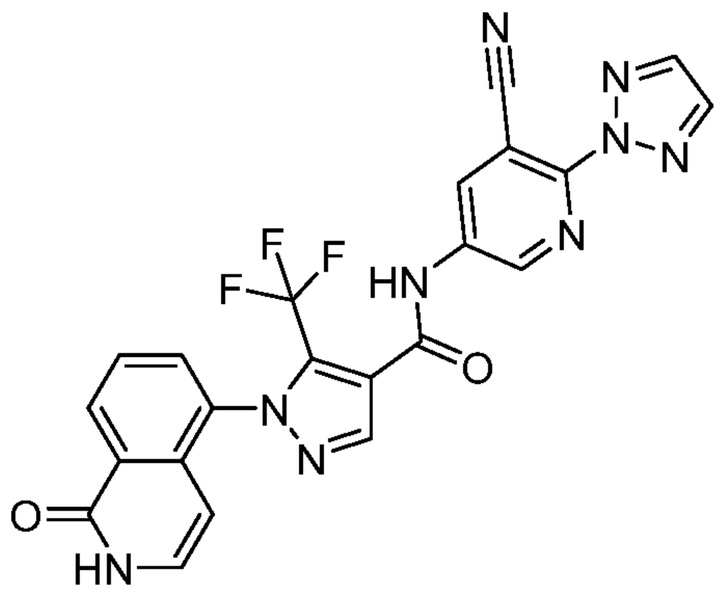


$POCl_3$ (5.26 g, 30.3 mmol) was added to a solution of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (7.0 g, 17.2 mmol), 5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (3.96 g, 18.9 mmol) in pyridine (20 mL). The mixture was stirred at rt for 3h, 50 mL sat. $NaHCO_3$ (500 mL) added to the mixture, extracted with CH_2Cl_2 (500 mL x 2). The organic layer was washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (5% to 60% (v/v) CH_3CN and

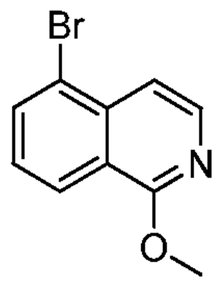
H_2O with 0.05% HCl) and concentrated to dryness to afford the title compound (5.7 g, 64.4% yield) as a white solid. LCMS (ESI) m/z M+1: 515.2. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.54 (s, 3 H), 5.67 (d, J=7.50 Hz, 1 H), 7.28 (dd, J=7.17, 5.84 Hz, 1 H), 7.66 (t, J=7.83 Hz, 1 H), 7.93 (dd, J=7.61, 0.99 Hz, 1 H), 8.14 - 8.20 (m, 2 H), 8.43 (t, J=3.97 Hz, 2 H), 8.51 (s, 1 H), 10.59 (s, 1 H), 11.61 (br d, J=5.29 Hz, 1 H).

Example 113

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 113**



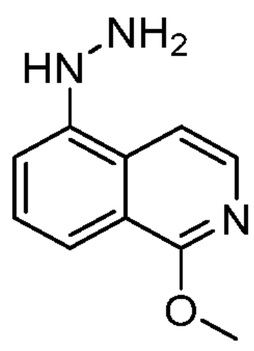
A. 5-bromo-1-methoxyisoquinoline, **113a**



, **113a**

Iodomethane (9.50 g, 66.95 mmol) was added to a solution of 5-bromoisoquinolin-1(2H)-one (5 g, 22.32 mmol), Ag_2CO_3 (18.46 g, 66.95 mmol) in CH_3CN (100 mL). The mixture was stirred at 40°C for 16 h. The mixture was filtered and washed with ethyl acetate (100 mL x 3). The filtrate was collected and concentrated under reduced pressure, and the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100:1 to 10:1). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **113a** (2 g, 37.6% yield) as a white oil.

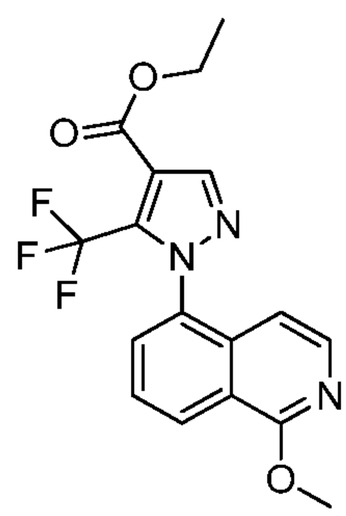
B. 5-hydrazinyl-1-methoxyisoquinoline, **113b**



, **113b**

The mixture of $\{Pd(cinnamyl)Cl\}_2$ (217.607 mg, 0.420 mmol) and Mor-DalPhos (389.476 mg, 0.840 mmol) in dioxane (60 mL) was purged with argon (4x). The resulting clear yellow solution was stirred at room temp under argon for 10 min. **cpd 113a** (2 g, 8.401 mmol) and t-BuONa (1612.896 mg, 16.801 mmol) was added to the mixture and the mixture was purged with argon (4x). The resulting yellow reaction was stirred at room temp for 5 min and was then treated with hydrazine hydrate (858.230 mg, 16.801 mmol) via syringe. The reaction was purged with argon (4x). Then the mixture was stirred at 50 °C under argon for 4 h. The mixture was filtered and washed with ethyl acetate (50 mLx 3). The filtrate was collected and concentrated to afford crude **cpd 113b** (1.6 g) as a yellow solid which was used directly for the next step.

C. Ethyl 1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **113c**

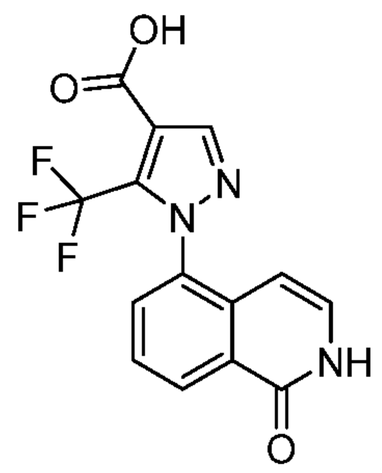


, **113c**

A solution of 5-hydrazinyl-1-methoxyisoquinoline, **cpd 113b** (1.6 g, 8.46 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3- oxobutanoate (3.05 g, 12.68 mmol), triethylamine (2.562 g, 25.368 mmol) in EtOH (50 mL) was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100:0 to 10:1).

The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **cpd 113c** (2.2 g, 71.2% yield) as a yellow solid. LCMS (ESI) m/z M+1: 365.9.

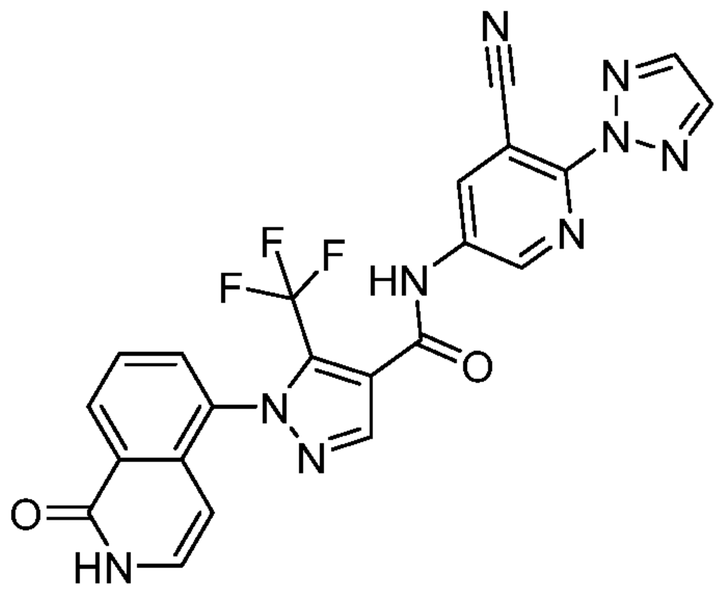
D. 1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **113d**



, **113d**

Ethyl 1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **cpd 113c** (1 g, 2.74 mmol) was added to HCl (10 mL). The mixture was stirred at 130 °C for 3h and concentrated under reduced pressure to afford **cpd 113d** (530 mg, 55.5% yield) as brown solid which used directly for the next step. LCMS (ESI) m/z M+H: 323.9.

E. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 113**

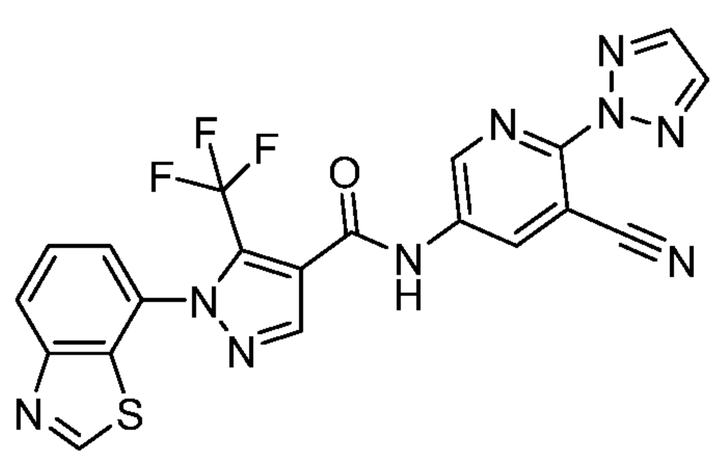


1-(1-Oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **cpd 113d** (170 mg, 0.37 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile, (69.15 mg, 0.37 mmol), pyridine (0.15 mL, 1.86 mmol) were dissolved

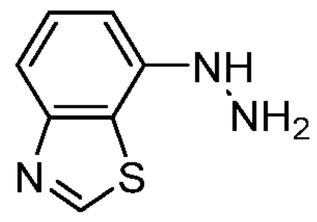
in CH_2Cl_2 (10 mL), and phosphorus oxychloride (0.14 mL, 1.49 mmol) was added. The mixture was stirred at 25 °C for 2 h. Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (46 mg, 24.6%). LCMS (ESI) m/z M+1: 491.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.62 (1 H, br d, J=5.51 Hz), 11.30 (1 H, s), 9.06 (1 H, d, J=2.65 Hz), 8.85 (1 H, d, J=2.43 Hz), 8.53 (1 H, s), 8.42 (1 H, d, J=7.94 Hz), 8.29 (2 H, s), 7.89 - 7.98 (1 H, m), 7.66 (1 H, t, J=7.94 Hz), 7.28 (1 H, dd, J=7.28, 6.17 Hz), 5.64 (1 H, d, J=7.28 Hz).

Example 114

1-(benzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 114**



A. 7-hyrazinylbenzo[d]thiazole, **114a**

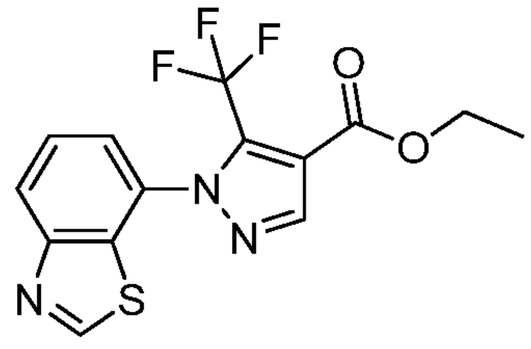


, **114a**

7-bromobenzo[d]thiazole (300 mg, 1.40 mmol), palladium(ii)(pi-cinnamyl) chloride dimer (36.3 mg, 0.07 mmol), N-[2-(di-1-adamantylphosphino)phenyl]morpholine (64.97 mg, 0.14 mmol) and sodium tert-butoxide (269.35 mg, 2.80 mmol) was dissolved in dioxane (20 mL) under N_2 atmosphere. Hydrazine hydrate (140.30 mg, 2.80 mmol) was added and stirred at 50°C for 2 h. The combined mixture was filtered and the solid was

washed by 10 mL ethyl acetate. The solvent was concentrated under reduced pressure to afford the title compound (200 mg, 86.4 %) as brown solid.

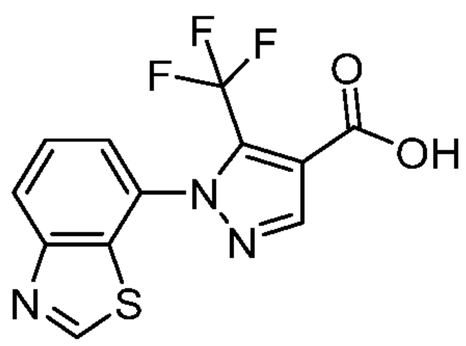
B. ethyl 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **114b**



, 114b

7-hydrazinylbenzo[d]thiazole (200 mg, 1.21 mmol) was dissolved in ethanol (5 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (436.11 mg, 1.82 mmol) was added. The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was concentrated under reduced pressure to afford the crude product as yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 70/30) to afford the title compound (195 mg, 43.6%) as white solid. LCMS (ESI) m/z M+1: 342.0.

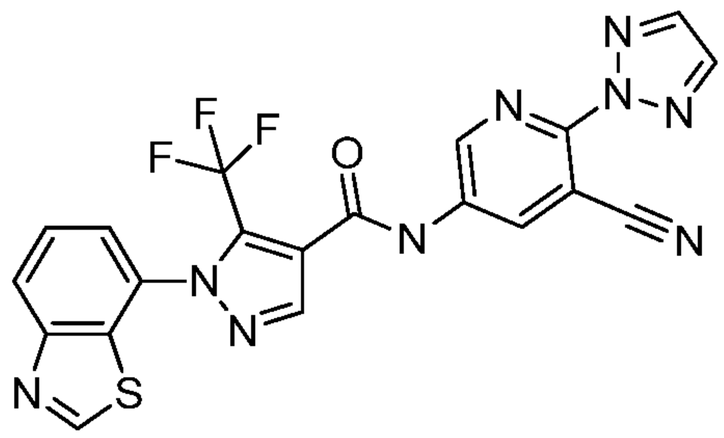
C. 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **114c**



, 114c

Ethyl 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (195 mg, 0.53 mmol) was dissolved in THF (10 mL) and water (10 mL) sodium hydroxide (31.64 mg, 0.79 mmol) was added. The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was adjusted to pH=5 using HCl (2 N), extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude the title compound (140 mg, 81.8%) as brown solid. LCMS (ESI) m/z M+1: 313.9.

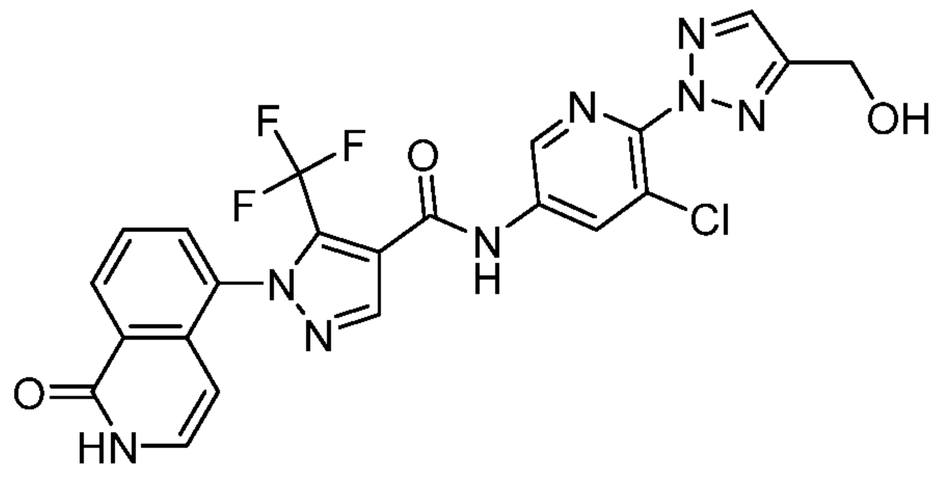
D. 1-(benzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 114**



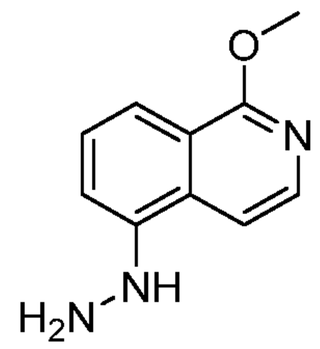
1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (140 mg, 0.37 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (81.71 mg, 0.44 mmol), pyridine (173.59 mg, 2.20 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (224.33 mg, 1.46 mmol) was added. The mixture was stirred at 25 °C for 4 h. Sat.$NaHCO_3$ (40 mL) was added and extracted with CH_2Cl_2 (40 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as brown oil, which was purified by preparative HPLC (25% to 55% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (49.0 mg, 27.8%). LCMS (ESI) m/z M+1: 481.9. ^{1}H NMR (400MHz, DMSO-d6) δ = 11.52 (s, 1H), 9.00 (d, J=2.6 Hz, 1H), 8.78 (d, J=2.6 Hz, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.37 (dd, J=1.4, 2.5 Hz, 1H), 8.27 (s, 2H), 7.28 (dd, J=1.3, 4.6 Hz, 1H), 7.20 (dd, J=2.6, 4.4 Hz, 1H).

Example 115

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 115**



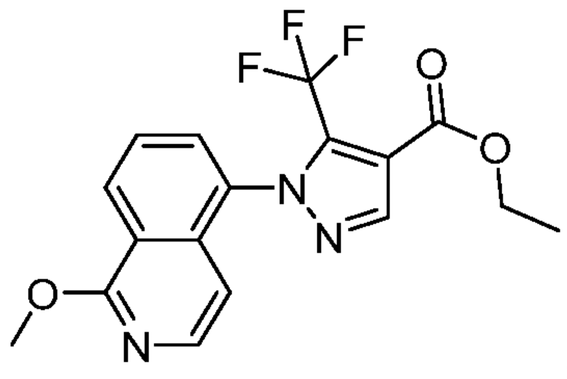
A. 5-hydrazinyl-1-methoxyisoquinoline, **115a**



, **115a**

The mixture of $\{Pd(cinnamyl)Cl\}_2$ (457 mg, 0.88 mmol) and Mor-DalPhos (818 mg, 1.76 mmol) in dioxane (50 mL) was evacuated with argon (4x). The resulting clear yellow solution was stirred at room temp under argon for 10 min. 5-Bromo-1-methoxyisoquinoline (4.2 g, 17.6 mmol) and sodium *tert*-butoxide (3.39 g, 35.3 mmol) was added to the mixture and the mixture was evacuated with argon (4x). The resulting yellow reaction was stirred at room temp for 5 min and was then treated with hydrazine (1.77 g, 35.3 mmol) via syringe. Then the mixture was stirred at 50 °C under argon for 2 h. The precipitate was filtered, washed with ethyl acetate (200 mL) and the dried under reduced pressure to afford the product (3.4 g).

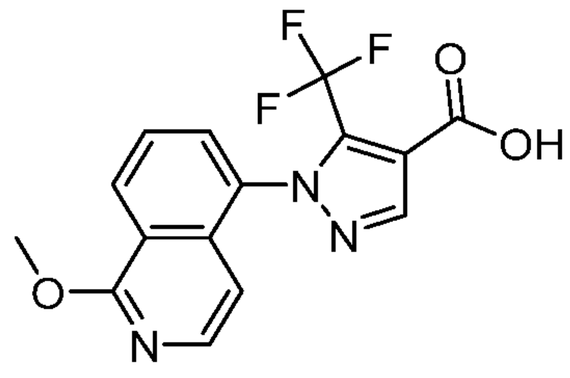
B. ethyl 1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **115b**



, **115b**

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (8.89 g, 37.0 mmol), 5-hydrazinyl-1-methoxyisoquinoline (3.4 g, 18.5 mmol), and ethanol (200 mL) was stirred at 80 °C for 3 h before cooling to room temperature. The resulting solution was concentrated to dryness under reduced pressure, and then purified by column chromatography over silica gel (petroleum ether/ ethyl acetate=100:0 to 70:30) to afford product as white solid (5.4 g, 80%).

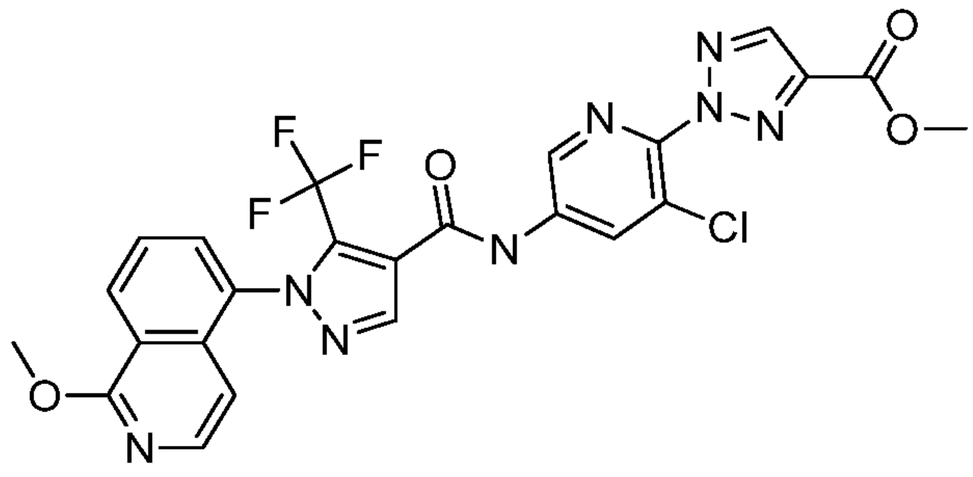
C. 1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **115c**



, **115c**

Sodium hydroxide (1.15 g, 28.7 mmol) was added to a solution of ethyl 1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (3.0 g, 8.2 mmol) in THF/H_2O (2:1, 15 mL), and the mixture was heated at 23°C for 2 h. The solvent was concentrated under reduced pressure, 1M HCl solution was added to the mixture to adjust the pH to ~5, and the mixture extracted with EtOAc(30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the product as a yellow solid (2.5 g, 90.3% yield). LC-MS: (ES, *m/z*): $[M+1]^+$ 338.0.

D. methyl 2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylatee, **115d**

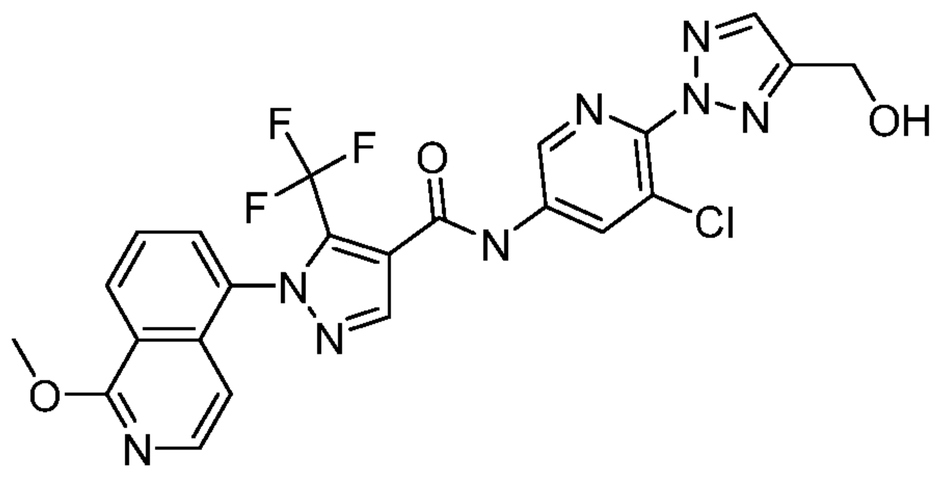


, **115d**

1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (1000 mg, 2.97 mmol), methyl 2-(5-amino-3-chloropyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate (827.30 mg, 3.26 mmol), $POCl_3$ (545.58 mg, 3.56 mmol) were dissolved in DCM (6 mL), and pyridine (703.63 mg, 8.90 mmol) was added. The mixture was stirred at 25 °C for 1 h, sat.$NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were

concentrated under reduced pressure to afford a crude product as a brown oil, which was purified by FFS (petroleum ether/ ethyl acetate=50:50 to petroleum ether/ ethyl acetate=0:100). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as a yellow oil. LCMS (ESI) m/z M+1: 573.1.

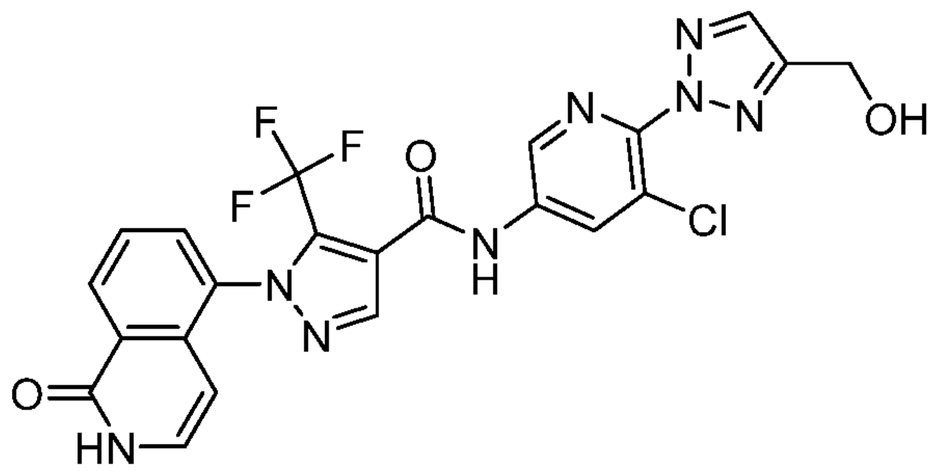
E. N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **115e**



, **115e**

Methyl 2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylatee (250 mg, 0.38 mmol) was dissolved in THF (5 mL) at 0 °C, $LiAlH_4$ (49.85 mg, 1.31 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. Water (80 uL) was added to the mixture at 0 °C and the mixture was stirred for 10 min. NaOH (80 uL, 15% in water) was added to the mixture at 0 °C and the mixture was stirred for 10 min. Water (240 uL) was added to the mixture at 0 °C and the mixture was stirred for 10 min. $MgSO_4$ was added to the mixture and the mixture was filtered. The filtrate was concentrated to give the crude product as a brown oil (200 mg ,86.8%). LCMS (ESI) m/z M+1: 545.0.

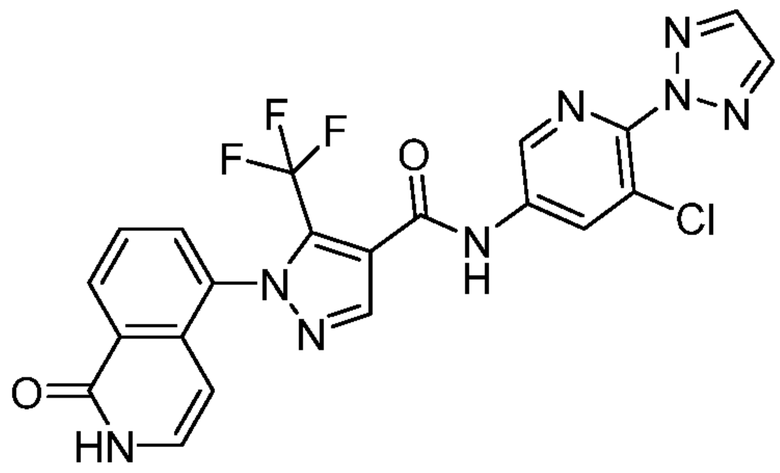
C. N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 115**



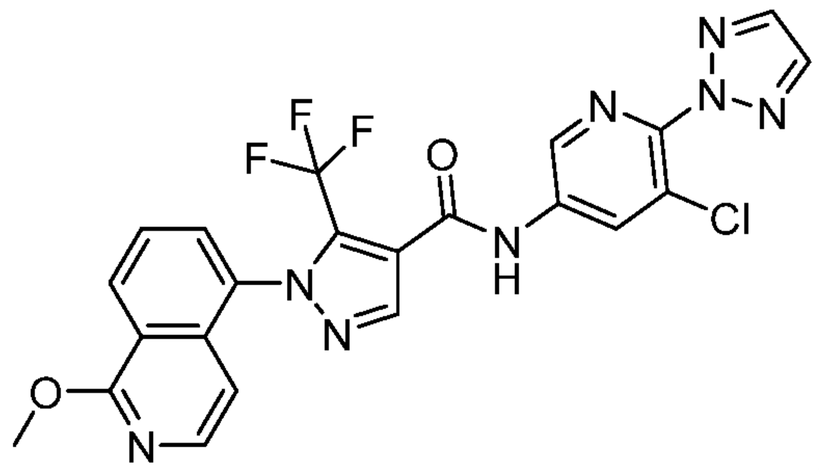
N-(5-Chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (200 mg, 0.33 mmol), and con.HCl (4 mL) was added i-PrOH (8 mL), stirred at 60 °C for 2 h. The mixture was concentrated under reduced pressure to afford crude product as a brown oil, which was purified by preparative HPLC (75 % to 45 % (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (108 mg, 62.4%). LCMS (ESI) m/z M+1: 530.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4.63 (s, 2 H), 5.63 (d, J=7.06 Hz, 1 H), 7.28 (dd, J=7.39, 5.84 Hz, 1 H), 7.65 (t, J=7.83 Hz, 1 H), 7.94 (d, J=7.50 Hz, 1 H), 8.05 (s, 1 H), 8.42 (d, J=7.94 Hz, 1 H), 8.52 (s, 1 H), 8.63 (d, J=2.20 Hz, 1 H), 8.81 (d, J=2.21 Hz, 1 H), 11.22 (s, 1 H), 11.62 (br d, J=5.95 Hz, 1 H).

Example 116

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 116**



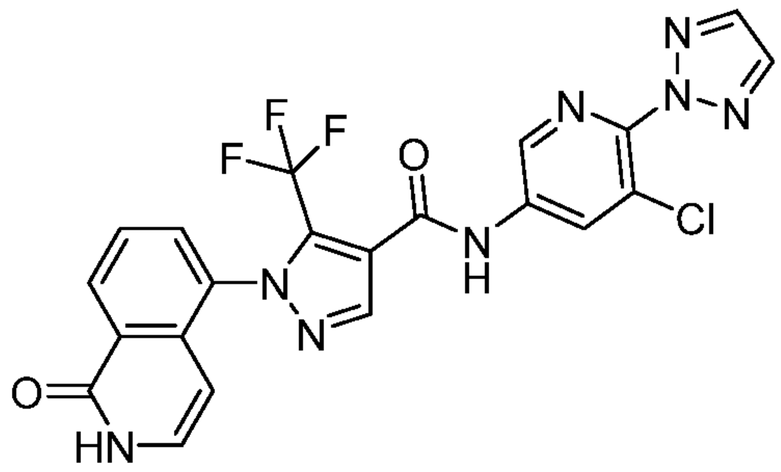
A. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **116a**



, **116a**

1-(1-Methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (200 mg, 0.587 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (117.16 mg, 0.60 mmol), $POCl_3$ (108.05 mg, 0.71 mmol) were dissolved in DCM (8 mL), and pyridine (139.35 mg, 1.76 mmol) was added. The mixture was stirred at 25 °C for 1 h, sat. $NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude product as a brown oil, which was purified by preparative HPLC (50% to 20% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (142 mg, 46.7%). LCMS (ESI) m/z M+1: 514.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 4.10 (s, 3 H), 6.56 (d, J=6.17 Hz, 1 H), 7.78 - 7.85 (m, 1 H), 8.06 (d, J=6.39 Hz, 1 H), 8.10 (d, J=5.95 Hz, 1 H), 8.18 (s, 2 H), 8.45 (d, J=8.16 Hz, 1 H), 8.56 (s, 1 H), 8.66 (d, J=2.21 Hz, 1 H), 8.83 (d, J=2.21 Hz, 1 H), 11.25 (s, 1 H).

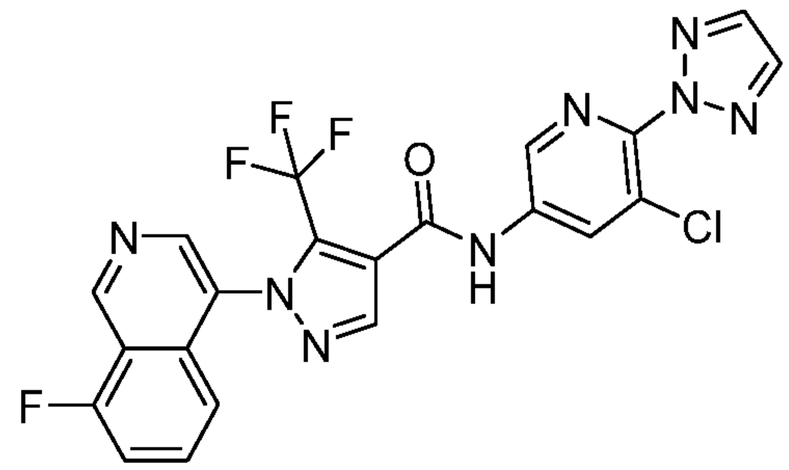
B. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 116**



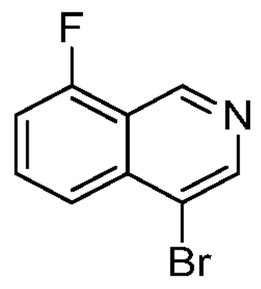
N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (70 mg, 0.14 mmol), and con.HCl (4 mL) was added i-PrOH (8 mL), stirred at 60°C for 2 hrs. The mixture was concentrated under reduced pressure to afford crude as yellow oil, which was purified by preparative HPLC (84 % to 54 % (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (47 mg, 69.4%). LCMS (ESI) m/z M+1: 500.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.63 (d, J=7.50 Hz, 1 H), 7.27 (dd, J=7.17, 6.06 Hz, 1 H), 7.65 (t, J=7.83 Hz, 1 H), 7.93 (d, J=7.06 Hz, 1 H), 8.16 (s, 2 H), 8.41 (d, J=7.94 Hz, 1 H), 8.53 (s, 1 H), 8.64 (d, J=2.21 Hz, 1 H), 8.82 (d, J=2.20 Hz, 1 H), 11.25 (s, 1 H), 11.62 (br d, J=5.73 Hz, 1 H).

Example 117

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 117**



A. 4-bromo-8-fluoroisoquinoline, 117a

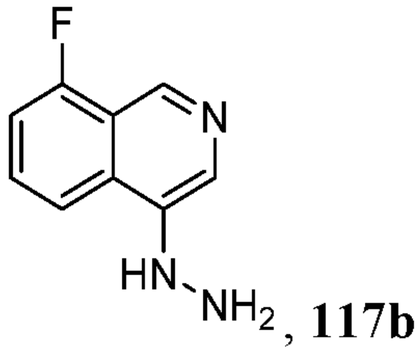


, **117a**

To a solution of 8-fluoroisoquinoline (0.5 g, 3.40 mmol) in CCl_4 (15 mL) was added 1-bromopyrrolidine-2,5-dione (604.78 mg, 3.40 mmol) and (E)-3,3'-(diazene-1,2-diyl)bis(2-methylpropanenitrile) (55.8 mg, 0.34 mmol).The mixture was stirred at 80°C for 3 h. The solvent was concentrated under reduced pressure to give crude product, which was purified by FCC(petroleum ether/ ethyl acetate=1:0 to petroleum ether/ ethyl

acetate=1:1) to afford the title compound (0.21 g, 27.1%) as a yellow oil. LCMS (ESI) m/z M+1: 225.9. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 9.44 (1 H, s), 8.78 (1 H, s), 7.93 (1 H, br d, J=8.38 Hz), 7.74 (1 H, td, J=7.94, 5.51 Hz), 7.27 - 7.36 (1 H, m).

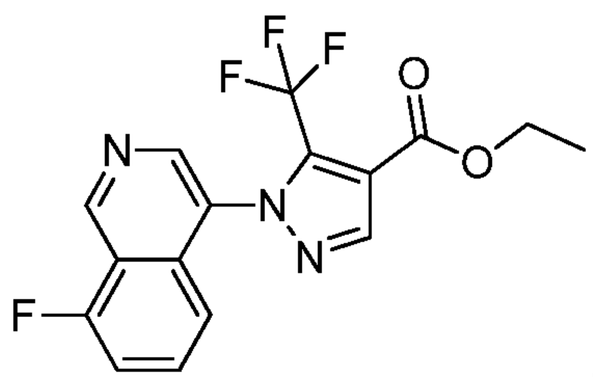
B. 8-fluoro-4-hydrazinylisoquinoline, **117b**



, **117b**

Palladium(ll)(pi-cinnamyl) chloride dimer (23.81 mg, 0.046 mmol) and 4-(2-(di((3S,5S,7S)-adamantan-1-yl)phosphino)phenyl)morpholine (42.62 mg, 0.092 mmol) was added to dioxane (8 mL), immediately evacuated with N_2. The resulting solution was stirred at room temp under N_2 for 10 min. Then was charged with sodium 2-methylpropan-2-olate (176.69 mg, 1.84 mmol) and 4-bromo-8-fluoroisoquinoline (210 mg, 0.92 mmol), sealed, and evacuated with N_2. The resulting mixture was stirred at room temp for 5 min and was then treated with hydrazine hydrate (92.04 mg, 1.84 mmol) via syringe. The mixture was stirred at 50 °C under N_2 for 1.5 hrs, filtered. The filtrate was concentrated under reduced pressure to give the crude product as a yellow solid (260 mg). The mixture was directly used for next step.

C. Ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **117c**

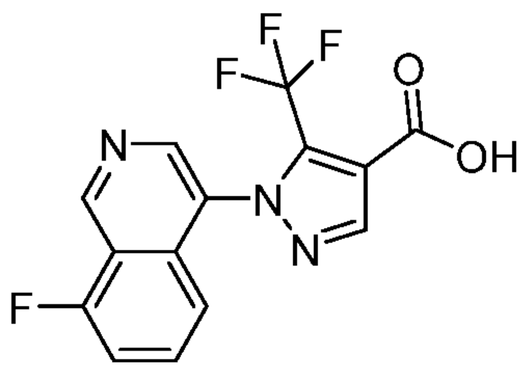


, 117c

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1.762 g, 7.34 mmol), 8-fluoro-4-hydrazinylisoquinoline (260 mg, 1.47 mmol) and ethanol (10 mL) was stirred at 80 °C for 2 h. The resultant solution was concentrated to dryness

under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100/0 to 70/30) to afford the title compound (0.22 g, 42.4%) as a yellow solid. LCMS (ESI) m/z M+1: 354.0.

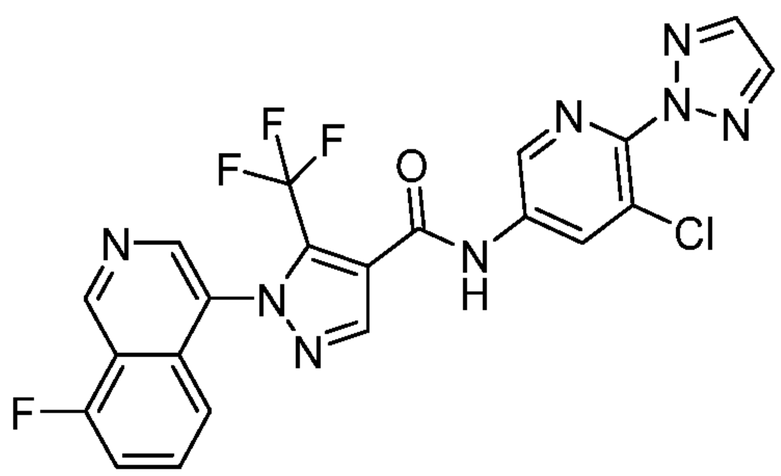
D. 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **117d**



, 117d

Sodium hydroxide (37.36 mg, 0.93 mmol) was added to a solution of ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (220 mg, 0.62 mmol) in THF/ H_2O=3:1(12 mL). The mixture was stirred at room temperature for 3 h. The solvent was concentrated under reduced pressure and 20 mL H_2O was added to the mixture. The mixture was acidified using 1M hydrochloric to pH=5 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrates were concentrated under reduced pressure to afford product as a yellow solid (160 mg, 79.0%).

E. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 117**

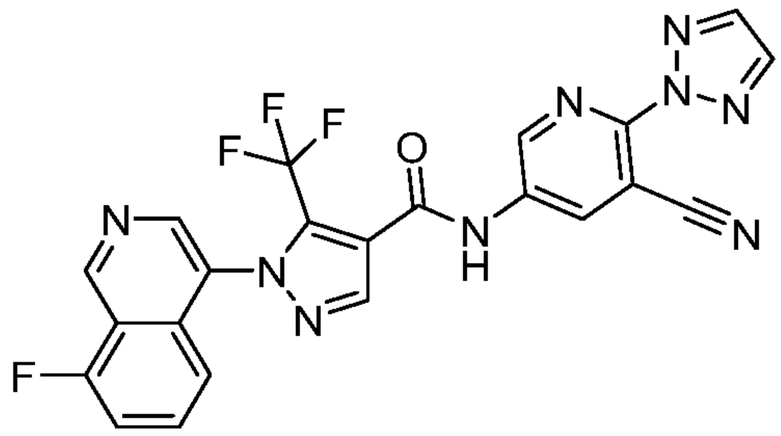


1-(8-Fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (80 mg, 0.25 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (48.12 mg, 0.25

mmol), pyridine (0.10 mL, 1.23 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (0.090 mL, 0.98 mmol) was added. The mixture was stirred at 25 °C for 2 h, Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mLx 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (43% to 73% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (35 mg, 28.2 %). LCMS (ESI) m/z M+1: 502.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.33 (1 H, s), 9.73 (1 H, s), 8.93 (1 H, s), 8.85 (1 H, d, J=1.98 Hz), 8.67 (1 H, d, J=2.21 Hz), 8.65 (1 H, s), 8.17 (2 H, s), 7.90 - 7.98 (1 H, m), 7.69 (1 H, dd, J=10.36, 8.38 Hz), 7.12 (1 H, d, J=8.60 Hz).

Example 118

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 118**

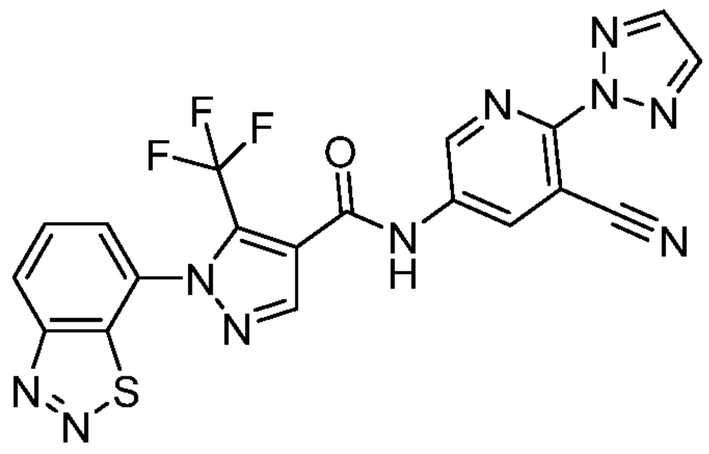


1-(8-Fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (80 mg, 0.25 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile, (45.8 mg, 0.25 mmol), pyridine (0.10 mL, 1.23 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (0.090 mL, 0.98 mmol) was added. The mixture was stirred at 25 °C for 2 h, Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (43% to 63% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (36 mg, 29.1 %). LCMS (ESI) m/z M+1: 493.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.40 (1 H, s), 9.73 (1 H, s), 9.09 (1 H, d, J=2.43 Hz), 8.93 (1 H,

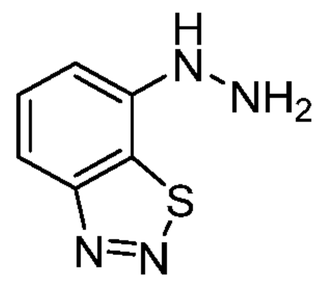
s), 8.87 (1 H, d, J=2.43 Hz), 8.65 (1 H, s) 8.29 (2 H, s), 7.89 - 7.99 (1 H, m), 7.64 - 7.72 (1 H, m), 7.12 (1 H, d, J=8.38 Hz).

Example 119

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 119**



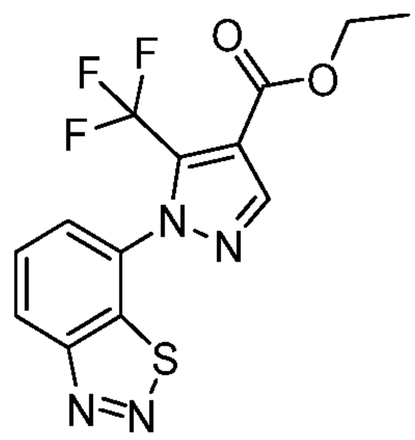
A. 7-hydrazinylbenzo[d][1,2,3]thiadiazole, **119a**



, **119a**

To a stirring solution of benzo[d][1,2,3]thiadiazol-7-amine (2 g, 13.23 mmol) in HCl (6 N, 50 mL) at -10° C was added a solution of sodium nitrite (1.37 g, 19.85 mmol) in H_2O (20 mL) below -20° C. The reaction mixture was stirred at rt for 0.5 hr. Then cooled to -20 °C, tin(ii) chloride dihydrate (5.97 g, 26.45 mmol) was added portions to the mixture and stirred for 1 h. The reaction mixture was basified with 3 M NaOH and the aqueous extracted with EtOAc (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude (2.5 g) as brown solid, which was used for the next step without further purification. LCMS (ESI) m/z M+1: 167.1.

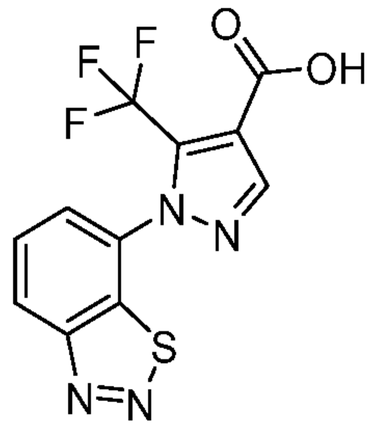
B. Ethyl 1-(benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **119b**



, 119b

7-Hydrazinylbenzo[d][1,2,3]thiadiazole (2.5 g, 5.71 mmol) was dissolved in ethanol (30 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (3.28 g, 13.64 mmol) was added and stirred at 70°C for 2 h before cooling to room-temperature. The combined mixture was concentrated under reduced pressure to afford crude product as yellow oil, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 85/15) to afford the title compound (1.2 g, 61.4%) as a yellow solid. LCMS (ESI) m/z M+1: 342.9.

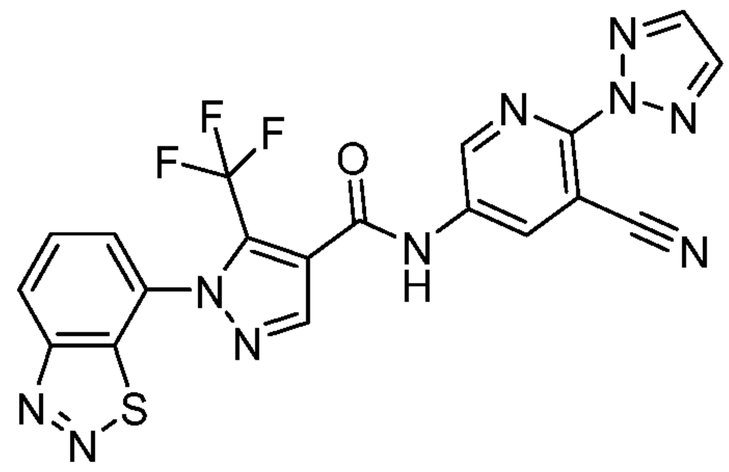
C. 1-(benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **119c**



, 119c

Ethyl 1-(benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (1.2 g, 3.51 mmol) was dissolved in THF (8 mL) and water (8 mL). Lithium hydroxide (251.87 mg, 10.52 mmol) was added. The reaction mixture was stirred at 30 °C for 16 h. The reaction mixture was adjust to pH=5 using HCl (2 N), extracted with CH_2Cl_2/MeOH (10/1, 60 mLx 5). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude title compound (900 mg, 81.0%) as a yellow solid. LCMS (ESI) m/z M+1: 315.1.

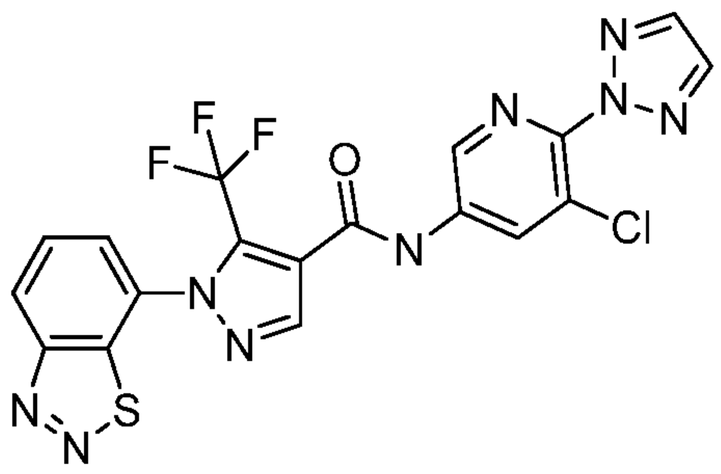
D. 1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 119**



1-(Benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (300 mg, 0.95 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile, (229.0 mg, 1.23 mmol), pyridine (449.05 mg, 5.68 mmol) were dissolved in CH_2Cl_2 (30 mL), and phosphorus oxychloride (435.23, 2.84 mmol) was added. The mixture was stirred at 25 °C for 2 h. Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as yellow oil, which was purified by preparative HPLC (45% to 75% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (200 mg, 43.1%). LCMS (ESI) m/z M+1: 483.0. ^{1}H NMR (400MHz, DMSO-d6) δ= 11.47 (s, 1H), 9.08 (d, J=2.4 Hz, 1H), 8.99 (d, J=8.4 Hz, 1H), 8.85 (d, J=2.2 Hz, 1H), 8.63 (s, 1H), 8.31 (s, 2H), 8.15 - 8.10 (m, 1H), 8.06 - 7.99 (m, 1H).

Example 120

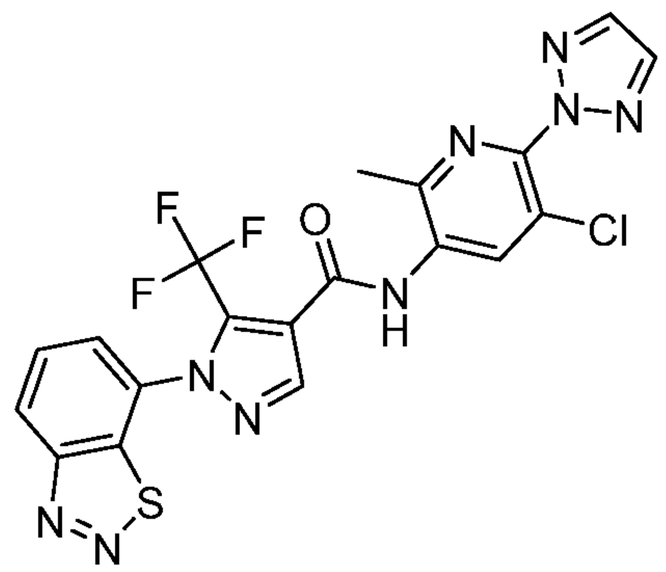
1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 120**



1-(Benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.28 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, (53.95 mg, 0.28 mmol), pyridine (130.9 mg, 1.66 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (126.87, 0.83 mmol) was added. The mixture was stirred at 25 °C for 2 h. Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mLx 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as yellow oil, which was purified by preparative HPLC (45% to 75% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (18 mg, 13.2%). LCMS (ESI) m/z M+1: 492.0. ^{1}H NMR (400MHz, DMSO-d6) δ= 11.43 (s, 1H), 8.99 (d, J=8.2 Hz, 1H), 8.84 (d, J=2.2 Hz, 1H), 8.66 (d, J=2.2 Hz, 1H), 8.64 (s, 1H), 8.20 (s, 2H), 8.15 - 8.10 (m, 1H), 8.06 - 8.00 (m, 1H).

Example 121

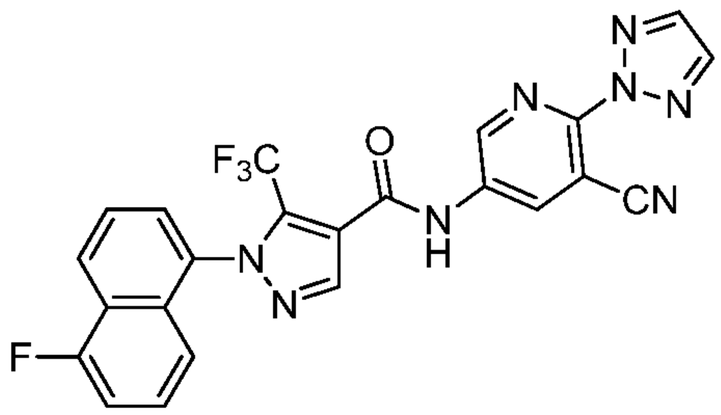
1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 121**



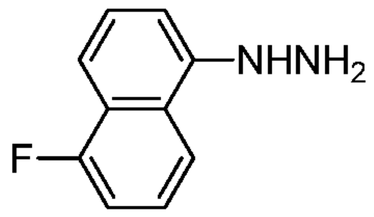
1-(Benzo[d][1,2,3]thiadiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (149.93 mg, 0.47 mmol), 5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, (109.09 mg, 0.52 mmol), pyridine (224.52 mg, 2.84 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (217.62 mg, 1.42 mmol) was added. The mixture was stirred at 25 °C for 2 h. Sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (45% to 75% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (102 mg, 42.4%). LCMS (ESI) m/z M+1: 505.9. ^{1}H NMR (400MHz, DMSO-d6) δ= 10.73 (s, 1H), 8.98 (d, J=8.2 Hz, 1H), 8.63 (s, 1H), 8.47 (s, 1H), 8.19 (s, 2H), 8.13 - 8.09 (m, 1H), 8.06 - 8.01 (m, 1H), 2.56 (s, 3H).

Example 122

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 122**



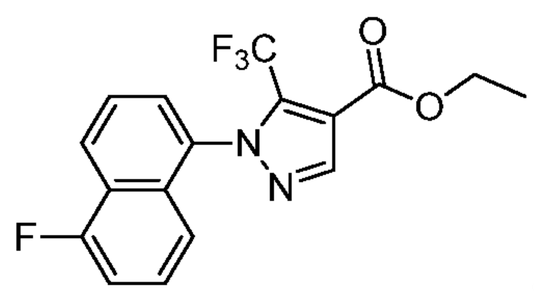
A. (5-fluoronaphthalen-1-yl)hydrazine, **122a**



, **122a**

A mixture of $\{Pd(cinnamyl)Cl\}_2$ (11.51 mg, 0.022 mmol) and Mor-DalPhos (20.60 mg, 0.044 mmol) in dioxane (2 mL) was evacuated with argon (4x). The resulting clear yellow solution was stirred at room temp under argon for 10 min. 1-Bromo-5-fluoronaphthalene (100 mg, 0.44 mmol) and t-BuONa (85.31 mg, 0.89 mmol) was added to the mixture and the mixture was evacuated with argon (4x). The resulting yellow mixture was stirred at room temp for 5 min and was then treated with hydrazine hydrate (45.40 mg, 0.889 mmol) via syringe. The reaction mixture was evacuated with argon (4x). Then the mixture was stirred at 50°C under argon for 4hrs. The mixture was filtered and washed with ethyl acetate (5 mL x 3). The filtrate was collected and concentrated to afford crude product (100 mg, >100% yield) as a brown solid which was used directly for the next step.

B. Ethyl 1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **122b**

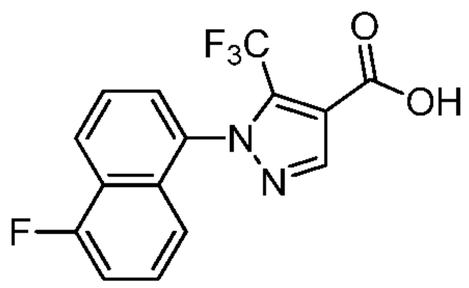


, 122b

A solution of (5-fluoronaphthalen-1-yl)hydrazine, **122a** (100 mg, 0.57 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (204.48 mg, 0.85 mmol), triethylamine (171.97 mg, 1.70 mmol) in EtOH (10 mL) was stirred at 80 °C for 12 h. The

mixture was concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 20:1 to 1:1). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **122b** (100 mg, 46.7% yield) as a yellow solid. LCMS (ESI) m/z M+1: 352.9.

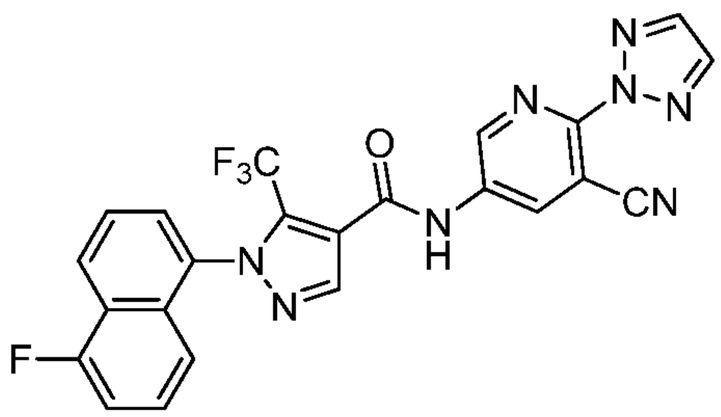
C. 1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **122c**



, **122c**

A solution of ethyl 1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole -4-carboxylate, **122b** (100 mg, 0.27 mmol), LiOH (22.23 mg, 0.53 mmol) in MeOH (10 mL), THF (10 mL) and water (10 mL) was stirred at rt for 3h. To the mixture was added 5% $KHSO_4$ to adjust the pH to 3~4. Water (100 mL) and ethyl acetate (100 mL) were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford **122c** (90 mg, 94.1% yield) as a yellow solid used for the next step directly. LCMS (ESI) m/z M+H: 324.8

D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 122**

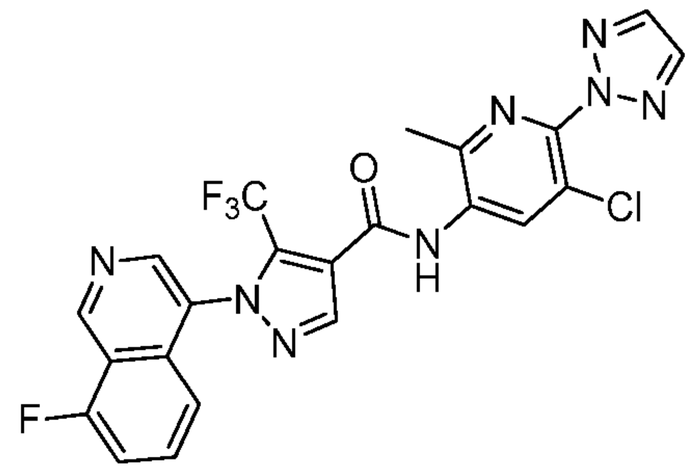


$POCl_3$ (76.46 mg, 0.50 mmol) was added to a solution of 1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **122c** (90 mg, 0.25 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (46.42 mg, 0.25 mmol), pyridine (49.30 mg 0.62

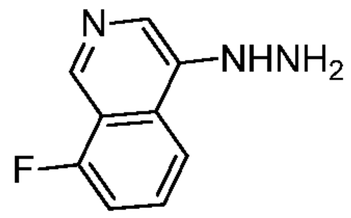
mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 2 h, 50 mL water and 50 mL CH_2Cl_2 were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (47% to 77% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (33.5 mg 26.5% yield) as a white solid. LCMS (ESI) m/z M+1: 492.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 9.08 (d, J=2.43 Hz, 1 H), 8.86 (d, J=2.43 Hz, 1 H), 8.58 (s, 1 H), 8.32 (d, J=8.38 Hz, 1 H), 8.28 (s, 2 H), 7.90 (d, J=7.28 Hz, 1 H), 7.74 - 7.83 (m, 1 H), 7.60 (td, J=8.10, 5.62 Hz, 1 H), 7.49 (dd, J=10.47, 7.61 Hz, 1 H), 6.93 (d, J=8.38 Hz, 1 H).

Example 123

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 123**



A. 8-fluoro-4-hydrazinylisoquinoline, **123a**

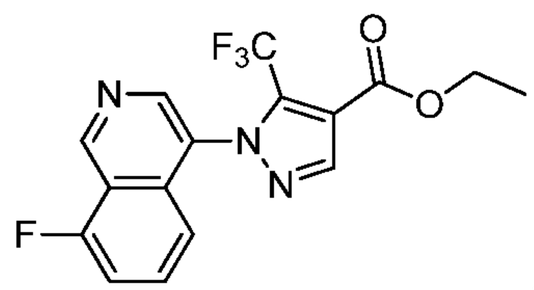


, **123a**

A mixture of $\{Pd(cinnamyl)Cl\}_2$ (68.76 mg, 0.13 mmol) and Mor-DalPhos (123.06 mg, 0.27 mmol) in dioxane (10 mL) was evacuated with argon (4x). The resulting clear yellow solution was stirred at room temp under argon for 10 min. 4-bromo-8-fluoroisoquinoline (600 mg, 2.65 mmol) and t-BuONa (509.63 mg, 5.31 mmol) was added to the mixture and the mixture was evacuated with argon (4x). The resulting yellow reaction was stirred at room temp for 5 min and was then treated with hydrazine hydrate (271.18 mg, 5.31 mmol) via syringe. The reaction mixture was evacuated with argon (4x).

Then the mixture was stirred at 50 °C under argon for 2 h. The mixture was filtered and washed with ethyl acetate (50 mL x 3), the filtrate was collected and concentrated to afford crude **123a** (510 mg, >100% yield) as a brown solid, used directly for the next step.

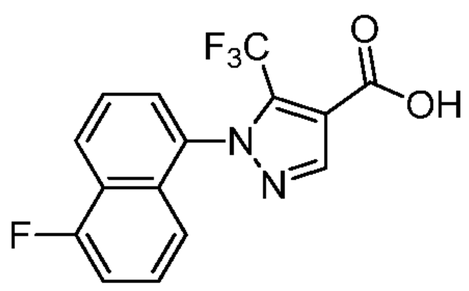
B. Ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **123b**



, **123b**

A solution of 8-fluoro-4-hydrazinylisoquinoline, **123a** (510 mg, 2.88 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1037.0 mg, 4.32 mmol), triethylamine (872.17 mg, 8.64 mmol) in EtOH (20 mL) was stirred at 80 °C for 12 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 20:1 to 5:1). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **123b** (510 mg, 40.7% yield) as a yellow solid. LCMS (ESI) m/z M+1: 353.9.

C. 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **123c**

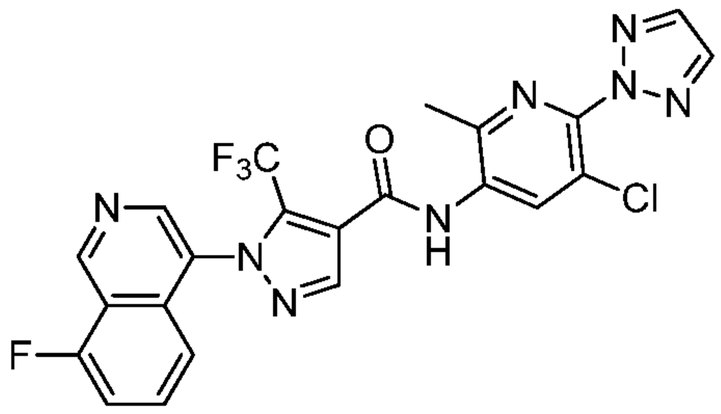


, **123c**

A solution of ethyl 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole -4-carboxylate, **123b** (510 mg, 1.17 mmol), LiOH (98.21 mg, 2.34 mmol) in THF (20 mL) and water (20 mL) was stirred at rt for 2 h. The mixture was added 5% $KHSO_4$ to adjust pH 3~4. Water (100 mL) and ethyl acetate (100 mL) were added to the mixture. The

organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **123c** (420 mg) as a yellow solid , used directly for the next step.. LCMS (ESI) m/z M+H: 325.9 .

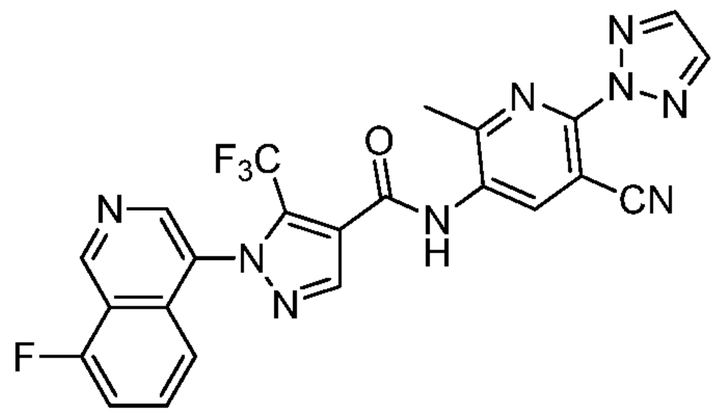
D. N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 123**



$POCl_3$ (198.02 mg, 1.29 mmol) was added to a solution of 1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **123c** (210 mg, 0.65 mmol), 5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (162.44 mg, 0.78 mmol), pyridine (127.69 mg 1.61 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 3h, 50 mL H_2O and 50 mL CH_2Cl_2 were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and the filtrate concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (37% to 67% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (86.0 mg 25.8% yield) as a white solid. LCMS (ESI) m/z M+1: 516.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 10.66 (s, 1 H), 9.72 (s, 1 H), 8.91 (s, 1 H), 8.62 (s, 1 H), 8.42 (s, 1 H), 8.16 (s, 2 H), 7.94 (td, J=8.10, 5.62 Hz, 1 H), 7.68 (dd, J=10.36, 7.94 Hz, 1 H), 7.13 (d, J=8.38 Hz, 1 H), 2.54 (s, 3 H).

Example 124

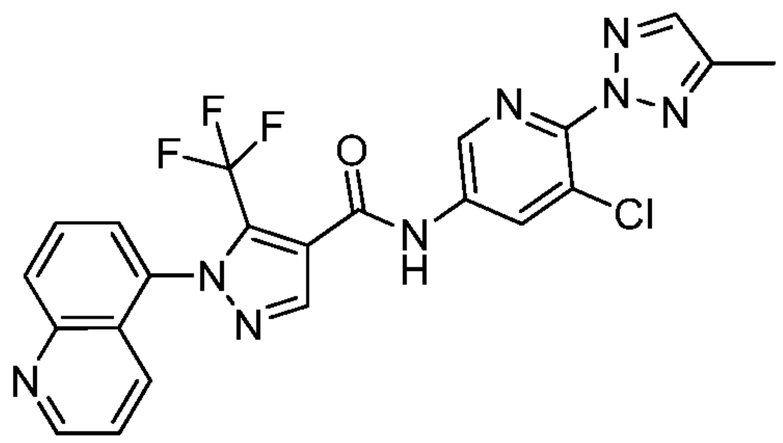
N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 124**



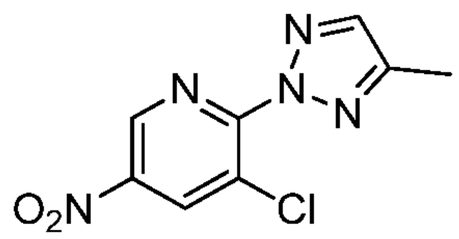
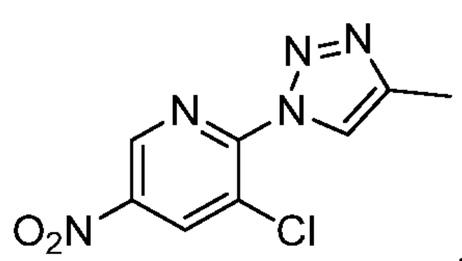
$POCl_3$ (94.27 mg, 0.62 mmol) was added to a solution of 1-(8-fluoroisoquinolin -4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.31 mmol), 5-amino-6-methyl-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (73.87 mg, 0.37 mmol), pyridine (60.81 mg 0.77 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 3h, 50 mL H_2O and 50 mL CH_2Cl_2 were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (30% to 60% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (37.6 mg 24.1% yield) as a white solid. LCMS (ESI) m/z M+1: 507.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 10.71 (s, 1 H), 9.72 (s, 1 H), 8.91 (s, 1 H), 8.64 (d, J=15.88 Hz, 2 H), 8.29 (s, 2 H), 7.90 - 7.98 (m, 1 H), 7.64 - 7.72 (m, 1 H), 7.13 (d, J=8.60 Hz, 1 H), 2.64 (s, 3 H).

Example 125

N-(5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **125**

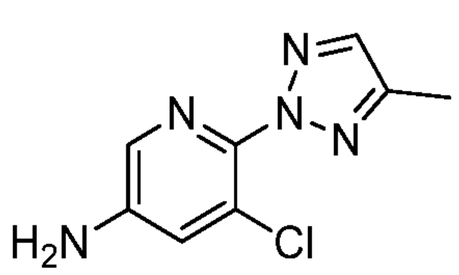
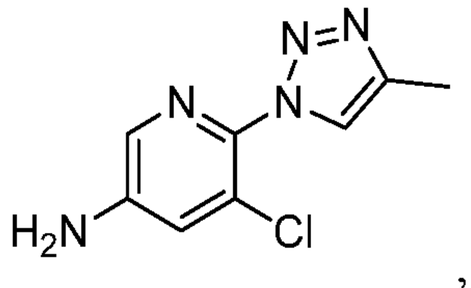


A. mixture of 3-chloro-2-(4-methyl-2H-1,2,3-triazol-2-yl)-5-nitropyridine and 3-chloro-2-(4-methyl-1H-1,2,3-triazol-1-yl)-5-nitropyridine, **125a**



, **1a**

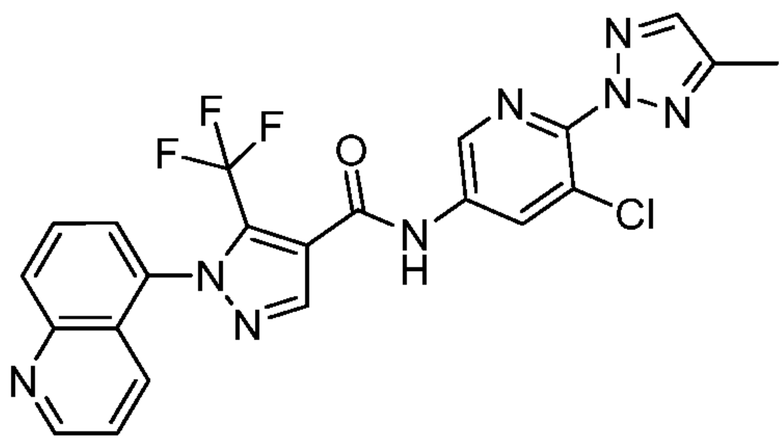
A solution of 4-methyl-1H-1,2,3-triazole (500 mg, 6.02 mmol), 2,3-dichloro-5-nitropyridine (1277.42 mg, 6.62 mmol), K_2CO_3 (2491.22 mg, 18.05 mmol) in CH_3CN (5 mL) was stirred at rt for 12 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 20:1 to 1:1). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **125a** (1.1 g, 76.3%) as a yellow solid. LCMS (ESI) m/z M+1: 239.7.

B. mixture of 5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-amine and 5-chloro-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-amine, **125b**



, **125b**

Zn (1491.96 mg, 22.95 mmol) was added to a solution of mixture of 3-chloro-2-(4-methyl-2H-1,2,3-triazol-2-yl)-5-nitropyridine and 3-chloro-2-(4-methyl-1H-1,2,3-triazol-1-yl)-5-nitropyridine**, 125a** (1.1 g, 2.30 mmol) in aqNH_4Cl (30 mL) and H_2O (30 mL). The mixture was stirred at rt for 16 h. To the suspension was added aq $NaHCO_3$ to adjust to pH 9~10, and the mixture was filtered through a pad of diatomaceous earth. The filter cake was washed with CH_2Cl_2 (100 mL×3). The combined filtrates were washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford mixture of 5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-amine and 5-chloro-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-amine, **125b** (1 g) as a brown solid, used directly for the next step. LCMS (ESI) m/z M+H: 209.7

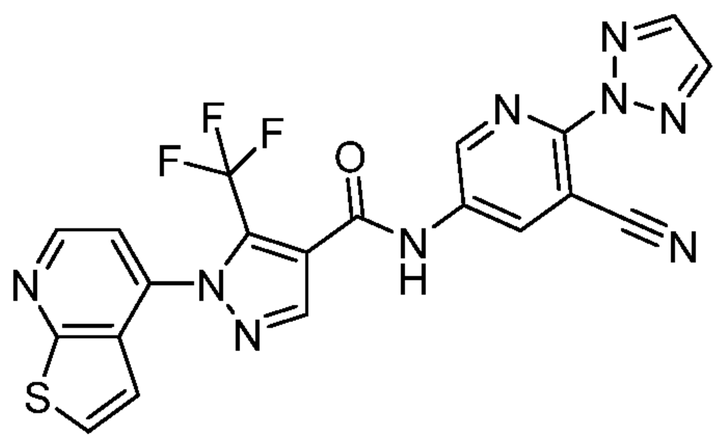
C. N-(5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 125**



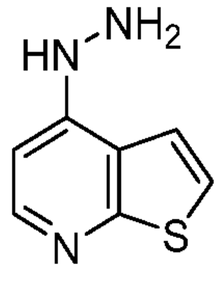
$POCl_3$ (182.86 mg, 1.19 mmol) was added to a solution of **125b** (300 mg, 0.72 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (183.19 mg, 0.60 mmol), pyridine (117.91 mg 1.49 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 2h, 50 mL H_2O and 50 mL CH_2Cl_2 were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (208 mg 69.8% yield) as a white solid. LCMS (ESI) m/z M+1: 499.0. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.45 (s, 1 H), 9.06 (t, J=2.54 Hz, 1 H), 8.89 (s, 1 H), 8.60 - 8.75 (m, 2 H), 8.33 (d, J=8.38 Hz, 1 H), 7.88 - 8.03 (m, 3 H), 7.68 (d, J=2.65 Hz, 2 H), 2.34 (s, 3 H).

Example 126

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 126**



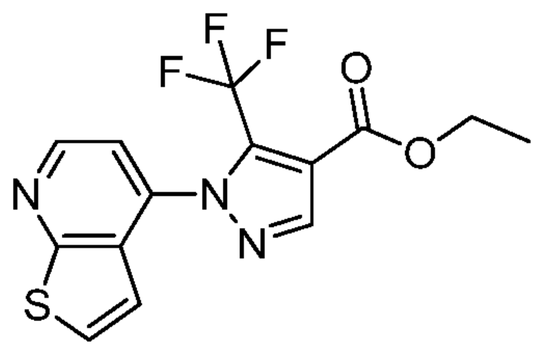
A. 4-hydrazinylthieno[2,3-b]pyridine, **126a**



, **126a**

A solution of 4-chlorothieno[2,3-b]pyridine (600 mg, 3.54 mmol) in hydrazine (5 mL, 98%) was stirred at 100°C overnight. The solid was filtered and washed by 2 mL water. The solid was collected and dried to afford **126a** (550 mg, 88.2% yield) as a white solid. LCMS (ESI) m/z M+1: 165.9.

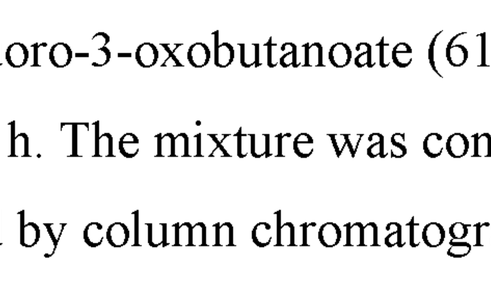
B. ethyl 1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **126b**



, **126b**

A solution of 4-hydrazinylthieno[2,3-b]pyridine (300 mg, 1.70 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (613.23 mg, 2.55 mmol), in EtOH (5 mL) was stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 20/80). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **126b** (500 mg, 86.1% yield) as a yellow solid.

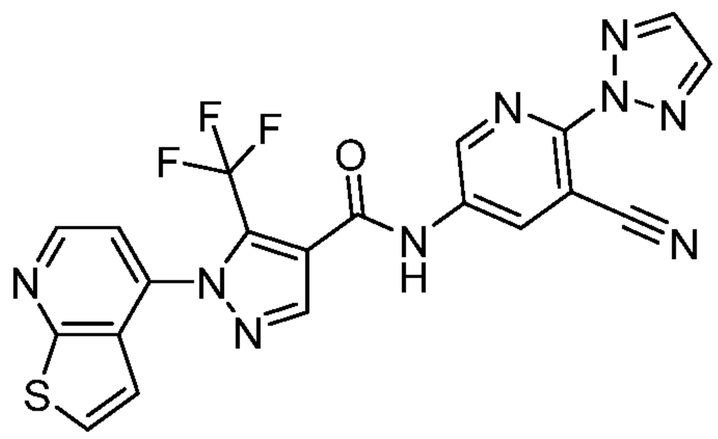
C. 1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **126c**



, **126c**

A solution of ethyl 1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **126b** (150 mg, 0.44 mmol), LiOH (18.44 mg, 0.44 mmol) in EtOH /H_2O (2/1, 2 mL) was stirred at room temperature overnight. 1N HCl solution was added to neutralize the reaction solution. The mixture was extracted with ethyl acetate (5 mLx 3). The separated organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated to afford **126c** (137 mg, crude product) as a yellow solid. LCMS (ESI) m/z M+1: 313.9.

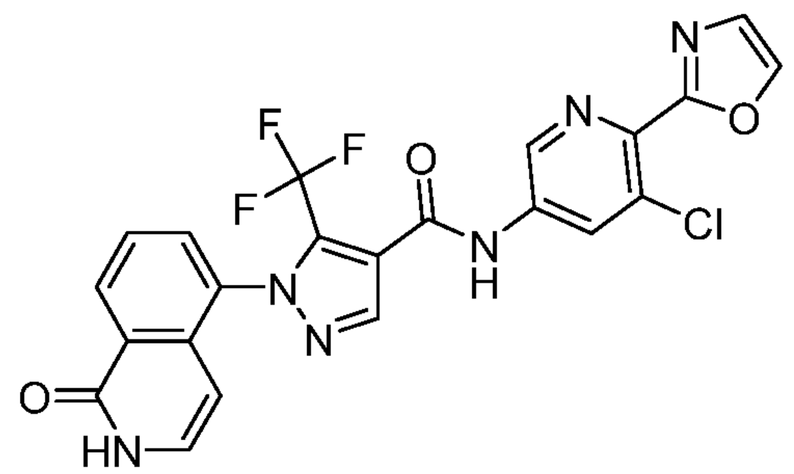
D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 126**



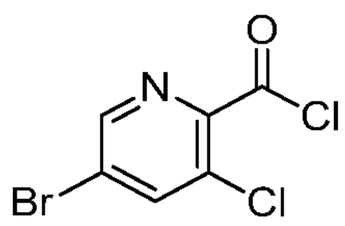
Phosphorus oxychloride (41.66 uL, 0.45 mmol) was added to a solution of 1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **126c** (70 mg, 0.22 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (62.40 mg, 0.34 mmol), pyridine (180.73 uL, 2.24 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 2 h, 5 mL H_2O was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (42% to 72% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (50 mg, 46.4%). LCMS (ESI) m/z M+1: 481.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.17 (d, J=6.17 Hz, 1 H), 7.73 (d, J=5.07 Hz, 1 H), 8.13 (d, J=6.17 Hz, 1 H), 8.31 (s, 2 H), 8.62 (s, 1 H), 8.84 (d, J=4.85 Hz, 1 H), 8.87 (d, J=2.43 Hz, 1 H), 9.08 (d, J=2.43 Hz, 1 H), 11.36 (s, 1 H).

Example 127

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, Cpd 127



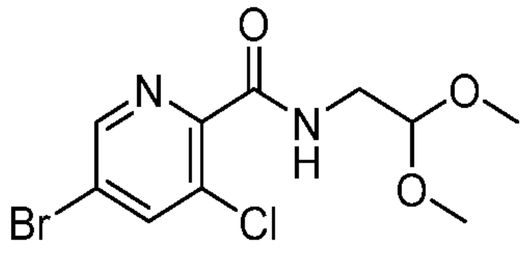
A. 5-bromo-3-chloropicolinoyl chloride, **127a**



, **127a**

5-bromo-3-chloropicolinic acid (15 g, 63.44 mmol) was suspended in CH_2Cl_2 (250 mL) and stirred at 0 °C. oxalyl chloride (15 mL, 176.09 mmol) was added dropwise then DMF (drops) added. The reaction mixture was stirred at 0 °C for 1 h and stirred at 20 °C for 1 h. The yellow solution was concentrated under reduced pressure to afford the compound (17 g) as a yellow solid.

B. 5-bromo-3-chloro-N-(2,2-dimethoxyethyl)picolinamide, **127b**

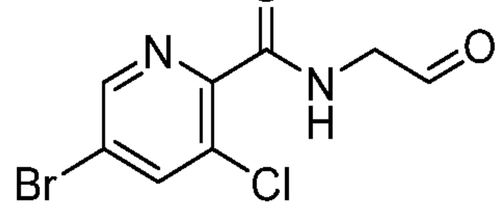


, 127b

5-Bromo-3-chloropicolinoyl chloride (17 g, 66.69 mmol) was dissolved in CH_2Cl_2 (250 mL) and added dropwise to the mixture of 2,2-dimethoxyethanamine (14.02g, 133.39 mmol) and TEA (13.50 g, 133.39 mmol) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. H_2O (300 mL) was added and extracted with CH_2Cl_2 (300 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as a brown oil, which was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2/ethyl acetate from 100/0 to 80/20). The

desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title compound (16 g, 74.1%) as a yellow solid.

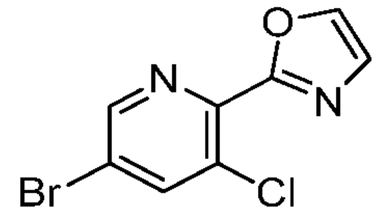
C. 5-bromo-3-chloro-N-(2-oxoethyl)picolinamide, **127c**



, 127c

To a solution of 5-bromo-3-chloro-N-(2,2-dimethoxyethyl)picolinamide (16 g, 49.45 mmol) in MeCN (160 mL) was added 2 N HCl (160 mL). The reaction mixture was stirred at rt for 16 h. The reaction mixture was adjust to pH 7.5 using sat. $NaHCO_3$, extracted with EtOAc (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude (12 g, 87.5%) as a yellow solid. LCMS (ESI) m/z M+1: 278.8.

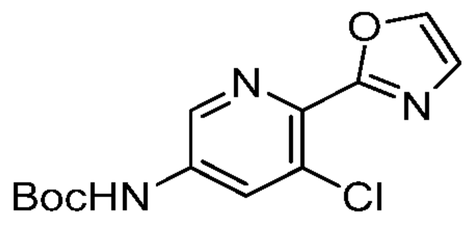
D. 2-(5-bromo-3-chloropyridin-2-yl)oxazole, **127d**



, 127d

5-Bromo-3-chloro-N-(2-oxoethyl)picolinamide (12 g, 43.24 mmol) was dissolved in dioxane (200 mL) and phosphorus oxychloride (19.89 g, 129.73 mmol) added. The reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was poured into water (800 mL), stirred at rt for 0.5 h, then extracted with EtOAc (400 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford a black oil. The black oil was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 70/30) to afford the title compound (1.5 g, 13.3%) as a yellow solid. LCMS (ESI) m/z M+1: 258.9.

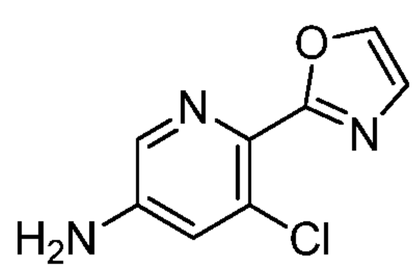
E. tert-butyl (5-chloro-6-(oxazol-2-yl)pyridin-3-yl)carbamate, **127e**



, **127e**

2-(5-Bromo-3-chloropyridin-2-yl)oxazole (1.5 g, 5.78 mmol) and *tert*-butyl carbamate (1.35 g, 11.56 mmol) were dissolved in dioxane (30 mL), $Pd_2(dba)_3$ (264.67 mg, 0.29 mmol), Xantphos (333.48 mg, 0.58 mmol) and cesium carbonate (3.77 g, 11.56 mmol) were added and purged with N_2 for 1 min. The reaction mixture was stirred at 90 °C for 16 h. The combined mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (50 mL x 3). The filtrates were concentrated under reduced pressure to afford a crude product as a yellow oil, which was purified by flash column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 40/60). The desired fraction was collected and the solvent was concentrated under reduced pressure to afford the title compound (970 mg, 61.4%) as a yellow solid. LCMS (ESI) m/z M+1: 296.1.

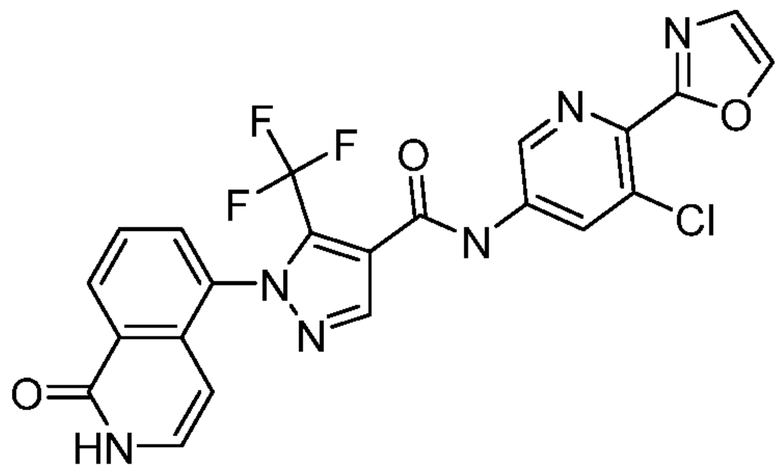
F. 5-chloro-6-(oxazol-2-yl)pyridin-3-amine, **127f**



, **127f**

Tert-Butyl (5-chloro-6-(oxazol-2-yl)pyridin-3-yl)carbamate (970 mg, 3.28 mmol) was dissolved in CH_2Cl_2 (5 mL) and HCl/dioxane (5.4 mL, 21.6 mmol) was added. The reaction mixture was stirred at 30 °C for 4 h. The reaction mixture was concentrated under reduced pressure to afford crude as a yellow oil, and adjust to pH 8 using sat .Na_2CO_3, extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the product (650 mg, 95.4%) as a yellow oil. LCMS (ESI) m/z M+1: 196.1.

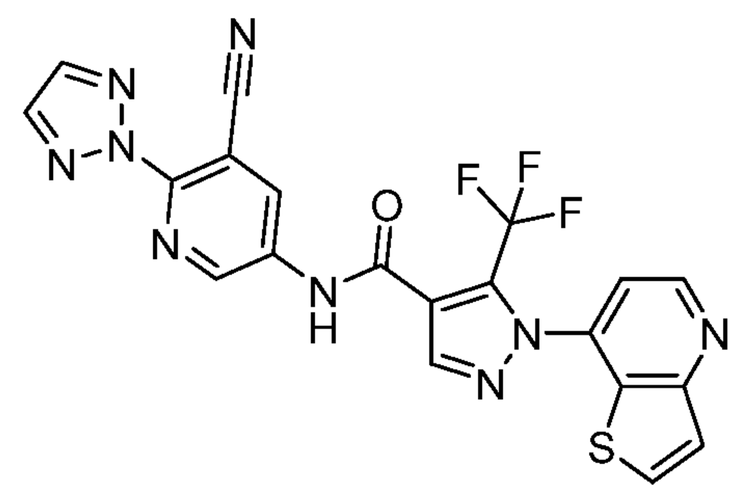
G. N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide **Cpd 127**



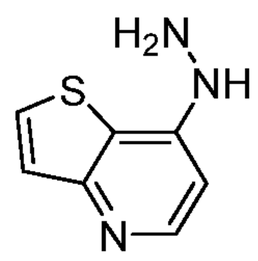
1-(1-Oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (876.66 mg, 2.25 mmol), 5-chloro-6-(oxazol-2-yl)pyridin-3-amine (400 mg, 2.05 mmol) and pyridine (970.52 mg, 12.27 mmol) were dissolved in CH_2Cl_2 (40 mL), and phosphorus oxychloride (940.66 mg, 6.14 mmol) was added. The mixture was stirred at 25 °C for 3 h, sat. $NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (34% to 54% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (240 mg, 23.2%). LCMS (ESI) m/z M+1: 500.9. ^{1}H NMR (400MHz, DMSO-d6) δ= 11.64 (br d, J=5.3 Hz, 1H), 11.29 (s, 1H), 8.97 (s, 1H), 8.63 - 8.53 (m, 2H), 8.44 (d, J=8.2 Hz, 1H), 8.34 (s, 1H), 7.95 (d, J=7.7 Hz, 1H), 7.67 (t, J=7.9 Hz, 1H), 7.51 (s, 1H), 7.30 (t, J=6.6 Hz, 1H), 5.66 (d, J=7.3 Hz, 1H).

Example 128

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 128**



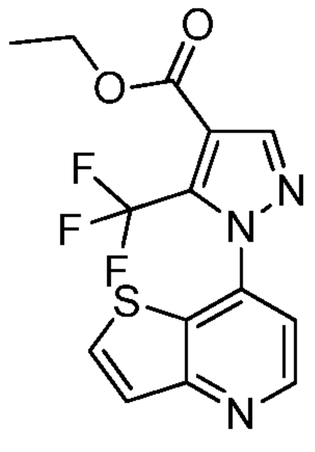
A. 7-hydrazinylthieno[3,2-b]pyridine, **128a**



, **128a**

7-chlorothieno[3,2-b]pyridine (180 mg, 1.06 mmol) in $NH_2NH_2.H_2O$ (7 mL) was reacted at 26°C for 16 h. The mixture was extracted with 20 x 3 mL CH_2Cl_2, the solvent was concentrated under reduced pressure the give the desired compound.

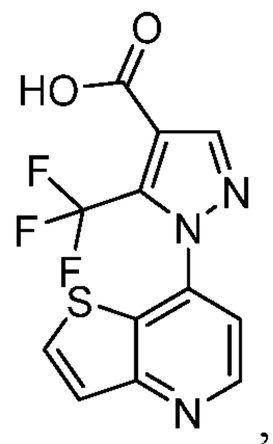
B. ethyl 1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **128b**



, **128b**

7-Hydrazinylthieno[3,2-b]pyridine (90 mg, 0.55 mmol) was added to a solution of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (196.25 mg, 0.82 mmol) in EtOH (5 mL) was reacted at 80°C for 3 h. The mixture was concentrated under reduced pressure, then was purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate=60:40). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as brown oil. LCMS (ESI) m/z M+1: 342.2.

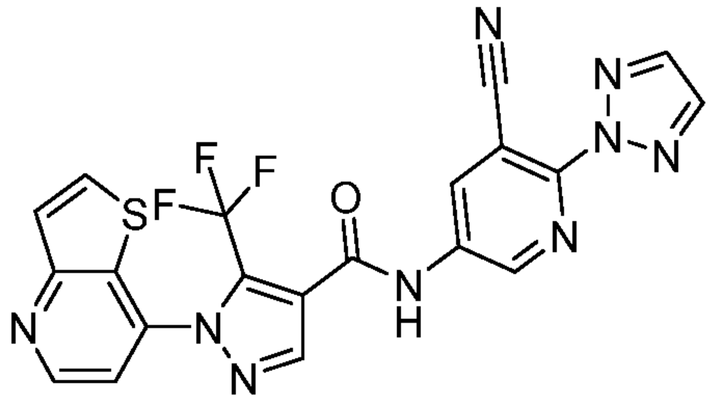
C. 1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **128c**



, **128c**

NaOH (25.23 mg, 0.63 mmol) was added to a solution of ethyl 1-(thieno[3,2-b]pyridin-7-yl) -5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (75 mg, 0.21 mmol) in EtOH/H20=1:1 (3 mL) was reacted at 28°C for 2 h. The solvent was concentrated under reduced pressure the give the desired compound.. LCMS (ESI) m/z M+1: 314.2

D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 128**

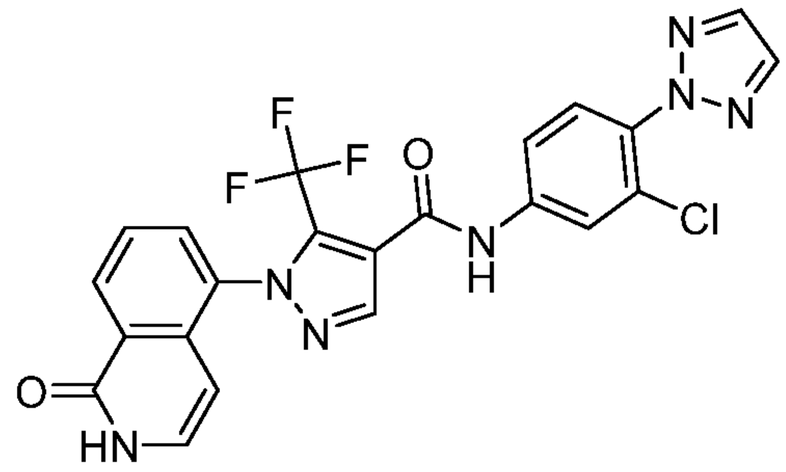


1-(Thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.19 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (42.76 mg, 0.23 mmol), $POCl_3$ (35.21 mg, 0.23 mmol) were dissolved in DCM (2 mL), and pyridine (45.41 mg, 0.57 mmol) was added. The mixture was stirred at 25 °C for 2 h, sat.NH_4Cl (20 mL) was added and extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as a yellow oil, which was purified by preparative HPLC (73% to 43% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (46 mg, 49.7%). LCMS (ESI) m/z M+1: 481.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm

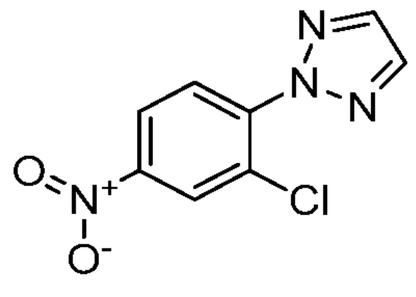
7.67 (br d, J=4.63 Hz, 1 H), 7.75 (d, J=5.51 Hz, 1 H), 8.21 - 8.38 (m, 1 H), 8.23 - 8.37 (m, 2 H), 8.74 (s, 1 H), 8.87 - 8.96 (m, 2 H), 9.14 (d, J=2.21 Hz, 1 H), 11.66 (s, 1 H).

Example 129

N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 129**



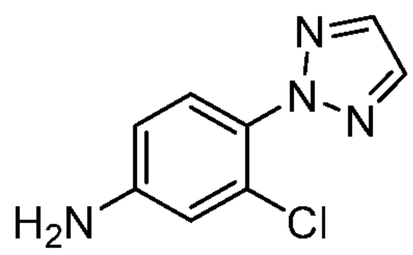
A. 2-(2-chloro-4-nitrophenyl)-2H-1,2,3-triazole, **129a**



, **129a**

2-Chloro-1-fluoro-4-nitrobenzene (3 g, 17.09 mmol), 1H-1,2,3-triazole (1.30g, 18.80 mmol) and potassium carbonate (3.54 g, 25.63 mmol) were added to DMF (50 mL) and stirred at 55 °C for 3 hr. The reaction mixture was concentrated under reduced pressure to afford crude as a yellow solid. Sat.NH_4Cl (100 mL) was added and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40) to afford the title compound (1.9 g, 49.5%) as a yellow solid. ^1H NMR (400MHz, CHLOROFORM-d) δ = 8.49 (d, J=2.5 Hz, 1H), 8.28 (dd, J=2.5, 8.8 Hz, 1H), 7.97 (s, 2H), 7.93 (d, J=8.8 Hz, 1H), 7.95 - 7.91 (m, 1H).

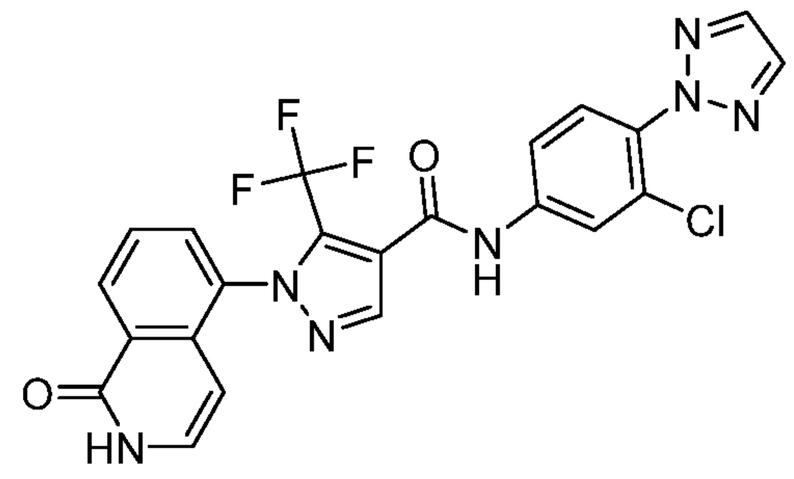
B. 3-Chloro-4-(2H-1,2,3-triazol-2-yl)aniline, **129b**



, 129b

2-(2-Chloro-4-nitrophenyl)-2H-1,2,3-triazole (1.9 g, 8.46 mmol) was dissolved in THF (20 mL), Fe (2.83 g, 50.76 mmol), NH_4Cl (2.72 g, 50.76 mmol) and H_2O (20 mL) were added. The reaction mixture was stirred at 80 °C for 3 hr. The reaction mixture was filtered through a pad of Diatomaceous earth and the pad was washed with EtOAc (30 mL×3). The filtrates were concentrated to dryness to give crude as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 70/30). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford (1.5 g, 89.5%) as a yellow solid. LCMS (ESI) m/z M+1: 194.8.

C. N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **129**

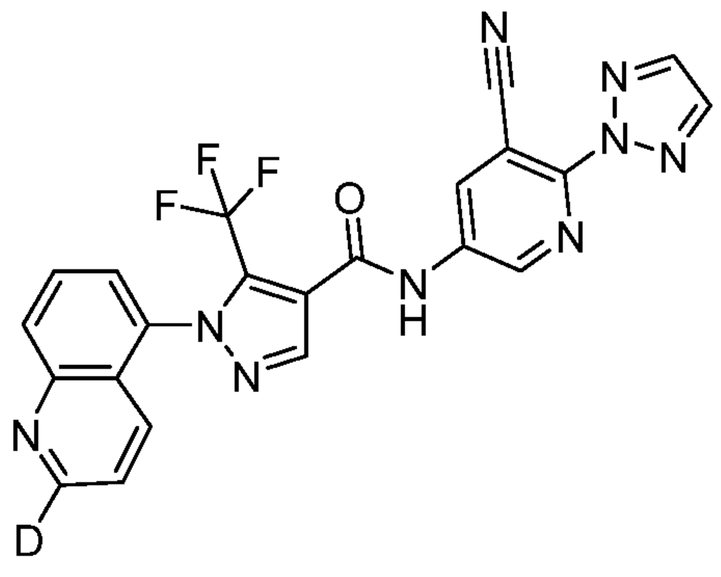


1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (300 mg, 0.77 mmol), 3-chloro-4-(2H-1,2,3-triazol-2-yl)aniline (182.95 mg, 0.92 mmol) and pyridine (608.89 mg, 7.70 mmol) were dissolved in CH_2Cl_2 (15 mL), and phosphorus oxychloride (354.09 mg, 2.31 mmol) was added. The mixture was stirred at 25 °C for 3 h, sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (40% to 40% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (135 mg, 34.8%). LCMS (ESI) m/z M+1: 499.9. ^{1}H NMR (400MHz, DMSO-d6) δ= 11.64 (br d, J=5.5 Hz, 1H), 11.02 (s, 1H),

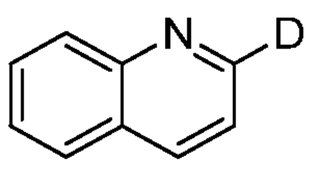
8.52 (s, 1H), 8.44 (d, J=8.2 Hz, 1H), 8.17 (d, J=2.0 Hz, 1H), 8.15 (s, 2H), 7.94 (d, J=7.5 Hz, 1H), 7.86 (dd, J=2.1, 8.7 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.30 (t, J=6.6 Hz, 1H), 5.67 (d, J=7.1 Hz, 1H).

Example 130

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 130**



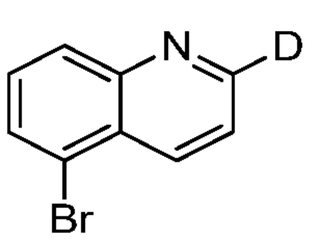
A. 2-D-quinoline, **130a**



, **130a**

A solution of quinoline-2-carboxylic acid (1.5 g, 8.66 mmol) , silver(I) carbonate (238.85 mg, 0.87 mmol) and deuteroxide (9 mL) in DMSO(45 m L) was stirred at 140°C for 16 h. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give the crude product as colorless oil, which was purified by FCC (petroleum ether: ethyl acetate=100:0 to petroleum ether/ ethyl acetate=0:100) to afford the title compound (0.88 g, 78.049 %) as a colorless oil.

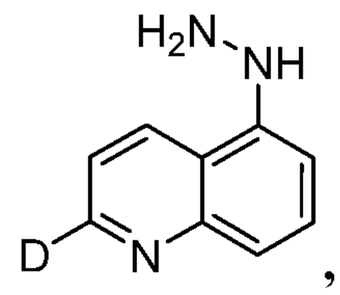
B. 5-bromo-2D-quinoline, **130b**



, **130b**

1-Bromopyrrolidine-2,5-dione(1.203 g, 6.76 mmol) was added to a solution of 2-D-quinoline(0.88 g, 6.76 mmol) in conc.H_2SO_4 (15 mL). The reaction mixture was poured onto 75 mL crushed ice, pH was adjusted to 9.0 using coned aq NH_3, the alkaline slurry was then extracted with ethyl acetate (3 x 30 mL). The combined organic fractions were washed with 1.0 M NaOH then water, dried ($MgS0_4$), filtered, concentrated to give crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 0:100) to afford relatively high purity product, which was purified by preparative HPLC (10% to 40% (v/v) CH_3CN and H_2O with 0.05% ammonia hydroxide) and lyophilized to dryness to afford the title compound (390 mg, 27.6 %). ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.70 (1 H, d, J=8.78 Hz), 8.18 (1 H, d, J=8.53 Hz), 8.09 (1 H, d, J=7.53 Hz), 7.77 - 7.87 (2 H, m).

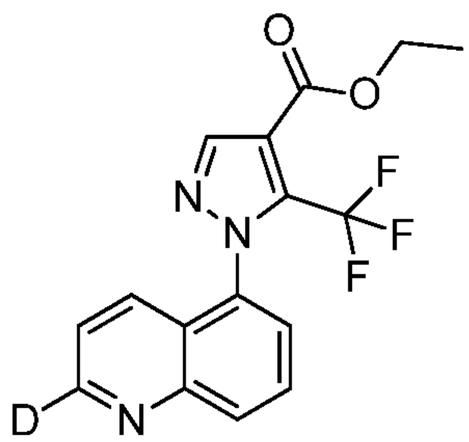
C. 2-D-5-hydrazinylquinoline, **130c**



, 130c

Palladium(ll)(pi-cinnamyl) chloride dimer (24.78 mg, 0.048 mmol) and 4-(2-(di((3S,5S,7S)-adamantan-1-yl)phosphino)phenyl)morpholine (44.35 mg, 0.096 mmol) was added to dioxane (10 mL), immediately purged with N_2. The resulting solution was stirred at room temp under N_2 for 10 min, and then charged with sodium 2-methylpropan-2-olate (183.88 mg, 1.91 mmol) and 5-bromo-2-D-quinoline(200 mg, 0.96 mmol). The reaction vessel was sealed, and purged with N_2. The resulting reaction was stirred at room temp for 5 min and was then treated with hydrazine hydrate (95.78 mg, 1.91 mmol) via syringe. The reaction was stirred at 50 °C under N_2 for 1.5 h. The mixture was filtered, the filtrate was concentrated under reduced pressure to give the crude product as a yellow solid (140 mg, 91.4%) which directly used for the next step without further purification.

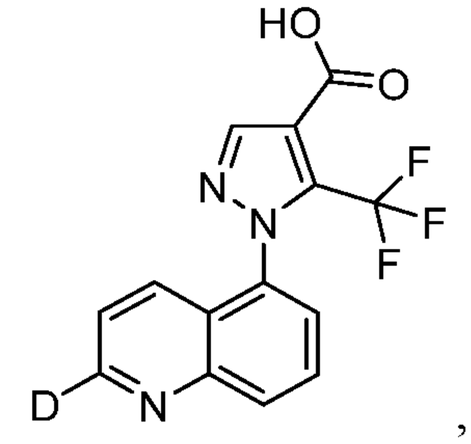
D. ethyl 1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **130d**



, 130d

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, (1.05 g, 4.37 mmol), 2-D-5-hydrazinylquinoline (140 mg, 0.87 mmol), and ethanol (10 mL) was stirred at 80 °C for 2 h. The resultant solution was concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100/0 to 50/50) to afford the title compound (0.26 g, 87.7%) as a yellow solid. LCMS (ESI) m/z M+1: 336.9.

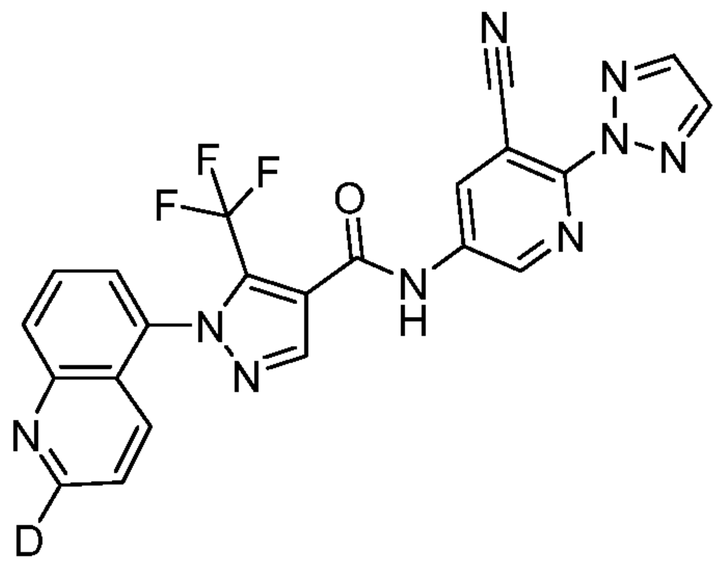
E. 1-(2-Dquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **130e**



, 130e

Sodium hydroxide (45.96 mg, 1.15 mmol) was added to a solution of ethyl 1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (260 mg, 0.77 mmol) in THF/ H_2O 3:1 (12 mL). The mixture was reacted at room temperature for 16 h, the solvent was concentrated under reduced pressure and 20 mL H_2O was added to the mixture. The mixture was acidified by 1M hydrochloric to pH 5 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrates were concentrated under reduced pressure to afford the product as a white solid (200 mg, 84.695%).

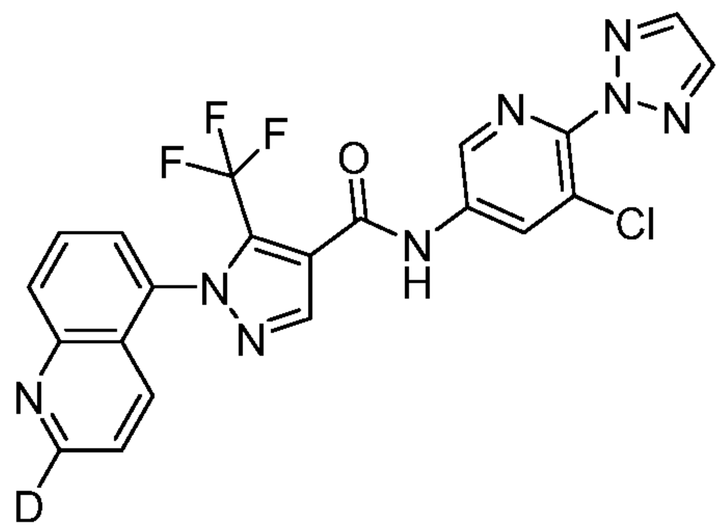
F. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 130**



1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.32 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile, (60.40 mg, 0.32 mmol), pyridine (0.13 mL, 1.62 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (0.12 mL, 1.30 mmol) was added. The mixture was stirred at 25 °C for 2 h, sat.$NaHCO_3$ (20 mL) was added and the mixture extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (21% to 51% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (45 mg, 28.8 %). LCMS (ESI) m/z M+1: 477.0. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 12.20 (1 H, s), 9.93 (1 H, d, J=2.51 Hz), 9.71 (1 H, d, J=2.51 Hz), 9.43 (1 H, s), 9.12 - 9.18 (3 H, m), 8.73 - 8.84 (2 H, m), 8.42 - 8.53 (2 H, m).

Example 131

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-Dquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 131**

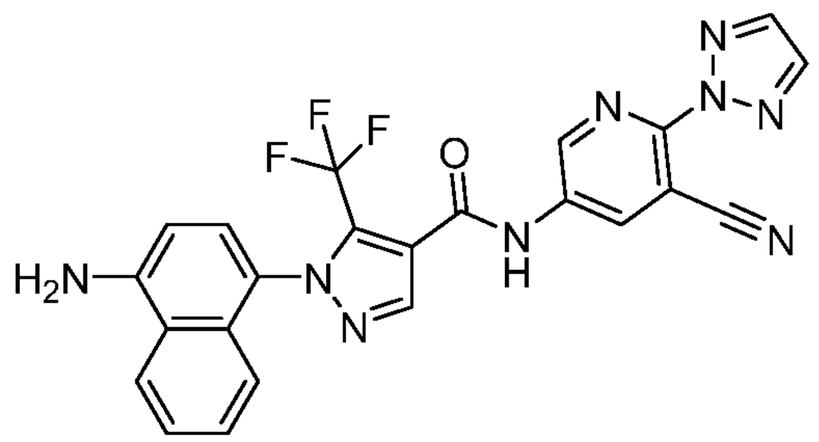


D

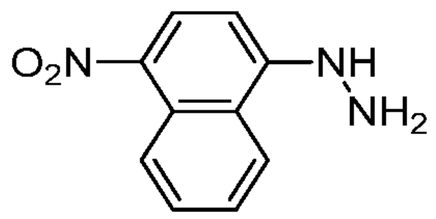
1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (240.00 mg, 0.78 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, (152.31 mg, 0.78 mmol), pyridine (0.31 mL, 3.89 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (0.285 mL, 3.12 mmol) was added. The mixture was stirred at 25 °C for 2 h, sat. $NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (25% to 55% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (183 mg, 48.4 %). LCMS (ESI) m/z M+1: 485.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.40 (1 H, s), 8.91 (1 H, d, J=2.01 Hz), 8.72 (1 H, d, J=2.01 Hz), 8.66 (1 H, s), 8.36 (1 H, d, J=8.28 Hz), 8.21 (2 H, s), 7.93 - 8.05 (2 H, m), 7.64 - 7.74 (2 H, m).

Example 132

1-(4-aminonaphthalen-1-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 132**



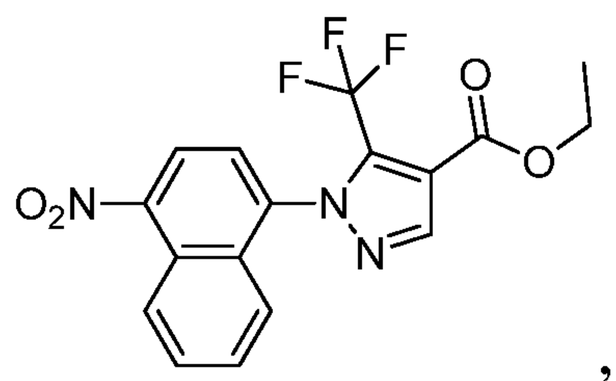
A. (4-nitronaphthalen-1-yl)hydrazine, **132a**



, 132a

A solution of 1-fluoro-4-nitronaphthalene (670 mg, 3.51 mmol) in iPrOH(20 mL) was added $N_2H_4.H_2O$ (460 mg, 9.19 mmol) and heated to 60 °C for 2 hrs. After cooled to RT, the solid was collected, washed with H_2O (5 mL) and EtOH (5 mL), and then dried under vacuo to give product as a yellowish solid (500 mg,70.2%).

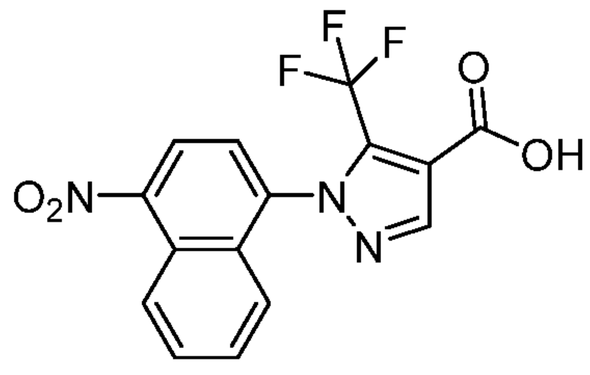
B. ethyl 1-(4-nitronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **132b**



, 132b

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (827.39 mg, 3.445 mmol), (4-nitronaphthalen-1-yl)hydrazine (500 mg, 2.461 mmol) and ethanol (30 mL) was stirred at 25 °C for 2 h. The resultant solution was concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100/0 to 0/100) to afford the title compound (0.8 g, 85.7%) as a yellow oil. LCMS (ESI) m/z M+1: 380.0.

C. 1-(4-nitronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **132c**

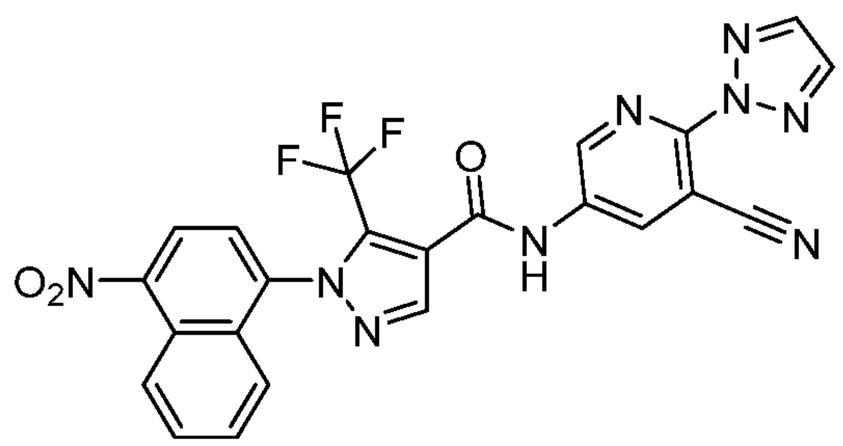


, 132c

Sodium hydroxide (126.54 mg, 3.16 mmol) was added to a solution of ethyl 1-(4-nitronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (800 mg, 2.11 mmol)

in THF/ H_2O 1:1 (20 mL). The mixture was stirred at room temperature for 16 h, the solvent was concentrated under reduced pressure and 20 mL H_2O was added to the mixture. The mixture was acidified using 1M hydrochloric to pH 5 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, the filtrates were concentrated under reduced pressure to afford product as a yellow solid (630 mg, 85.0%). LCMS (ESI) m/z M+1: 352.0.

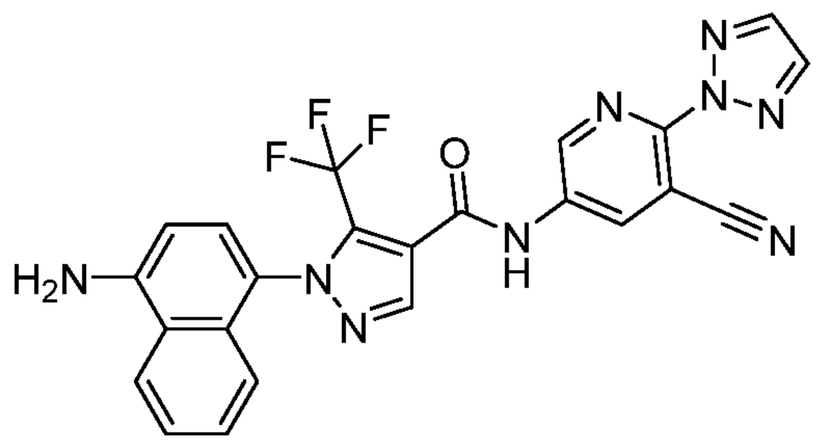
D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-nitronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 132d**



, 132d

1-(4-Nitronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (400 mg, 1.14 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile, (212.02 mg, 1.14 mmol), pyridine (0.46 mL, 5.69 mmol) were dissolved in CH_2Cl_2 (20 mL), and phosphorus oxychloride (0.42 mL, 4.56 mmol) was added. The mixture was stirred at 25 °C for 2 h, sat. $NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100/0 to 0/100) to afford the title compound (0.41 g, 61.7%) as a yellow solid. LCMS (ESI) m/z M+1: 520.1.

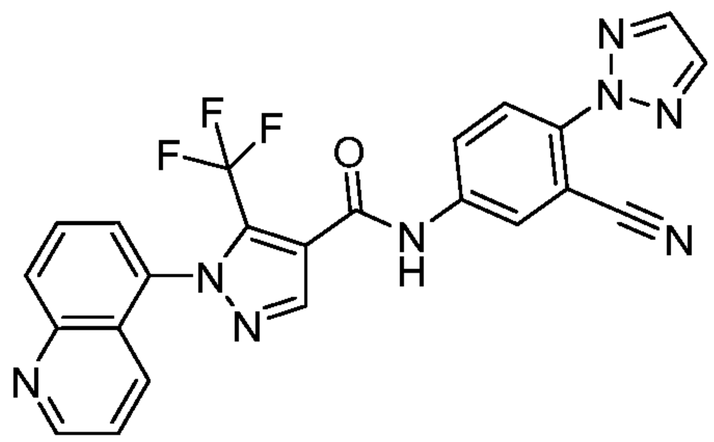
E. 1-(4-Aminonaphthalen-1-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 132**



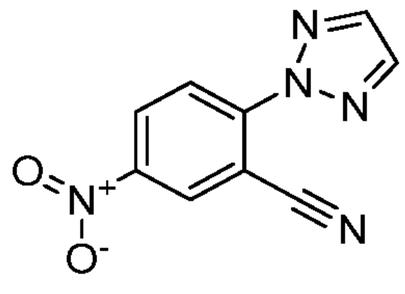
Fe (196.27 mg, 3.52 mmol) and NH_4Cl (188.0 mg, 3.52 mmol) were added to the mixture of N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-nitronaphthalen-1-yl)-5(trifluoromethyl)-1H-pyrazole-4-carboxamide (410 mg, 0.70 mmol) in THF (20 mL), H_2O (10 mL), MeOH (10 mL). The reaction was stirred at 70 °C for 2 h, filtered through a pad of diatomaceous earth, and the pad was washed with EtOAc (20 mL x 2). The combined filtrates were concentrated to dryness to give a crude brown solid, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% ammonia hydroxide) and lyophilized to dryness to afford the title compound (220 mg, 63.4 %). LCMS (ESI) m/z M+1: 490.0. ^1H NMR (400 MHz, DMSO-d6) δ ppm 11.39 (1 H, s), 9.10 (1 H, d, J=2.20 Hz), 8.88 (1 H, d, J=2.43 Hz), 8.49 (1 H, s) 8.30 (2 H, s), 8.15 - 8.24 (1 H, m), 7.44 - 7.53 (2 H, m), 7.40 (1 H, d, J=7.94 Hz), 6.86 - 6.93 (1 H, m), 6.78 (1 H, d, J=8.16 Hz).

Example 133

N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 133**

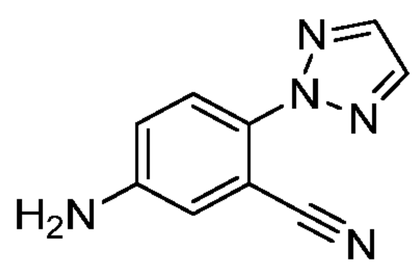


A. 5-nitro-2-(2H-1,2,3-triazol-2-yl)benzonitrile, **133a**


, **133a**

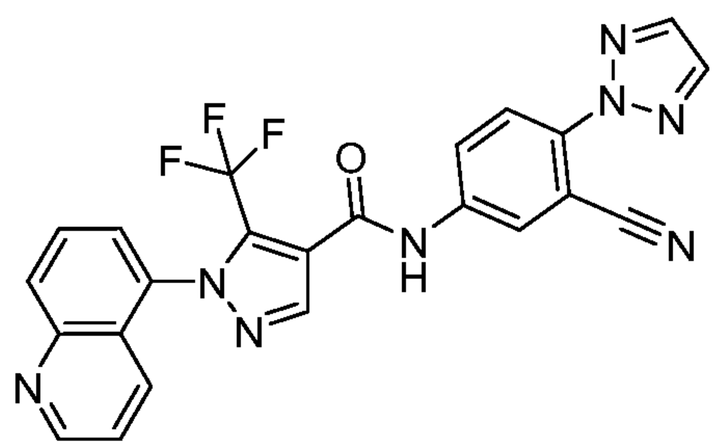
2-Fluoro-5-nitrobenzonitrile (500 mg, 3.01 mmol), 1H-1,2,3-triazole (228.68 mg, 3.31 mmol) and potassium carbonate (832.02 mg, 6.02 mmol) were added to MeCN (10 mL) and stirred at 25 °C for 16 h. The reaction mixture was filtered and the residue was washed with EtOAc (30 mL x 2). The combined organic layers were concentrated under reduced pressure to afford a crude yellow solid, which was purified by FCC (petroleum ether/ ethyl acetate from 100:0 to 70:30) to afford the title compound (600 mg, 92.6%) as a white solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.72 (d, J=2.6 Hz, 1H), 8.55 (dd, J=2.4, 9.0 Hz, 1H), 8.42 (d, J=9.3 Hz, 1H), 8.03 (s, 2H).

B. 5-amino-2-(2H-1,2,3-triazol-2-yl)benzonitrile, **133b**


133b

5-Nitro-2-(2H-1,2,3-triazol-2-yl)benzonitrile (600 mg, 2.79 mmol) was dissolved in THF (10 mL), Fe (1.25 g, 22.31 mmol), NH_4Cl (1.19 g, 22.31 mmol) and H_2O (10 mL) were added. The reaction mixture was stirred at 80 °C for 4 h, filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (20 mL×3). The filtrates were concentrated to dryness to give crude product as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 50/50). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title compound (440 mg, 82.1%) as a yellow oil. LCMS (ESI) m/z M+1: 186.1. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.08 (s, 2H), 7.57 (d, J=8.8 Hz, 1H), 6.99 (d, J=2.6 Hz, 1H), 6.94 (dd, J=2.6, 8.8 Hz, 1H), 5.98 (s, 2H).

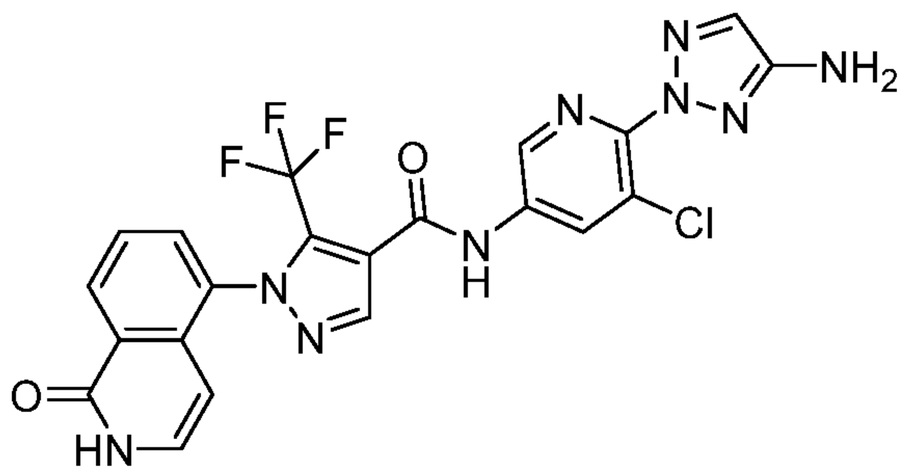
C. N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 133**



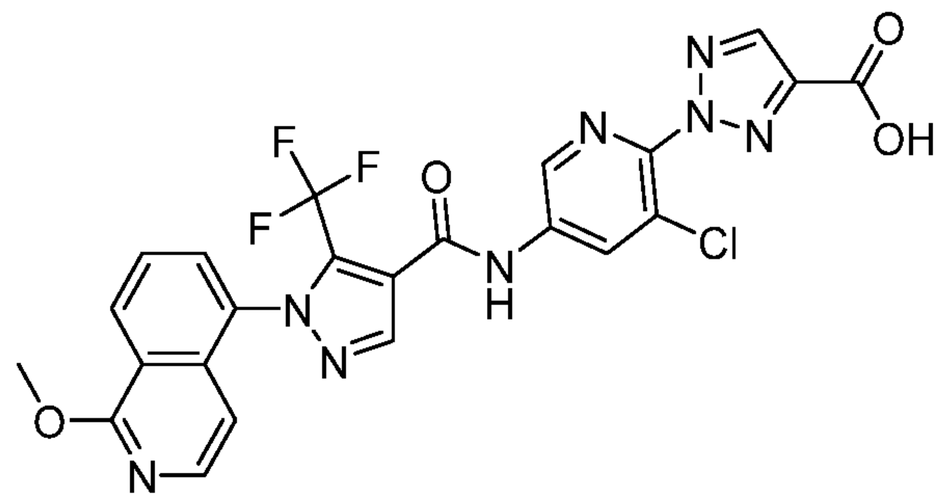
5-Amino-2-(2H-1,2,3-triazol-2-yl)benzonitrile (110.98 mg, 0.58 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (120 mg, 0.39 mmol) and pyridine (45.7 mg, 0.58 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (88.58 mg, 0.58 mmol) was added. The mixture was stirred at 25 °C for 16 h, sat.$NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow solid, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (87 mg, 47.8%). LCMS (ESI) m/z M+1: 474.9. ^1H NMR (400MHz, DMSO-d6) δ ppm 11.22 (s, 1H), 9.11 (dd, J=1.9, 3.9 Hz, 1H), 8.62 (s, 1H), 8.44 (d, J=2.2 Hz, 1H), 8.37 (d, J=8.2 Hz, 1H), 8.28 (s, 2H), 8.26 - 8.21 (m, 1H), 8.17 - 8.11 (m, 1H), 8.05 - 7.98 (m, 1H), 7.98 - 7.94 (m, 1H), 7.76 - 7.68 (m, 2H).

Example 134

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 134**



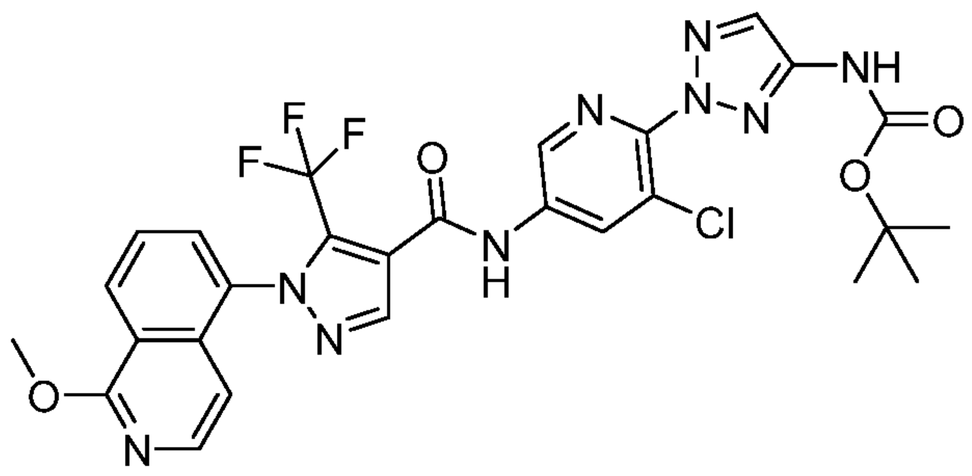
A. 2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid, **134a**



, **134a**

NaOH (72.62 mg, 1.82 mmol) was added to a solution of methyl 2-(3-chloro-5-(1-(1- methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate (600 mg, 0.91 mmol) in THF/H_2O 1:1 (10 mL) was reacted at 23 °C for 2 h. The solvent was concentrated under reduced pressure, 1M HCl solution was add to the mixture to adjust to pH 5 and a solid formed. The solid was collected to afford the product. LCMS (ESI) m/z M+1: 530.9.

B. *tert*-butyl(2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazol-4-yl)carbamate, **134b**

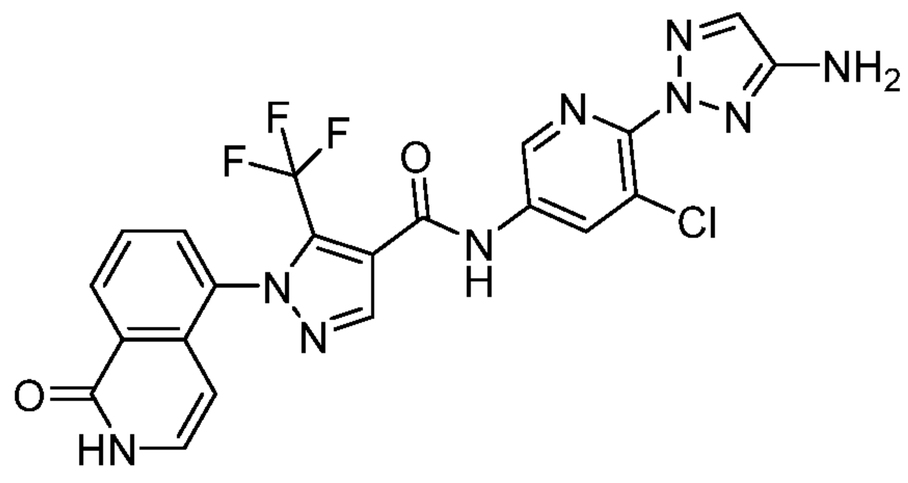


, **134b**

To a solution of 2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid (500 mg, 0.82 mmol) in t-BuOH (10 mL), DPPA (271.3 mg, 0.99 mmol) and TEA (249.4 ul, 2.47 mmol) were added under N_2 atmosphere. The mixture was stirred at 80 °C overnight, sat. $NaHCO_3$ (20 mL) was added and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as a brown oil. The crude product was purified by column

chromatography over silica gel (petroleum ether/ ethyl acetate=2:1 to petroleum ether/ ethyl acetate=1:2). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as a yellow solid. LCMS (ESI) m/z M+1: 630.0.

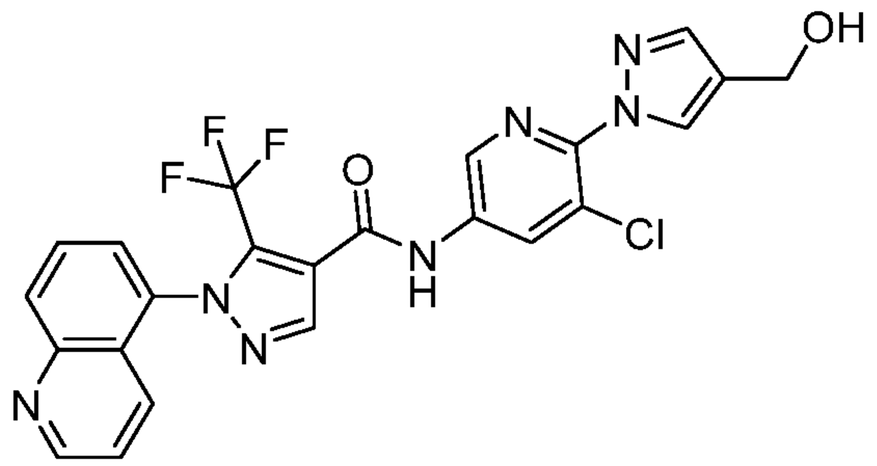
C. N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 134**



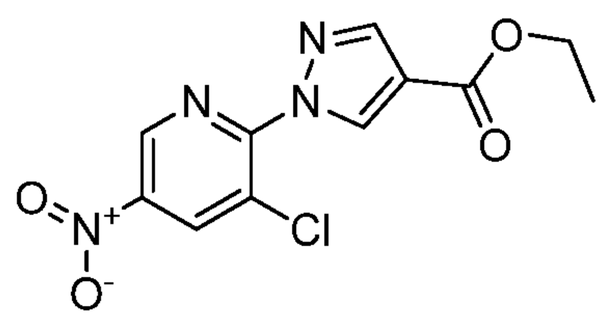
tert-Butyl (2-(3-chloro-5-(1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazol-4-yl)carbamate (180 mg, 0.27 mmol), and conc. HCl (2 mL) was added i-PrOH (4 mL), stirred at 60°C for 2 h. The mixture was concentrated under reduced pressure to afford crude product as a brown oil, which was purified by preparative HPLC (72 % to 42 % (v/v) CH_3CN and H_2O with 0.05% ammonia hydroxide) and lyophilized to dryness to afford the title compound (64 mg, 44.3%). LCMS (ESI) m/z M+1: 515.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.47 (s, 2 H), 5.64 (d, J=7.28 Hz, 1 H), 7.27 (d, J=7.28 Hz, 1 H), 7.31 (s, 1 H), 7.65 (t, J=7.94 Hz, 1 H), 7.92 (d, J=7.50 Hz, 1 H), 8.42 (d, J=7.94 Hz, 1 H), 8.54 (s, 1 H), 8.56 (d, J=2.43 Hz, 1 H), 8.77 (d, J=2.21 Hz, 1 H).

Example 135

N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 135**



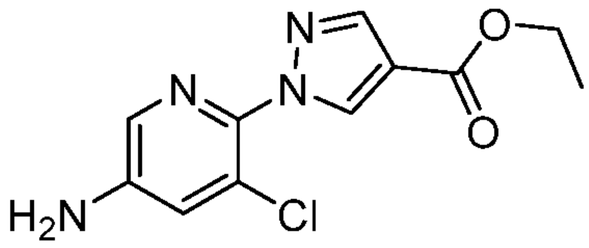
A. ethyl 1-(3-chloro-5-nitropyridin-2-yl)-1H-pyrazole-4-carboxylate, **135a**



, 135a

2,3-Dichloro-5-nitropyridine (500 mg, 2.59 mmol), ethyl 1H-pyrazole-4-carboxylate (435.7 mg, 3.11 mmol) and cesium carbonate (1.01 g, 3.11 mmol) were added to MeCN (10 mL) and stirred at 80 °C for 16 h. The reaction mixture was filtered and the residue was washed with EtOAc (20 mL x 3). The combined organic layers were concentrated under reduced pressure to afford crude product as a yellow solid, which was purified by FCC (petroleum ether/ethyl acetate from 100:0 to 70:30) to afford the title compound (650 mg, 84.6%) as a yellow solid.

B. ethyl 1-(5-amino-3-chloropyridin-2-yl)-1H-pyrazole-4-carboxylate, **135b**

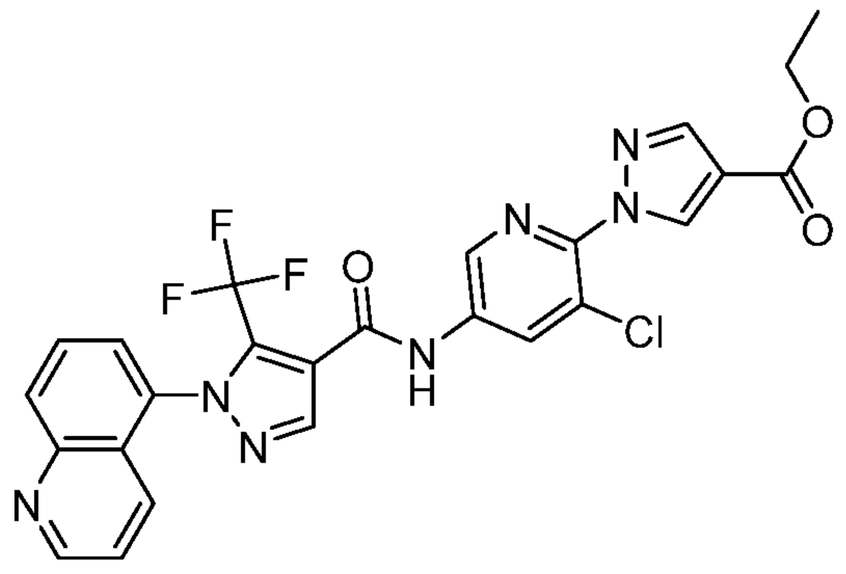


, 135b

Ethyl 1-(3-chloro-5-nitropyridin-2-yl)-1H-pyrazole-4-carboxylate (650 mg, 2.19 mmol) was dissolved in THF (10 mL), Fe (856.5 mg, 15.34 mmol), NH_4Cl (820.4 mg, 15.34 mmol) and H_2O (10 mL) were added. The reaction mixture was stirred at 80 °C for 2

h. The reaction mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (20 mL x 3). The filtrates were concentrated to dryness to give crude as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 70/30). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title compound (440 mg, 64.5%) as a yellow oil. LCMS (ESI) m/z M+1: 267.1.

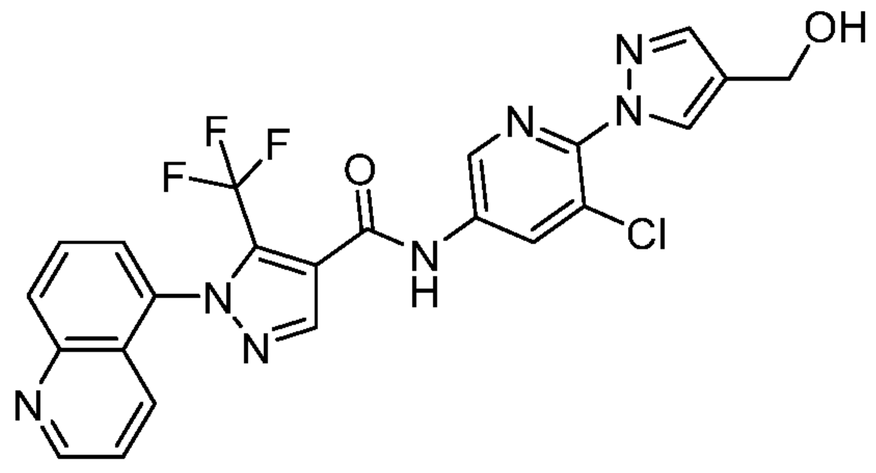
C. Ethyl 1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-pyrazole-4-carboxylate, **135c**



, 135c

Ethyl 1-(5-amino-3-chloropyridin-2-yl)-1H-pyrazole-4-carboxylate (293.93 mg, 0.94 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (220 mg, 0.71 mmol) and pyridine (83.77 mg, 1.06 mmol) were dissolved in CH_2Cl_2 (20 mL), and phosphorus oxychloride (162.39, 1.06 mmol) was added. The mixture was stirred at 30 °C for 16 h. Sat. $NaHCO_3$ (40 mL) was added and extracted with CH_2Cl_2 (40 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford (120 mg, 22.9%) as a yellow solid. LCMS (ESI) m/z M+1: 556.2.

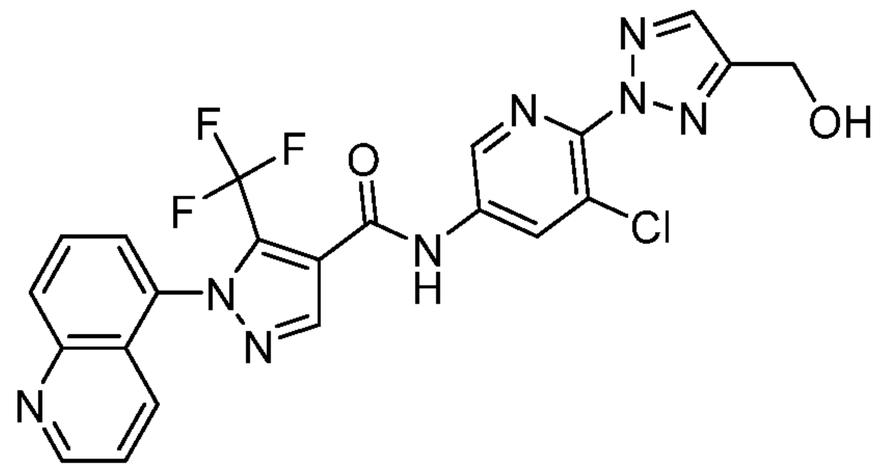
D. N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **135**



Ethyl 1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-pyrazole-4-carboxylate (120 mg, 0.20 mmol) was dissolved in THF (20 mL) and stirred at 0 °C, aluminum(III) lithium hydride (68.24 mg, 1.80 mmol) was added in portions. The reaction mixture was stirred at 30 °C for 1 h. H_2O (20 mL) was added and extracted with EtOAc (40 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford the crude product, which was purified by preparative HPLC (22% to 52% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (35 mg, 33.6%). LCMS (ESI) m/z M+1: 513.9. ^{1}H NMR (400MHz, DMSO-d6) □ ppm 11.56 (br s, 1H), 9.08 (br s, 1H), 8.91 (br s, 1H), 8.73 (br s, 1H), 8.63 (br s, 1H), 8.35 (br d, J=7.9 Hz, 1H), 8.09 (br s, 1H), 7.96 (br dd, J=6.9, 18.2 Hz, 2H), 7.81 - 7.62 (m, 3H), 4.43 (br s, 2H).

Example 136

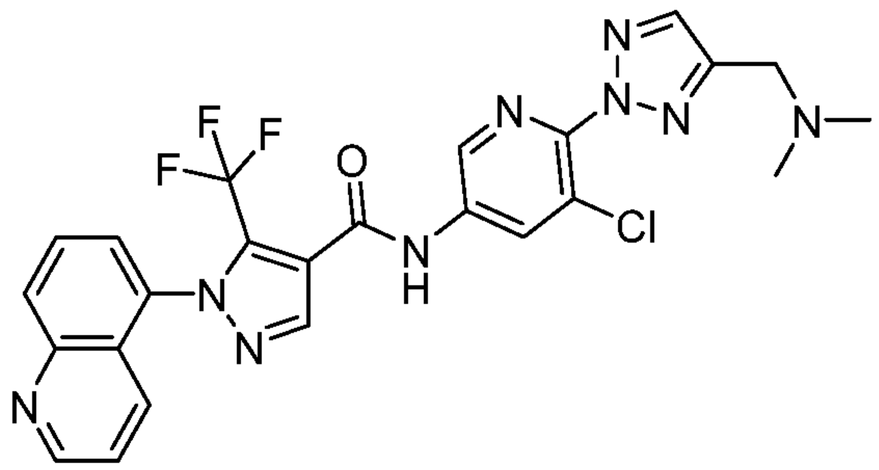
N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 136**



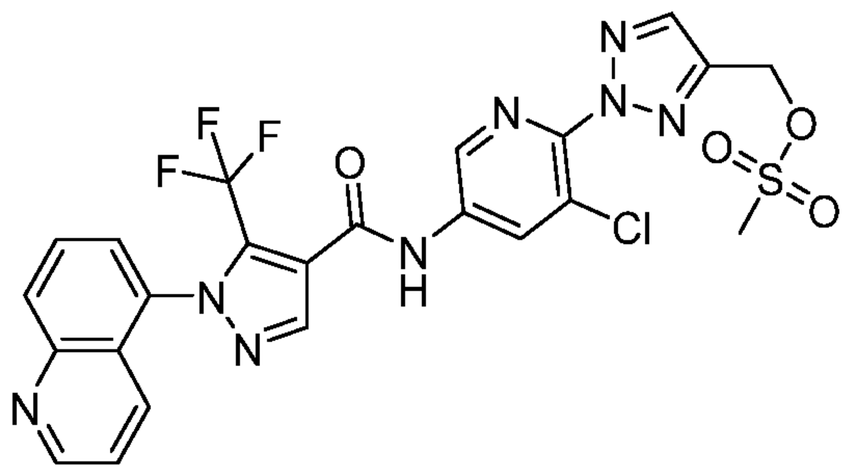
Methyl 2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate (86 mg, 0.079 mmol) was dissolved in THF (5 mL) at 0 °C, $LiAlH_4$ (84 mg, 2.21 mmol) was added in portions. The reaction mixture was stirred at 40 °C for 18 h, then H_2O (10 mL) was added and the mixture extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (76% to 46% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (17.3 mg, 5.0 %). LCMS (ESI) m/z M+1: 514.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 4.63 (s, 2 H), 7.69 - 7.83 (m, 2 H), 7.94 - 8.09 (m, 3 H), 8.37 (d, J=8.38 Hz, 1 H), 8.63 - 8.73 (m, 2 H), 8.91 (d, J=2.21 Hz, 1 H), 9.11 (dd, J=3.97, 1.54 Hz, 1 H), 11.51 (s, 1 H).

Example 137

N-(5-chloro-6-(4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 137**



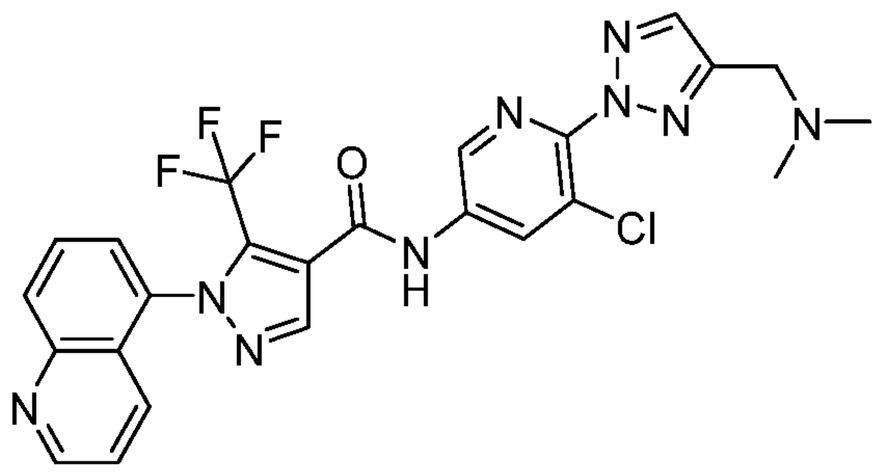
A. (2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazol-4-yl)methyl methanesulfonate, **137a**



, **137a**

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (420 mg, 0.79 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C. Triethylamine (239.84 mg, 2.37 mmol) was added, then methanesulfonyl chloride (135.75 mg, 1.19 mmol) was added dropwise and stirred at 0 °C for 1 h. The mixture concentrated, dried, and used directly for the next step.

B. N-(5-chloro-6-(4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 137**

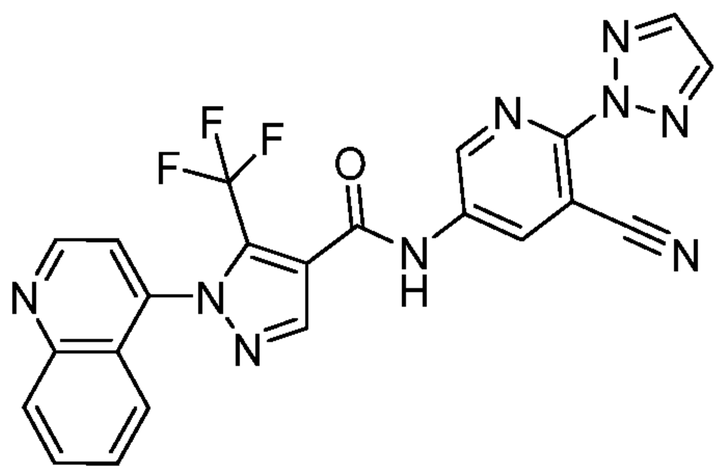


(2-(3-Chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazol-4-yl)methyl methanesulfonate (250 mg, 0.40

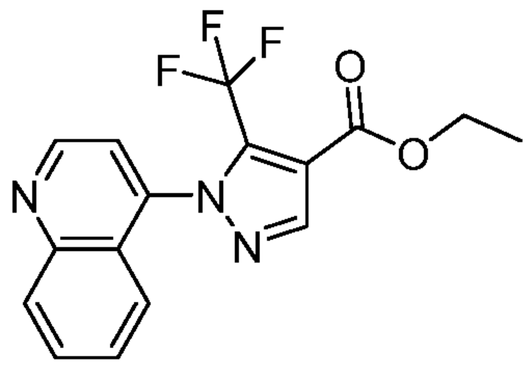
mmol) was added Me_2NH in THF (1M) (20 mL). The mixture was concentrated under reduced pressure to afford a crude product as a yellow oil, which was purified by preparative HPLC (84% to 54% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (201 mg, 92.7 %). LCMS (ESI) m/z M+1: 514.9. ^1H NMR (400 MHz, METHANOL-d4) δ ppm 2.99 (s, 6 H), 4.64 (s, 2 H), 8.17 - 8.26 (m, 3 H), 8.33 - 8.41 (m, 1 H), 8.48 - 8.60 (m, 2 H), 8.62 - 8.74 (m, 1 H), 8.77 (d, J=2.20 Hz, 1 H), 8.88 (br s, 1 H), 9.29 - 9.48 (m, 1 H).

Example 138

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 138**



A. ethyl 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **138a**

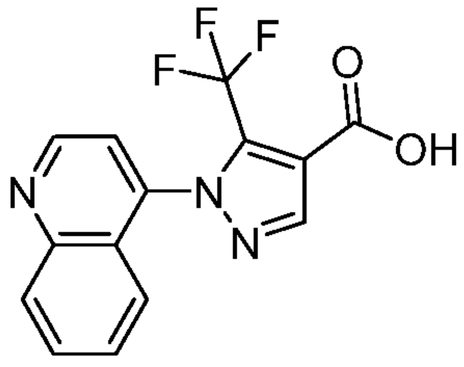


, **138a**

A solution of 4-hydrazinylquinoline, **60c** (300 mg, 1.89 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (543.15 mg, 2.26 mmol), in EtOH (5 mL) was stirred at 80 °C for 2 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 50/50). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford ethyl 1-(quinolin-4-yl)-5-

(trifluoromethyl)-1H-pyrazole-4-carboxylate (130 mg, 20.6% yield) as a yellow solid. LCMS (ESI) m/z M+1: 335.9.

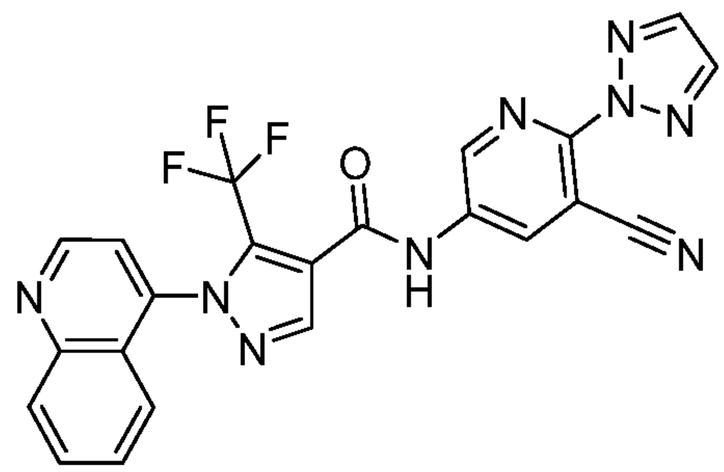
B. 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **138b**



, **138b**

A solution of ethyl 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **138a** (130 mg, 0.61 mmol), LiOH (16.27 mg, 0.39 mmol) in EtOH /H_2O (2/1, 2 mL) was stirred at room temperature for 2 h, 1N HCl solution was added to neutralize the reaction solution. The mixture was extracted with ethyl acetate (5 mL x 3). The separated organic layer was dried (Na_2SO_4), filtered, and the solvent was concentrated to afford 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **138b** (119 mg) as a yellow solid. LCMS (ESI) m/z M+1: 308.0.

C. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 138**

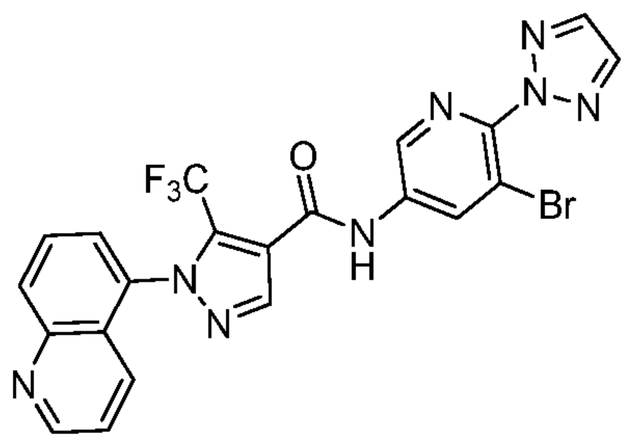


Phosphorus oxychloride (39.44 uL, 0.42 mmol) was added to a solution of 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **138b** (67.35 mg, 0.21 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (59.08 mg, 0.32 mmol), pyridine (171.12 uL, 2.12 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 2 h, 5 mL H_2O was added to the mixture and sat. $NaHCO_3$ was added to adjust the pH

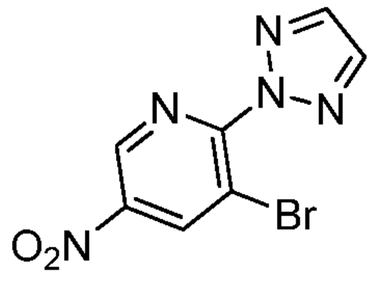
of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (40% to 70% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (57 mg, 56.4%). LCMS (ESI) m/z M+1: 475.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.33 (d, J=8.16 Hz, 1 H), 7.77 (t, J=7.61 Hz, 1 H), 7.91 - 7.98 (m, 2 H), 8.26 (d, J=8.60 Hz, 1 H), 8.32 (s, 2 H), 8.71 (s, 1 H), 8.91 (d, J=2.43 Hz, 1 H), 9.13 (d, J=2.43 Hz, 1 H), 9.19 (d, J=4.41 Hz, 1 H), 11.47 (s, 1 H).

Example 139

N-(5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 139**



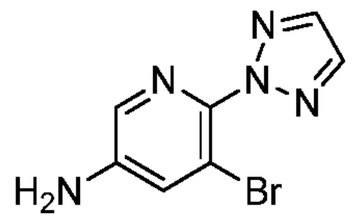
A. 3-bromo-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine, **139a**



, **139a**

A solution of 3-bromo-2-chloro-5-nitropyridine (1 g, 4.21 mmol), 1H-1,2,3-triazole (582 mg, 8.42 mmol), K_2CO_3 (1.74 g, 12.64 mmol) in CH_3CN (30 mL) was stirred at 50 °C for 12 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 20:1 to 1:1). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford 3-bromo-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine, **139a** (520 mg, 45.7%) as a yellow solid. LCMS (ESI) m/z M+1: 272.1.

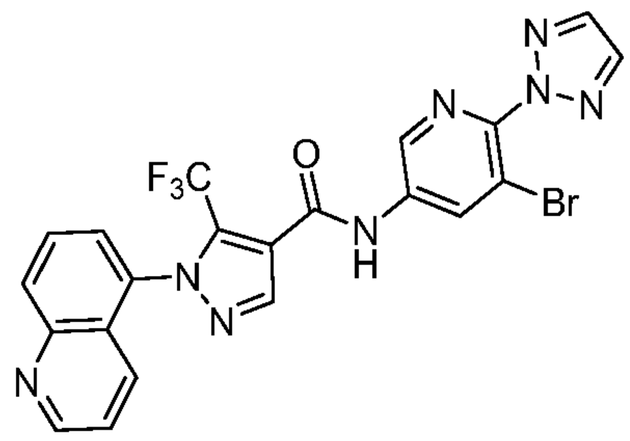
B. 5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, **139b**



, **139b**

Fe (323.50 mg, 5.78 mmol) was added to a solution of 3-bromo-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine, **139a** (520 mg, 1.93 mmol) and NH_4Cl (515.10 mg, 9.63 mmol) in MeOH (20 mL), THF (20 mL) and H_2O (10 mL). The mixture was stirred at 80 °C for 1h, and then aq. $NaHCO_3$ was added to the suspension to adjust the mixture to pH 9-10. The resulting mixture was filtered through a pad of diatomaceous earth and the filter cake was washed with CH_2Cl_2 (100 mL×3). The combined filtrates were washed with brine (200 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 1b (310 mg, 67.1%) as a brown solid, which was used directly in the next step. LCMS (ESI) m/z M+H: 242.1

C. N-(5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 139**

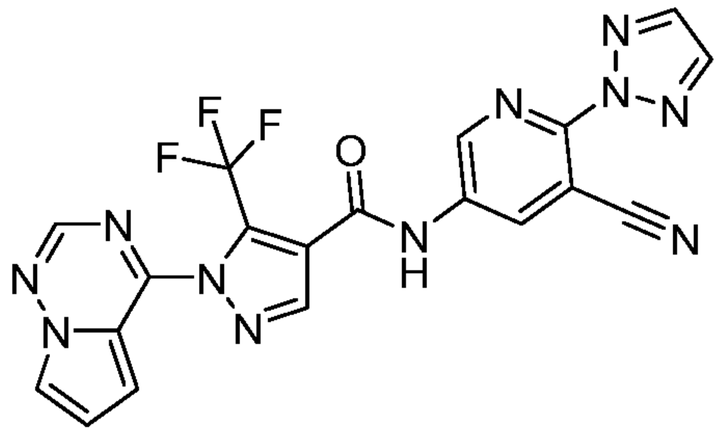


$POCl_3$ (232.263 mg, 1.515 mmol) was added to a solution of 5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, 5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, **139b** (200 mg, 0.83 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (232.69 mg, 0.76 mmol), pyridine (149.77 mg 1.89 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 2 h, then 50 mL H_2O and 50 mL CH_2Cl_2 were added to the mixture. The organic layer was washed with brine (50 mL), dried over $MgSO_4$ filtered, and the filtrate concentrated under reduced pressure to afford the crude product, which was

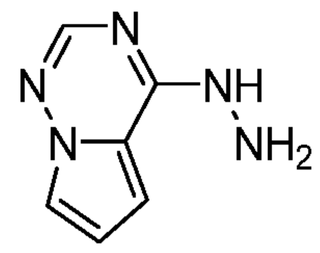
purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl). The desired fractions were lyophilized to dryness to afford the title compound (86.8 mg 20.8% yield) as a white solid. LCMS (ESI) m/z M+1: 528.9. ^1H NMR (400 MHz, DMSO-d6) δ ppm 11.45 (s, 1 H), 9.01 – 9.12 (m, 1 H), 8.89 – 8.99 (m, 1 H), 8.78 – 8.86 (m, 1 H), 8.64 – 8.72 (m, 1 H), 8.29 – 8.38 (m, 1 H), 8.15 (s, 2 H), 7.90 – 8.02 (m, 2 H), 7.69 (d, J=3.09 Hz, 2 H).

Example 140

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 140**



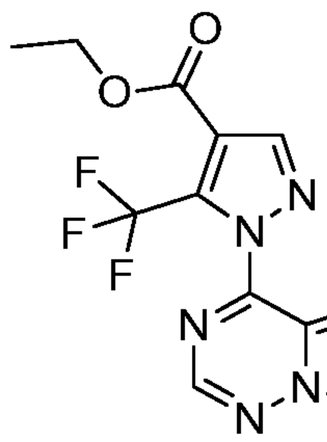
A. 4-hydrazinylpyrrolo[2,1-f][1,2,4]triazine, **140a**



, **140a**

4-Chloropyrrolo[2,1-f][1,2,4]triazine (200 mg, 1.302 mmol) was dissolved in hydrazine hydrate (8 mL). The reaction mixture was stirred at 40 °C for 2 h. The solvent was removed to afford product as a white solid (200 mg, 100%), which was used directly for the next step.

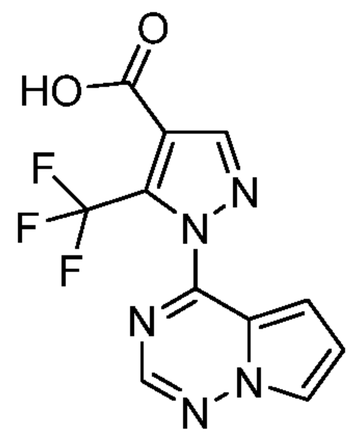
B. ethyl 1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **140b**



, 140b

4-Hydrazinylpyrrolo[2,1-f][1,2,4]triazine (200 mg, 1.34 mmol) was dissolved in ethanol (10 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (483.08 mg, 2.01 mmol) was added. The reaction mixture was stirred at 80 °C for 2 h, concentrated under reduced pressure to afford the crude product as a white solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40) to afford the title compound (200 mg, 43.4%) as a white solid. LCMS (ESI) m/z M+1: 326.0.

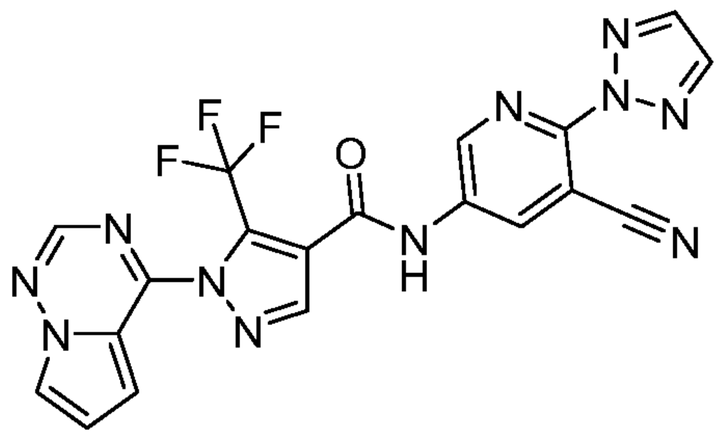
C. 1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **140c**



, 140c

Ethyl 1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (200 mg, 0.58 mmol) was dissolved in THF (10 mL) and water (10 mL). Sodium hydroxide (46.51 mg, 1.16 mmol) was added. The reaction mixture was stirred at 25 °C for 12 h, adjusted to pH 5 using HCl (2 N), and extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford crude the title compound (130 mg, 73.6%) as a yellow solid. LCMS (ESI) m/z M+1: 298.0.

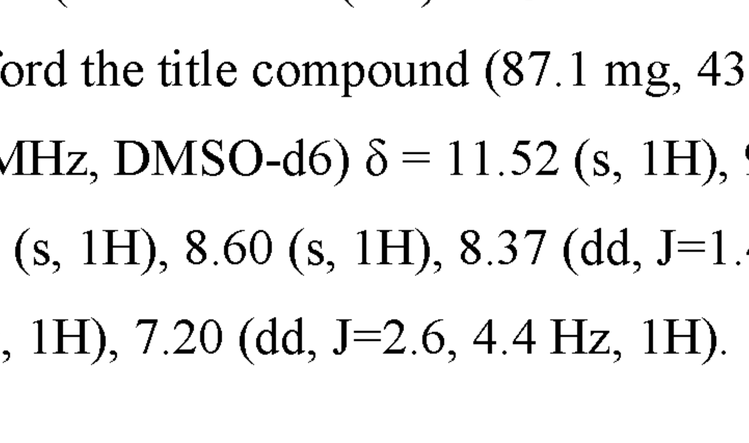
D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 140**



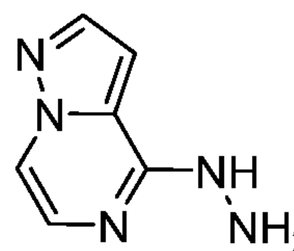
1-(Pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (130 mg, 0.43 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (95.57 mg, 0.51 mmol), pyridine (203.04 mg, 2.57 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (262.38, 1.71 mmol) was added. The mixture was stirred at 25 °C for 4 h, sat.$NaHCO_3$ (30 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (87.1 mg, 43.5%). LCMS (ESI) m/z M+1: 465.9. ^{1}H NMR (400MHz, DMSO-d6) δ = 11.52 (s, 1H), 9.00 (d, J=2.6 Hz, 1H), 8.78 (d, J=2.6 Hz, 1H), 8.63 (s, 1H), 8.60 (s, 1H), 8.37 (dd, J=1.4, 2.5 Hz, 1H), 8.27 (s, 2H), 7.28 (dd, J=1.3, 4.6 Hz, 1H), 7.20 (dd, J=2.6, 4.4 Hz, 1H).

Example 141

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 141**



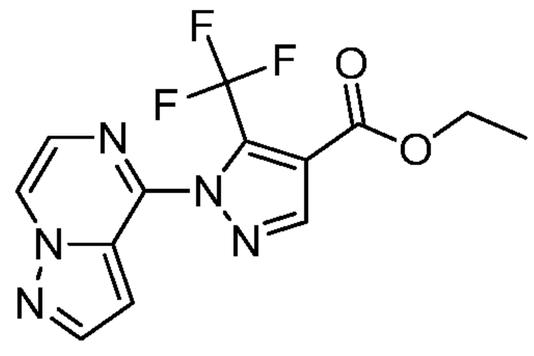
A. 4-hydrazinylpyrazolo[1,5-a]pyrazine, **141a**



, **141a**

4-Chloropyrazolo[1,5-a]pyrazine (300 mg, 1.95 mmol) was dissolved in hydrazine hydrate (10 mL). The reaction mixture was stirred at 25 °C for 2 h. The solvent was removed to afford product as a white solid (300 mg, 100%), which was used directly for the next step.

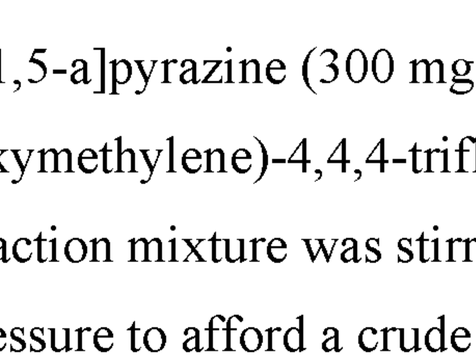
B. ethyl 1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **141b**



, 141b

4-Hydrazinylpyrazolo[1,5-a]pyrazine (300 mg, 2.01 mmol) was dissolved in ethanol (10 mL), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (966.16 mg, 4.02 mmol) was added. The reaction mixture was stirred at 80 °C for 2 h, then concentrated under reduced pressure to afford a crude product as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 60/40) to afford the title compound (500 mg, 61.2%) as a yellow solid. LCMS (ESI) m/z M+1: 326.0.

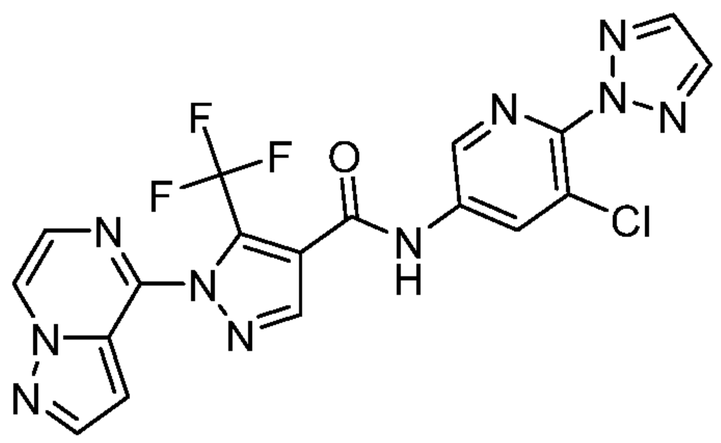
C. 1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **141c**



, 141c

Ethyl 1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (500 mg, 1.23 mmol) was dissolved in THF (10 mL) and water (10 mL). Sodium hydroxide (98.4 mg, 2.46 mmol) was added. The reaction mixture was stirred at 25 °C for 12 h, then adjusted to pH 5 using HCl (2 N). The mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and the filtrates were concentrated under reduced pressure to afford the crude the title compound (400 mg, 89.2%) as a yellow solid. LCMS (ESI) m/z M+1: 298.2.

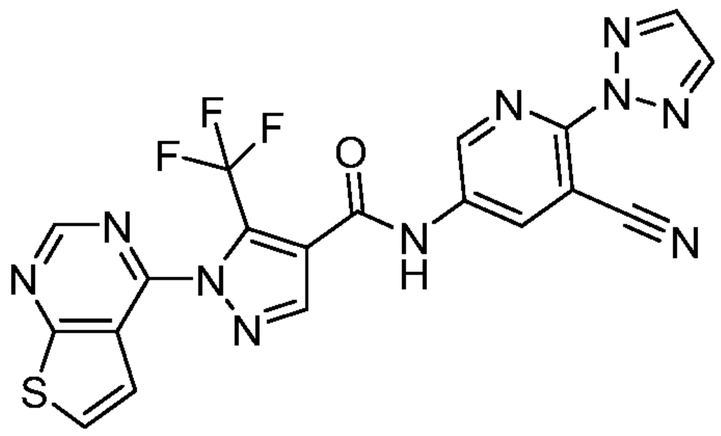
D. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 141**



1-(Pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (250 mg, 0.69 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (161.0 mg, 0.82 mmol), pyridine (325.52 mg, 4.12 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (420.67, 2.74 mmol) was added. The mixture was stirred at 25 °C for 4 h, then sat. $NaHCO_3$ (50 mL) was added and the mixture extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (45% to 75% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (22.4 mg, 6.6%). LCMS (ESI) m/z M+1: 474.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.42 (s, 1 H), 9.05 (dd, J=4.85, 0.88 Hz, 1 H), 8.81 (d, J=2.21 Hz, 1 H), 8.63 (d, J=2.43 Hz, 1 H), 8.60 (s, 1 H), 8.37 (d, J=2.43 Hz, 1 H), 8.17 (s, 2 H), 7.96 (d, J=4.63 Hz, 1 H), 7.11 (dd, J=2.32, 0.77 Hz, 1 H).

Example 142

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 142**

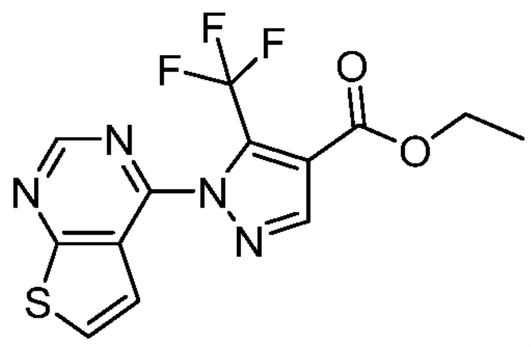


A. 4-hydrazinylthieno[2,3-d]pyrimidine, **142a**

, **142a**

A solution of 4-chlorothieno[2,3-d]pyrimidine (450 mg, 2.64 mmol) in hydrazine (5 mL, 98%) was stirred at 80°C for 2 h. The solid was filtered and washed by 2 mL water. The solid was collected and dried to afford 4-hydrazinylthieno[2,3-d]pyrimidine, **142a** (400 mg, 91.3% yield) as a white solid. LCMS (ESI) m/z M+1: 166.9.

B. ethyl 1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **142b**

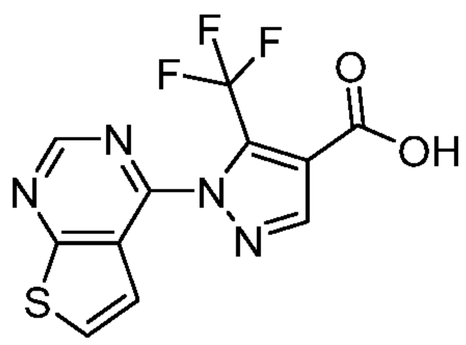


, **142b**

A solution of 4-hydrazinylthieno[2,3-d]pyrimidine, **142a** (400 mg, 2.41 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (1040 mg, 4.33 mmol), in EtOH (5 mL) was stirred at 80 °C for 1 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/

ethyl acetate from 100/0 to 70/30). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford ethyl 1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **142b** (700 mg, 85.0% yield) as a yellow solid. LCMS (ESI) m/z M+1: 343.1.

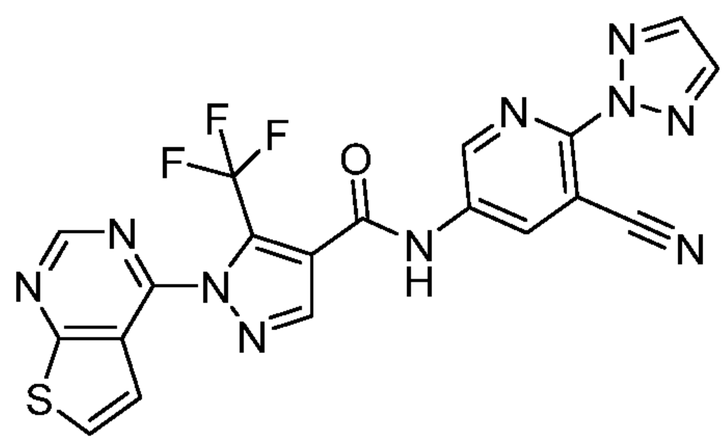
C. 1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **142c**



, **142c**

A solution of ethyl 1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **142b** (120 mg, 0.35 mmol), $LiOH.H_2O$ (22.07 mg, 0.53 mmol) in EtOH /H_2O (2/1, 3 mL) was stirred at room temperature overnight. 1N HCl solution was added to neutralize the reaction solution. The mixture was extracted with ethyl acetate (10 mL x 3). The separated organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated to afford **142c** (90 mg, 81.7% yield) as a yellow solid. LCMS (ESI) m/z M+1: 314.9.

D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 142**

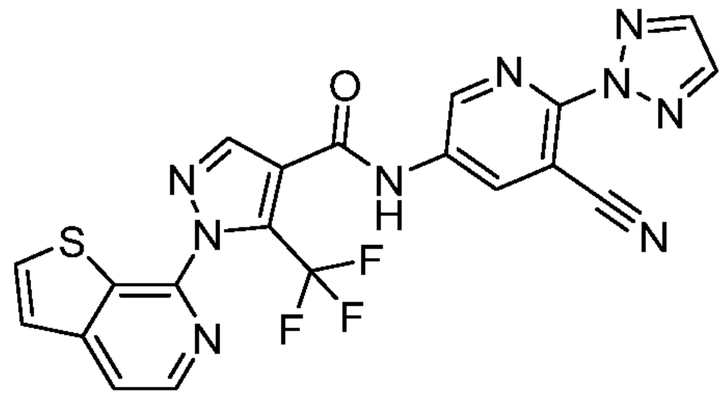


Phosphorus oxychloride (53.39 uL, 0.57 mmol) was added to a solution of 1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **142c** (90 mg, 0.29 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (58.65 mg, 0.32 mmol),

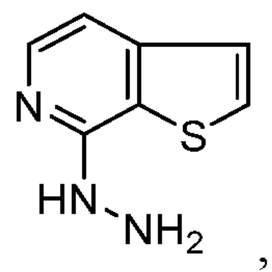
pyridine (231.64 uL, 2.86 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h, 5 mL H_2O was added to the mixture and sat. $NaHCO_3$ was added to adjust the pH of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3), the combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (36% to 66% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (40 mg, 27.9%). LCMS (ESI) m/z M+1: 482.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.78 (d, J=6.17 Hz, 1 H), 8.24 (d, J=6.17 Hz, 1 H), 8.32 (s, 2 H), 8.65 (s, 1 H), 8.85 (d, J=2.21 Hz, 1 H), 9.07 (d, J=2.21 Hz, 1 H), 9.21 (s, 1 H), 11.52 (s, 1 H).

Example 143

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 143**



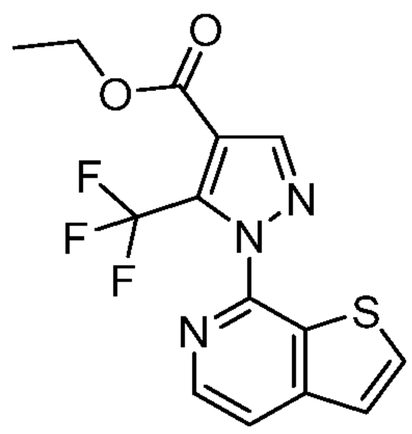
A. 7-hydrazinylthieno[2,3-c]pyridine, **143a**



, **143a**

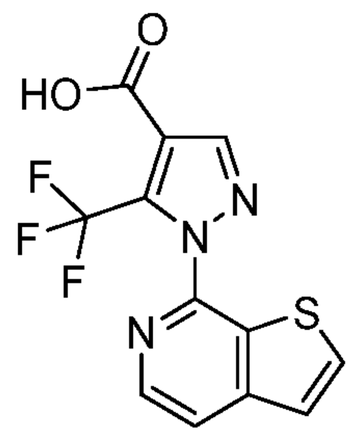
7-Chlorothieno[2,3-c]pyridine (300 mg, 1.06 mmol) in $NH_2NH_2.H_2O$ (5 mL) was stirred at 26 °C for 16 h. The mixture was extracted with CH_2Cl_2 (20 x 3 mL). The solvent was concentrated under reduced pressure the give the desired compound, used directly for the next step without further purification.

B. ethyl 1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **143b**


, **143b**

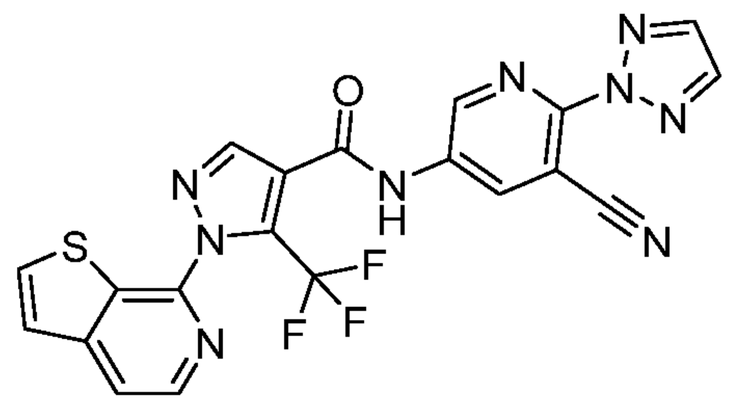
7-Hydrazinylthieno[2,3-c]pyridine (200 mg, 1.21 mmol) was added to a solution of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (436.11 mg, 1.82 mmol) in EtOH (5 mL) and was reacted at 80 °C for 3 h. The mixture was concentrated under reduced pressure, then was purified by FFS (petroleum ether/ ethyl acetate=100:0 to petroleum ether/ ethyl acetate 60:40). The desired fractions were collected and the solvent was concentrated under reduced pressure to give the product as a brown oil. LCMS (ESI) m/z M+1: 341.9.

C. 1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **143c**


, **143c**

NaOH (20.56 mg, 0.51 mmol) was added to a solution of ethyl 1-(thieno[2,3-c]pyridin-7- yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (120 mg, 0.34 mmol) in EtOH/H_2O=1:1 (5 mL) was reacted at 28 °C for 2 h. The solvent was concentrated under reduced pressure the give the desired compound. LCMS (ESI) m/z M+1: 313.9.

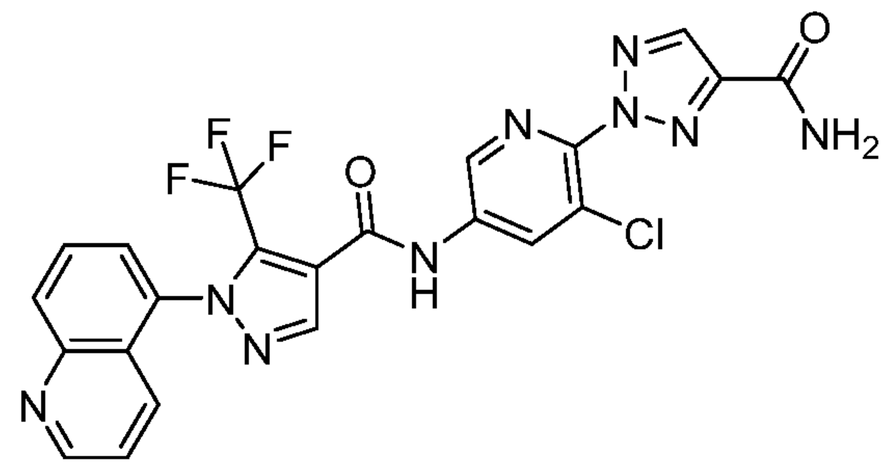
D. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 143**



1-(Thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (70 mg, 0.22 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (50 mg, 0.27 mmol), $POCl_3$ (41.18 mg, 0.27 mmol) were dissolved in DCM (2 mL), and pyridine (53.11 mg, 0.67 mmol) was added. The mixture was stirred at 25 °C for 2 h, then sat.NH_4Cl (20 mL) was added and the mixture extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude as a yellow oil, which was purified by preparative HPLC (54% to 27% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (46 mg, 49.7%). LCMS (ESI) m/z M+1: 482.1. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.73 (d, J=5.29 Hz, 1 H), 8.09 (d, J=5.29 Hz, 1 H), 8.25 - 8.35 (m, 3 H), 8.49 (d, J=5.29 Hz, 1 H), 8.57 (s, 1 H), 8.83 (d, J=2.43 Hz, 1 H), 9.05 (d, J=2.43 Hz, 1 H), 11.50 (s, 1 H).

Example 144

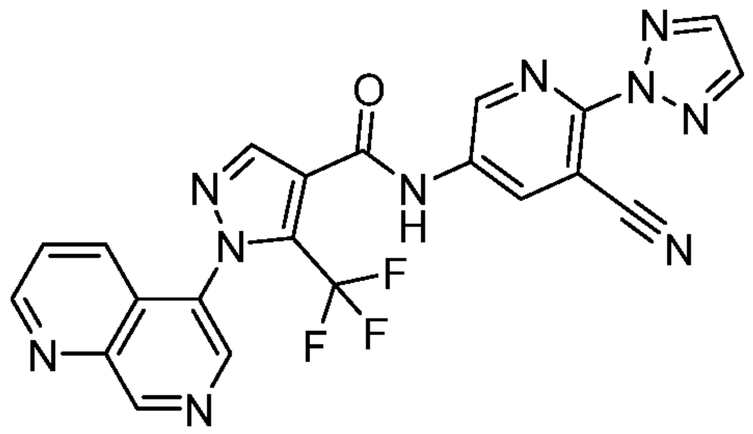
2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide**, Cpd 144**



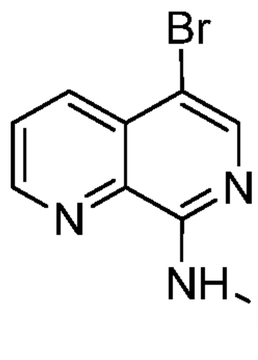
2-(3-Chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid (80 mg, 0.15 mmol), NH_4Cl (23.23 mg, 0.43 mmol), HATU (82.56 mg, 0.22 mmol) were dissolved in DMF (4 mL), and DIEA (93.54 mg, 0.72 mmol) was added. The mixture was stirred at 25 °C for 2 h, sat.NH_4Cl (20 mL) was added and extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford a crude product as a yellow oil, which was purified by preparative HPLC (66% to 36% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (44 mg, 47.5%). LCMS (ESI) m/z M+1: 529.2. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.74 - 7.87 (m, 3 H), 8.00 - 8.10 (m, 2 H), 8.15 (br s, 1 H), 8.42 (d, J=8.53 Hz, 1 H), 8.51 (s, 1 H), 8.73 - 8.81 (m, 2 H), 9.01 (d, J=2.26 Hz, 1 H), 9.16 (dd, J=4.27, 1.51 Hz, 1 H), 11.64 (s, 1 H).

Example 145

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 145**



A. 5-bromo-8-hydrazinyl-1,7-naphthyridine, **145a**

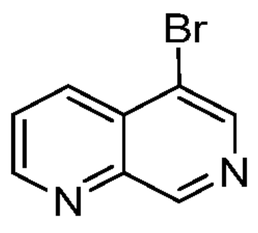


145a

5-Bromo-8-chloro-1,7-naphthyridine (800 mg, 3.29 mmol) was dissolved in hydrazine hydrate (5 mL). The reaction mixture was stirred at 50 °C for 2 h. The solvent

was removed to afford the desired product as a yellow oil (785 mg, 100%), which was used directly for the next step.

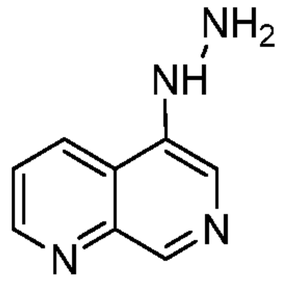
B. 5-bromo-1,7-naphthyridine, **145b**



, 145b

5-Bromo-8-hydrazinyl-1,7-naphthyridine (785 mg, 3.29 mmol) was dissolved in water (10 mL) and acetic acid (30 mL). Copper(II) sulfate (524.48 mg, 3.29 mmol) was added and stirred at 70 °C for 3 h. The solvent was removed, 30% $NH_3.H_2O$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 85/15) to afford the title compound (420 mg, 59.9%) as a yellow solid. LCMS (ESI) m/z M+1: 208.8.

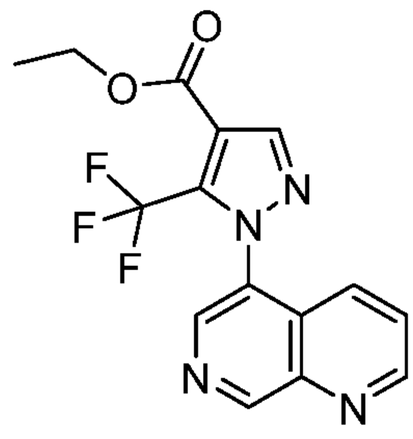
C. 5-hydrazinyl-1,7-naphthyridine, **145c**



, 145c

5-Bromo-1,7-naphthyridine (340 mg, 1.63 mmol), palladium(ii)(pi-cinnamyl) chloride dimer (42.13 mg, 0.081 mmol), N-[2-(di-1-adamantylphosphino)phenyl] morpholine (75.41 mg, 0.16 mmol) and sodium *tert*-butoxide (624.56 mg, 6.51 mmol) was dissolved in dioxane (10 mL) under N_2 atmosphere. Hydrazine hydrate (162.84 mg, 3.25 mmol) was added and stirred at 60 °C for 3 h. The mixture was filtered and the solid was washed with 10 mL CH_2Cl_2. The solvent was partioned between H_2O (10 mL) and CH_2Cl_2 (50 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the title compound (260 mg, 99.8%) as brown solid. LCMS (ESI) m/z M+1: 161.1.

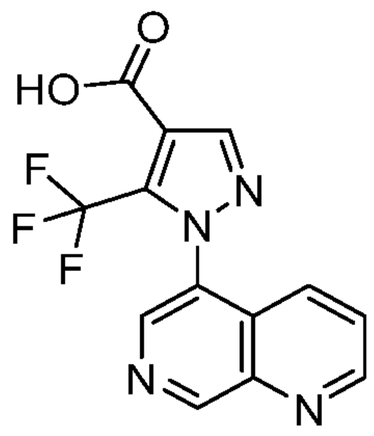
D. ethyl 1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **145d**



, 145d

5-Hydrazinyl-1,7-naphthyridine (260 mg, 1.62 mmol) was dissolved in ethanol (10 mL), and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (467.8 mg, 1.95 mmol) was added. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford the crude product as a yellow solid, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 50/50) to afford the title compound (100 mg, 17.3%) as a yellow solid. LCMS (ESI) m/z M+1: 337.0.

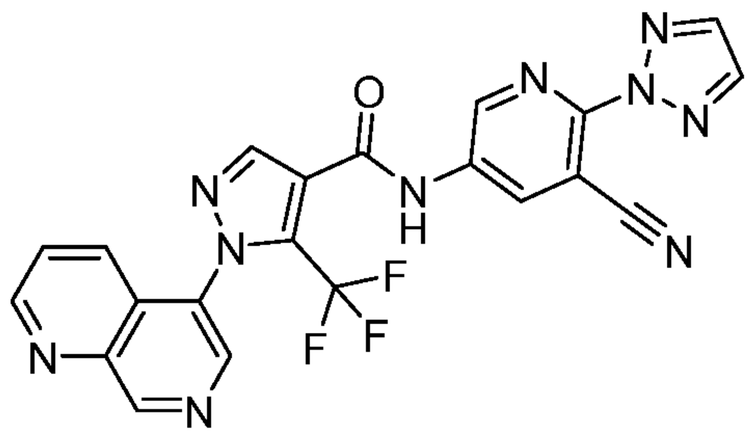
E. 1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **145e**



, 145e

Ethy1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (100 mg, 0.27 mmol) was dissolved in THF (10 mL) and water (10 mL). Lithium hydroxide (64.1 mg, 2.68 mmol) was added. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was adjusted to pH 5 using HCl (2 N), extracted with EtOAc (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude the title compound (75 mg, 90.9%) as a yellow solid. LCMS (ESI) m/z M+1: 309.0.

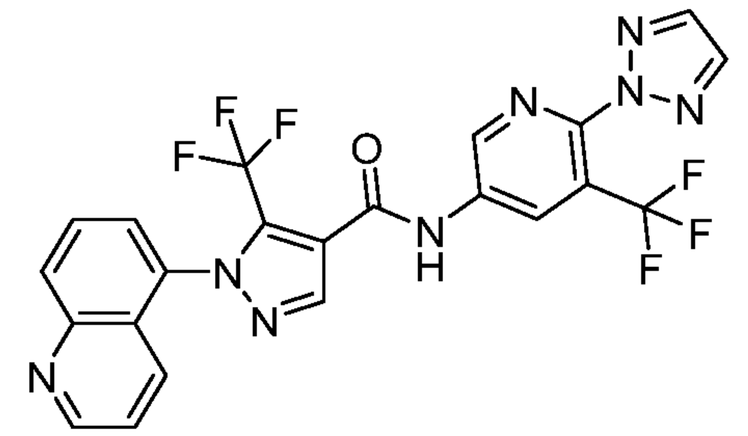
F. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 145**



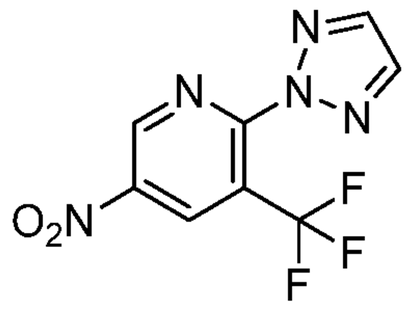
1-(1,7-Naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (75 mg, 0.24 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (54.36 mg, 0.29 mmol), pyridine (115.49 mg, 1.46 mmol) were dissolved in CH_2Cl_2 (10 mL), and phosphorus oxychloride (149.25 mg, 0.97 mmol) was added. The mixture was stirred at 25 °C for 4 h, sat. $NaHCO_3$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (22% to 52% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (35 mg, 30.2%). LCMS (ESI) m/z M+1: 477.0. ^{1}H NMR (400MHz, DMSO-d6) δ ppm 11.50 (s, 1H), 9.69 (s, 1H), 9.22 (dd, J=1.5, 4.2 Hz, 1H), 9.14 (d, J=2.4 Hz, 1H), 8.95 (s, 1H), 8.90 (d, J=2.4 Hz, 1H), 8.71 (s, 1H), 8.30 (s, 2H), 7.94 (dd, J=4.2, 8.6 Hz, 1H), 7.87 - 7.82 (m, 1H).

Example 146

N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 146**



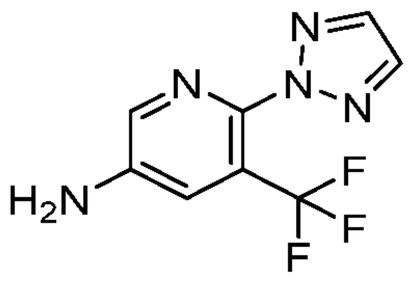
A. 5-nitro-2-(2H-1,2,3-triazol-2-yl)-3-(trifluoromethyl)pyridine, **146a**



, **146a**

To a solution of 3-chloro-4-fluoronitrobenzene (1.2 g, 6.84 mmol) and 2H-1,2,3-triazole (0.567 g, 8.20 mmol) in anhydrous DMA (5 mL) was added K_2CO_3 (1.89 g, 13.67 mmol). The reaction mixture was stirred at room temperature for 2 h. The mixture was filtered and washed with ethyl acetate (10 mL x 3). The filtrate was concentrated to dryness to give a crude product. The crude product was purified by a flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford 2-chloro-5-nitro-3-(trifluoromethyl)pyridine, **146a** (600 mg, 65.6% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.37 (s, 2 H), 9.16 (d, J=2.20 Hz, 1 H), 9.68 (d, J=2.21 Hz, 1 H).

B. 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine, **146b**

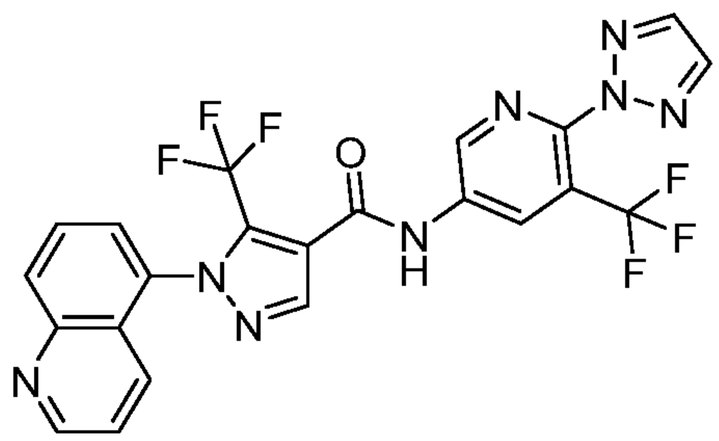


, **146b**

To a solution of 5-nitro-2-(2H-1,2,3-triazol-2-yl)-3-(trifluoromethyl)pyridine (550 mg, 1.78 mmol) in MeOH/THF/H_2O (5 mL/10 mL/5 mL) was added iron (593 mg, 10.61 mmol) and ammonium chloride (568 mg, 10.61 mmol). The reaction mixture was stirred at 70 °C for 2 h, sat. $NaHCO_3$ was added to the mixture to adjust the pH to 7~9. The reaction was filtered and the organic solvent was concentrated. The mixture was extracted with CH_2Cl_2 (10 mL x 3). The separated organic layer was dried ($MgSO_4$), filtered, and the solvent was concentrated to give a crude product as solid. The crude product was purified by a flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate

from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford ethyl 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine, **146b** (400 mg, 82.2% yield) as a white solid. LCMS (ESI) m/z M+1: 230.0; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 6.38 (s, 2 H), 7.43 (d, J=2.43 Hz, 1 H), 8.04 (s, 2 H), 8.08 (d, J=2.43 Hz, 1 H).

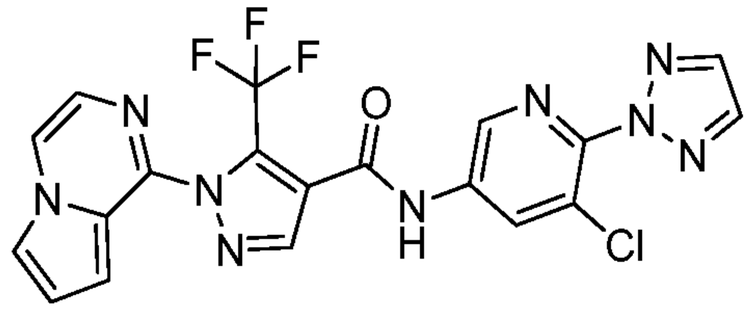
C. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoro-2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 146**



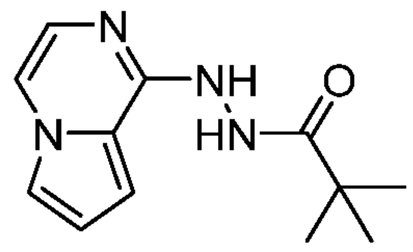
Phosphorus oxychloride (75.85 uL, 0.39 mmol) was added to a solution of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **3b** (100 mg, 0.33 mmol), 6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-amine (89.51 mg, 0.39 mmol), pyridine (263.26 uL, 3.26 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 2 h, 5 mL H_2O was added to the mixture and sat. $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3), the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (42% to 72% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (120 mg, 70.9%). LCMS (ESI) m/z M+1: 518.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.62 - 7.66 (m, 1 H), 7.68 - 7.72 (m, 1 H), 7.94 - 8.02 (m, 2 H), 8.22 (s, 2 H), 8.35 (d, J=7.94 Hz, 1 H), 8.63 (s, 1 H), 8.91 (d, J=1.98 Hz, 1 H), 9.08 (d, J=2.65 Hz, 1 H), 9.19 (s, 1 H), 11.45 (s, 1 H).

Example 147

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 147**



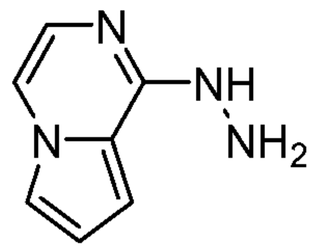
A. N'-(pyrrolo[1,2-a]pyrazin-1-yl)pivalohydrazide, **147a**



, 147a

The mixture of 1-chloropyrrolo[1,2-a]pyrazine (200 mg, 1.31 mmol) and pivalohydrazide (346.47 mg, 2.62 mmol) in MeCN (20 mL) was stirred at 80 °C for 24 h. The solvent was removed to give the crude product, the crude product was purified by FCC (petroleum ether/ ethyl acetate=100:0 to 70:30). The solvent was concentrated to get the crude product (200 mg, 61.5%).

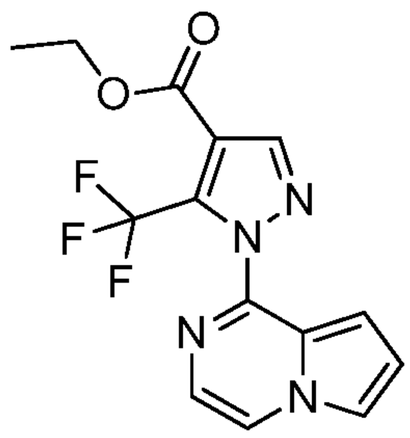
B. 1-hydrazinylpyrrolo[1,2-a]pyrazine, **147b**



, 147b

The mixture of N'-(pyrrolo[1,2-a]pyrazin-1-yl)pivalohydrazide (0.18 g, 0.73 mmol) and HCl in dioxane (1 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h. The solvent was removed to give the product as a white solid (133.85 mg, 100%).

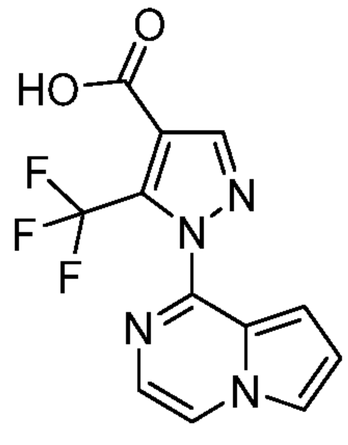
C. ethyl 1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **147c**



, 147c

A solution consisting of ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (348.25 mg, 1.45 mmol), 1-hydrazinylpyrrolo[1,2-a]pyrazine (133.85 mg, 0.73 mmol), DIEA (0.468 g, 3.63 mmol) and ethanol (20 mL) was stirred at 80 °C for 1 h. The resultant solution was concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100/0 to 70/30) to afford the title compound (0.15 g, 58.7%) as a yellow oil. LCMS (ESI) m/z M+1: 325.0.

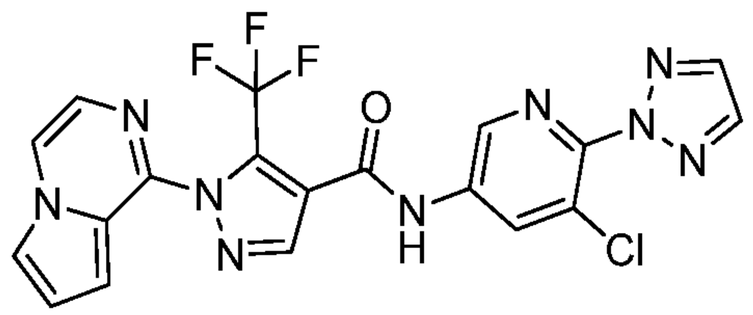
D. 1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **147d**



, 147d

Sodium hydroxide (34.05 mg, 0.85 mmol) was added to a solution of ethyl 1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (160 mg, 0.43 mmol) in THF/ H_2O=1:1(10 mL). The mixture was reacted at room temperature for 2 h, the solvent was concentrated under reduced pressure and 20 mL H_2O was added to the mixture. The mixture was acidified using 1M hydrochloric to pH 5 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrates were concentrated under reduced pressure to afford the product as a yellow solid (100 mg, 79.3%).

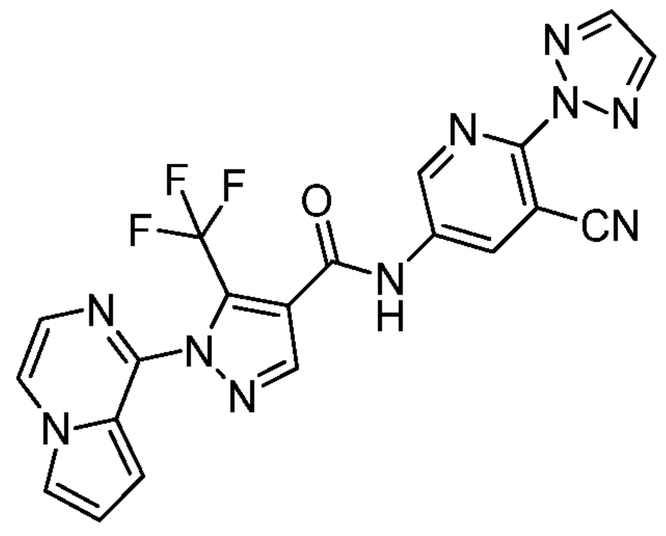
E. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 147**



1-(Pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.34 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, (66.04 mg, 0.34 mmol), pyridine (0.14 mL, 1.69 mmol) were dissolved in CH_2Cl_2 (5 mL), and phosphorus oxychloride (0.12 mL, 1.35 mmol) was added. The mixture was stirred at 25 °C for 2 h. Sat. $NaHCO_3$ (20 mL) was added and the mixture extracted with CH_2Cl_2 (30 mL x 2). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (38% to 68% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (66 mg, 40.6%). LCMS (ESI) m/z M+1: 473.9; ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 8.78 (1 H, s), 8.70 (1 H, d, J=2.20 Hz), 8.34 (1 H, s), 8.32 (1 H, d, J=4.85 Hz), 8.03 (2 H, s), 7.88 (1 H, s), 7.47 (1 H, d, J=4.85 Hz), 6.99 - 7.07 (1 H, m), 6.87 (1 H, d, J=4.19 Hz).

Example 148

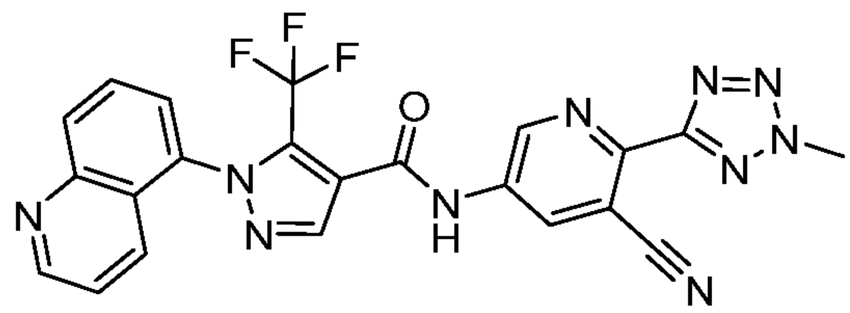
N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 148**



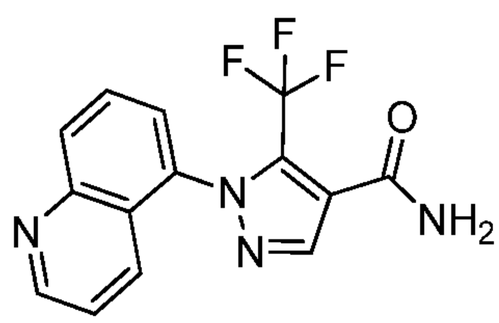
1-(Pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (180 mg, 0.18 mmol, 30% pure), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (33.94 mg, 0.18 mmol), pyridine (43.26 mg, 0.55 mmol) were dissolved in CH_2Cl_2 (3 mL), and phosphorus oxychloride (41.93 mg, 0.27 mmol) was added. The mixture was stirred at 25 °C for 16 h, sat. $NaHCO_3$ (20 mL) was added and extracted with CH2Cl2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a yellow oil, which was purified by preparative HPLC (43% to 63% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (11 mg, 12.9%). LCMS (ESI) m/z M+1: 454.9.0; ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 9.07 (br s, 1 H), 8.90 (s, 1 H), 8.31 - 8.39 (m, 2 H), 8.15 (br s, 2 H), 7.89 (d, J=1.32 Hz, 1 H), 7.48 (d,J=4.63 Hz, 1 H), 7.04 (dd, J=4.19, 2.65 Hz, 1 H), 6.87 (d, J=4.19 Hz, 1 H).

Example 149

N-(5-cyano-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 149**



A. 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **149a**

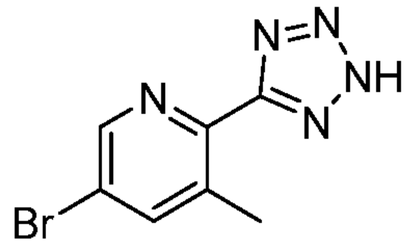


, **149a**

HATU (2.79 g, 7.32 mmol) was added to a solution of 1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid, **3b** (1.5 g, 4.88 mmol), NH_3/dioxane (19.53 mL, 9.77 mmol), DIEA (1.26 g, 9.77 mmol) in CH_2Cl_2. The mixture was stirred at rt for 16 h, 50 mL H_2O and 50 mL ethyl acetate were added to the mixture. The organic

layer was washed with brine (50 mL), dried over $MgSO_4$ and the filtrate concentrated under reduced pressure. The residue was purified by FCC (petroleum ether/ ethyl acetate=100:5 to 100:50) to afford the title compound (1 g, 63.8%) as a yellow solid.

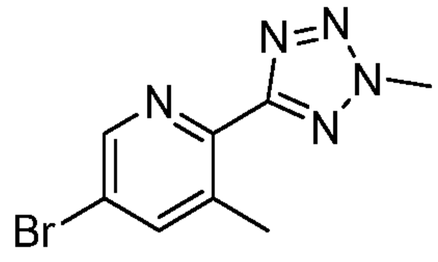
B. 5-bromo-3-methyl-2-(2H-tetrazol-5-yl)pyridine, **149b**



, **149b**

To a stirring solution of 5-bromo-3-methylpicolinonitrile (3.43 g, 17.39 mmol) in DMF (30 mL) was added zinc(II) chloride (2.37 g, 17.39 mmol) and sodium azide (1.47 g, 22.61 mmol). The reaction mixture was stirred at 95 °C for 16 h. The solution was used directly for the next step.

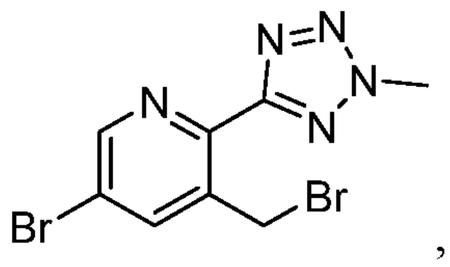
C. 5-bromo-3-methyl-2-(2-methyl-2H-tetrazol-5-yl)pyridine, **149c**



, **149c**

To a stirring solution of 5-bromo-3-methyl-2-(2H-tetrazol-5-yl)pyridine (2 g, 8.33 mmol) in DMF (30 mL) was added potassium carbonate (5.76 g, 41.66 mmol) and iodomethane (5.20 g, 36.66 mmol). The reaction mixture was stirred at 25 °C for 2 h and filtered. The filtrate was concentrated to dryness under reduced pressure to afford the crude product, which was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 60:40) to afford the title compound (480 mg, 23.1%) as a white solid.

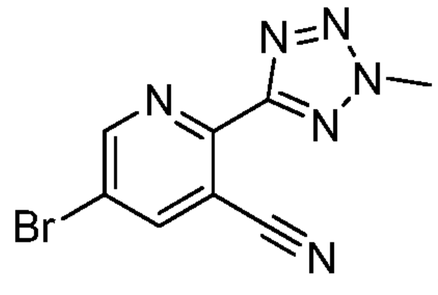
D. 5-bromo-3-(bromomethyl)-2-(2-methyl-2H-tetrazol-5-yl)pyridine, **149d**



, **149d**

Benzoic peroxyanhydride (28.60 mg, 0.12 mmol) was added to a solution of 5-bromo-3-methyl-2-(2-methyl-2H-tetrazol-5-yl)pyridine (0.3 g, 1.18 mmol) and 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione (185.67 mg, 0.65 mmol) in acetonitrile (10 mL). The mixture was stirred at 80 °C under N_2 for 4 h. The solvent was concentrated under reduced pressure and extracted with acetate (30 mL x 2). The combined organic layers were concentrated under reduced pressure to give crude product. The crude product was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to afford the title compound (326 mg, 24.5%) as a white solid. LCMS (ESI) m/z M+1: 333.8.

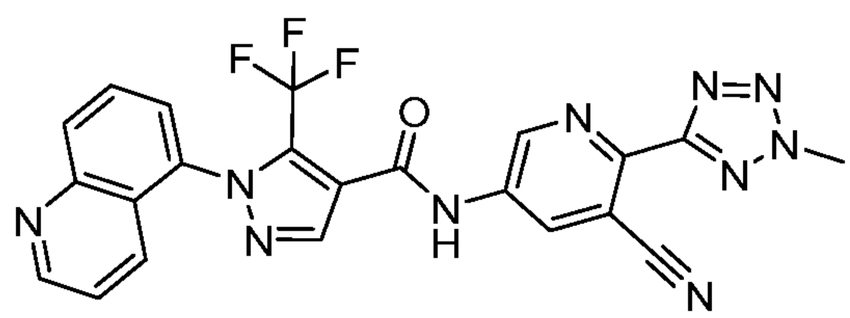
E. 5-bromo-2-(2-methyl-2H-tetrazol-5-yl)nicotinonitrile, **149e**



, **149e**

Diiodine (333.84 mg, 1.32 mmol) was added to a solution of 5-bromo-3-(bromomethyl)-2-(2-methyl-2H-tetrazol-5-yl)pyridine (296.00 mg, 0.26 mmol) in ammonia hydrate (5 mL). The mixture was stirred at 60 °C for 16 h. The solvent was concentrated under reduced pressure and extracted with acetate (30 mL x 2). The combined organic layers were concentrated under reduced pressure to give crude product. The crude product was purified by FCC (petroleum ether: ethyl acetate = 100:0 to 70:30) to afford the title compound (160 mg) as a white solid. LCMS (ESI) m/z M+1: 267.0.

F. N-(5-cyano-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 149**

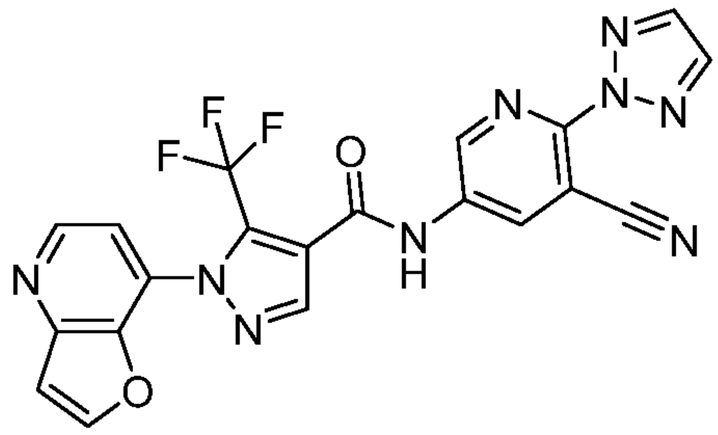


To a mixture of 5-bromo-2-(2-methyl-2H-tetrazol-5-yl)nicotinonitrile (160.0 mg, 0.31 mmol), 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (188.76

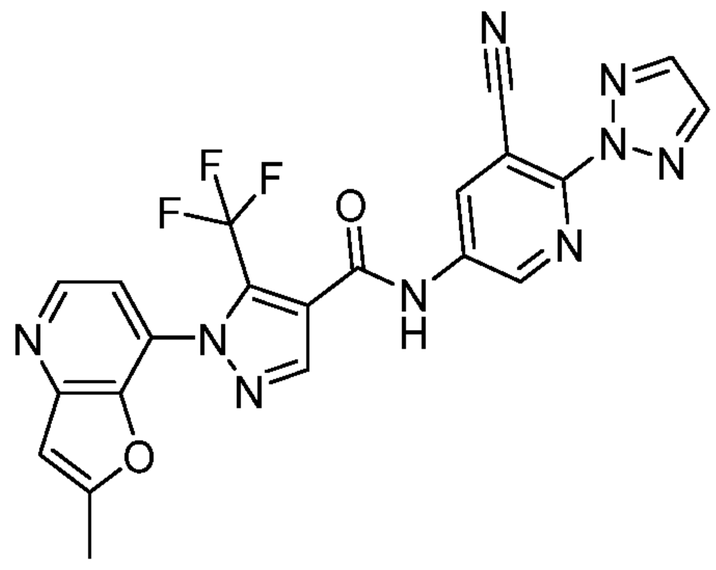
mg, 0.62 mmol), and sodium 2-methylpropan-2-olate (118.47 mg, 1.23 mmol) were dissolved in dioxane (10 mL) was added tris(dibenzylideneactone)dipalladium(0) (56.44 mg, 0.062 mmol) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphos phine) (35.67 mg, 0.062 mmol). The mixture was stirred at 100 °C for 12 h. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give the crude product as a yellow oil, which was purified by preparative HPLC (26% to 46% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (28 mg, 17.7%). LCMS (ESI) m/z M+1: 490.9; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 11.46 (1 H, s), 9.27 (1 H, d, J=2.43 Hz), 9.04 (1 H, d, J=2.43 Hz), 8.84 (1 H, d, J=2.43 Hz), 8.63 (1 H, s), 8.32 (1 H, d, J=8.38 Hz), 7.93 - 7.99 (1 H, m), 7.89 - 7.93 (1 H, m), 7.64 - 7.69 (1 H, m), 7.58 - 7.63 (1 H, m), 4.50 (3 H, s).

Example 150 and Example 151

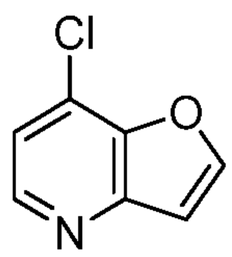
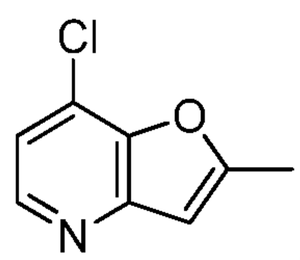
N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 150**



N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 151**

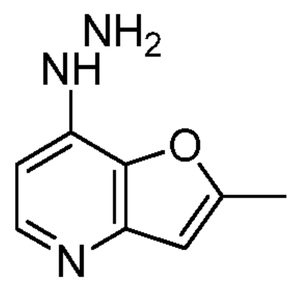
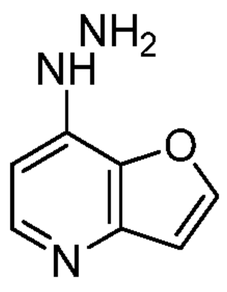


A. mixture of 7-chloro-2-methylfuro[3,2-b]pyridine with 7-chlorofuro[3,2-b]pyridine, **150a**



, **150a**

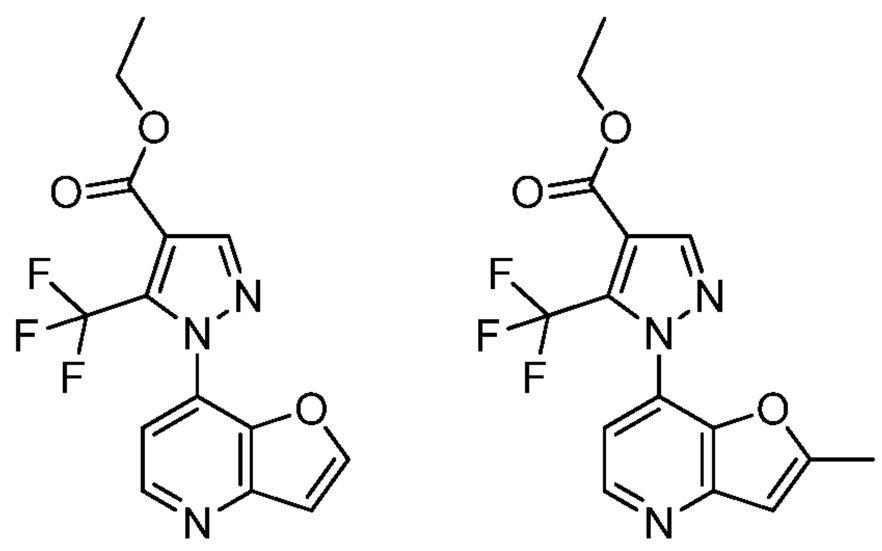
A mixture of 7-chloro-2-iodofuro[3,2-b]pyridine (180 mg, 0.66 mmol), dicyclohexyl(2',6'-diisopropoxy-[1,1'-biphenyl]-2-yl)phosphine (30 mg, 0.064 mmol), methylboronic acid (50 mg, 0.84 mmol), and K_3PO_4 (628 mg, 1.93 mmol) in dioxane (6 mL) and H_2O (1.5 mL) was added diacetoxypalladium (7.23 mg, 0.032 mmol) under N_2 and heated to 100 °C for 10 h. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered and the filtrates were concentrated under reduced pressure to afford the crude product. The residue was further purified by column chromatography (eluent: petrol ether/EtOAc=100:0 to 50:50). The desired fraction was collected and the solvent was removed to give the desired product as a brown oil. (80 mg, 35% yield).

B. mixture of 7-hydrazinyl-2-methylfuro[3,2-b]pyridine and 7-hydrazinylfuro[3,2-b]pyridine, **Cpd 150b**



, **150b**

A mixture of 7-chloro-2-methylfuro[3,2-b]pyridine and 7-chlorofuro[3,2-b]pyridine (80 mg, 0.23 mmol) and hydrazine hydrate (95 mg, 1.9 mmol) was heated to 50 °C overnight. The solvent was removed under reduced pressure and directly used for the next step.

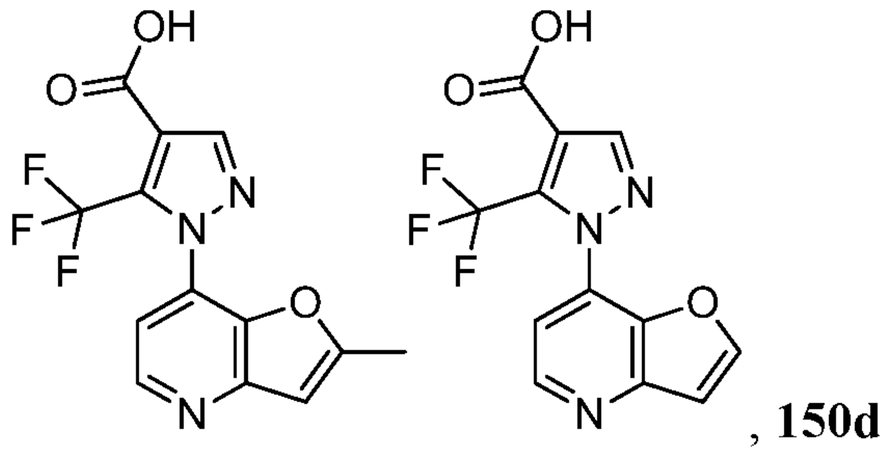
C. Mixture of ethyl 1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate and ethyl 1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **150c**



, **150c**

A mixture of 7-hydrazinyl-2-methylfuro[3,2-b]pyridine and 7-hydrazinylfuro[3,2-b]pyridine (65 mg, 0.21 mmol) was dissolved in ethanol (20 mL), and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (111.96 mg, 0.50 mmol) was added. The reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford the crude product as a brown oil, which was purified by FCC (eluent: petroleum ether/ethyl acetate from 100/0 to 50/50) to afford the title compound (50 mg, 35% yield) as a brown oil.

D. Mixture of 1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid and 1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **150d**

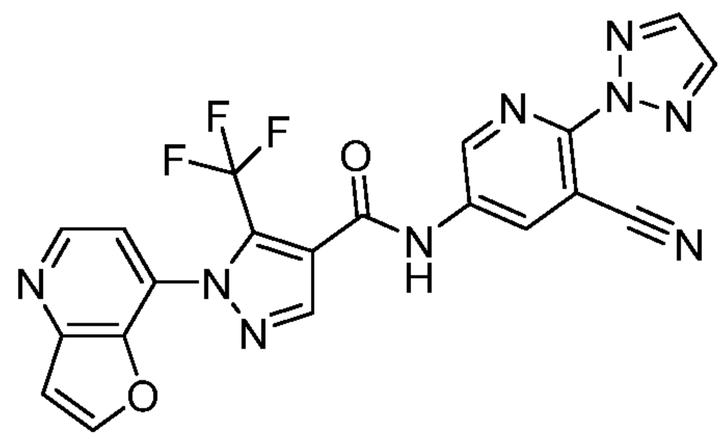


, **150d**

A mixture of ethyl 1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate and ethyl 1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (50 mg, 0.075 mmol) was dissolved in THF (5 mL) and water (1 mL). Lithium hydroxide (62.95 mg, 1.5 mmol) was added. The reaction mixture was

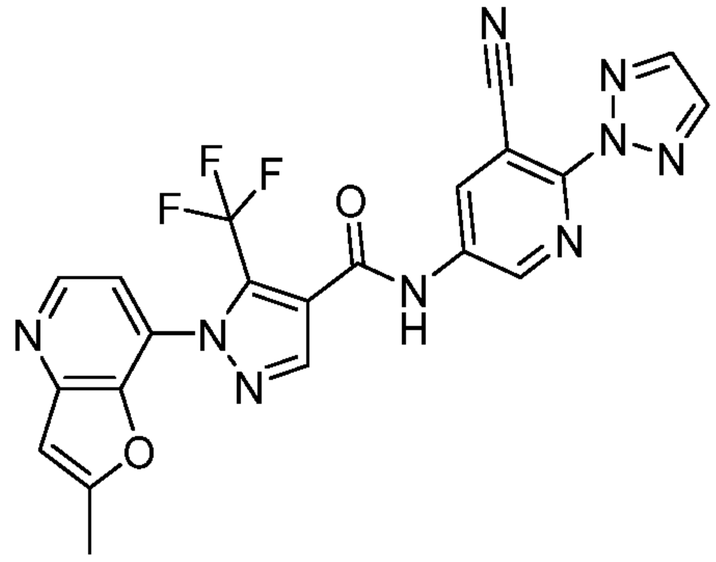
stirred at 25 °C for 1 h. THF was removed, and the resultant residue was washed with ether (5 mL). To the aqueous layer was added 3M HCl to adjust the mixture to pH 1, and the aqueous phase was extracted with EtOAc (5 mL x 3). The organic layers were dried over $MgSO_4$, filtered and the filtrates concentrated to afford the product as a brown oil (50 mg).

E. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 150**



, and

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **151**



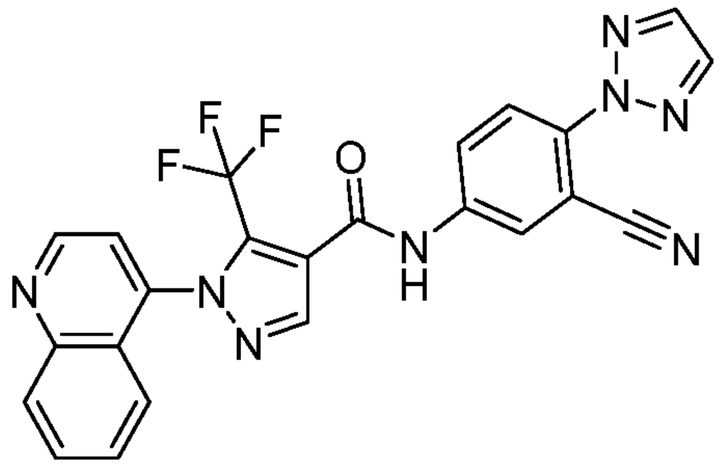
A mixture of 1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid and 1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (50 mg, 0.082 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (15.3 mg, 0.082 mmol), and pyridine (19.5 mg, 0.25 mmol) were dissolved in CH_2Cl_2 (3 mL), and phosphorus oxychloride (18.9 mg, 0.12 mmol) was added. The mixture was stirred at 25 °C for 16 h. Sat. $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a

yellow oil, which was purified by preparative HPLC (22% to 52% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 150** (5 mg, 13%). LCMS (ESI) m/z M+1: 465.9. 1H NMR (400 MHz, METHANOL-d_4) δ ppm 9.07 (br s, 1 H) 8.89 (d, J=2.43 Hz, 1 H) 8.79 (d, J=5.51 Hz, 1 H) 8.47 (s, 1 H) 8.34 (d, J=2.43 Hz, 1H) 8.14 (s, 2 H) 7.71 (d, J=5.29 Hz, 1 H) 7.28 (d, J=2.43 Hz, 1 H); and

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 151** (4 mg, 10%). ^{1}H NMR (400 MHz, METHANOL-d_4) δ ppm 9.06 (s, 1 H), 8.90 (d, J=2.65 Hz, 1 H), 8.71 (d, J=5.73 Hz, 1 H), 8.48 (s, 1 H), 8.14 (s, 2 H), 7.68 (d, J=5.73 Hz, 1 H), 6.98 (d, J=1.10 Hz, 1 H), 2.61 (d, J=0.88 Hz, 3 H). LC-MS: (ES, *m/z*): $[M+1]^+$ 480.0.

Example 152

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoro-2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 152**

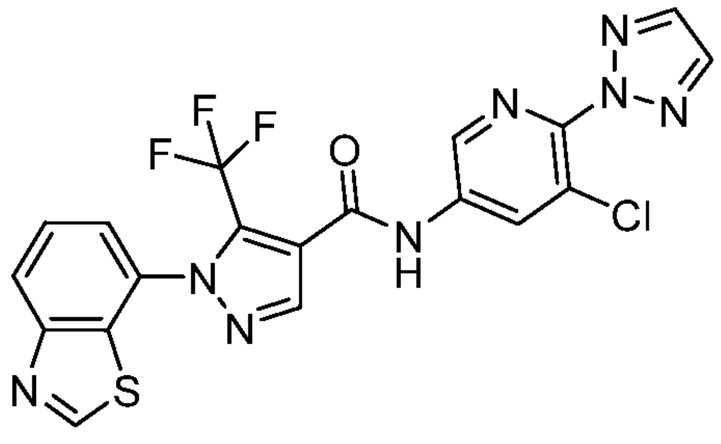


Phosphorus oxychloride (48.54 uL, 0.52 mmol) was added to a solution of 1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, (80 mg, 0.26 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)benzonitrile (53.04 mg, 0.29 mmol), pyridine (210.61 uL, 2.60 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h, then 5 mL H_2O was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by

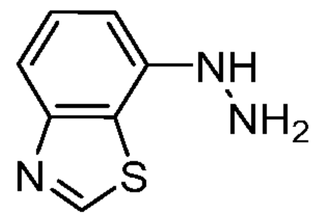
preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (45 mg, 36.2%). LCMS (ESI) m/z M+1: 475.0. ^1H NMR (400 MHz, DMSO-d6) δ ppm 7.34 (d, J=8.16 Hz, 1 H), 7.76 (t, J=7.28 Hz, 1 H), 7.90 (d, J=4.41 Hz, 1 H), 7.92 - 7.98 (m, 1 H), 8.11 - 8.16 (m, 1 H), 8.22 (d, J=2.21 Hz, 1 H), 8.24 (s, 1 H), 8.26 - 8.28 (m, 2 H), 8.43 (d, J=2.20 Hz, 1 H), 8.67 (s, 1 H), 9.18 (d, J=4.63 Hz, 1 H), 11.22 (s, 1 H).

Example 153

1-(benzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 153**



A. 7-hydrazinylbenzo[d]thiazole, **153a**

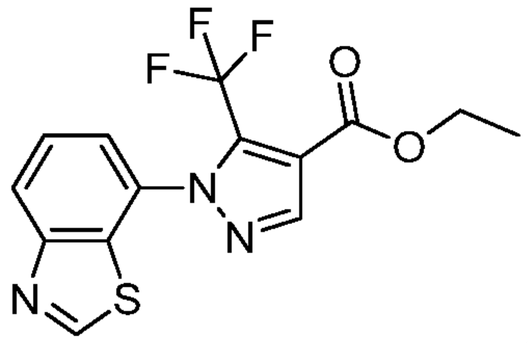


, **153a**

A mixture of palladium(II)(pi-cinnamyl) chloride dimer (24.2 mg, 0.047 mmol) and N-[2-(di-1-adamantylphosphino)phenyl]morpholine (43.31 mg, 0.093 mmol) in dioxane (2.5 mL) was purged with argon (4x). The resulting clear yellow solution was stirred at room temperature under argon for 10 min. 7-Bromobenzo[d]thiazole (200 mg, 0.93 mmol) and t-BuONa (179.56 mg, 1.87 mmol) were added to the mixture and purged with argon (4x). The resulting yellow reaction was stirred at room temperature for 5 min and then treated with hydrazine (93.53 mg, 1.87 mmol) via syringe and purged with argon (4x). Then the mixture was stirred at 50 °C under argon for 2 h. The mixture was filtered and

washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure to afford 7-hydrazinylbenzo[d]thiazole (150 mg, crude product) as a black solid.

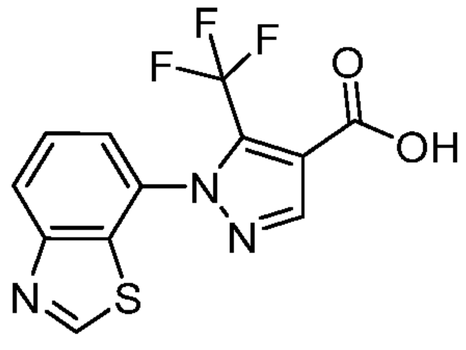
B. ethyl 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **153b**



, **153b**

A solution of 7-hydrazinylbenzo[d]thiazole, **153a** (150 mg, 0.91 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (327 mg, 1.36 mmol) in EtOH (20 mL) was stirred at 80 °C for 3 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 70/30). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title product (130 mg, 42.0 % yield) as a yellow solid.

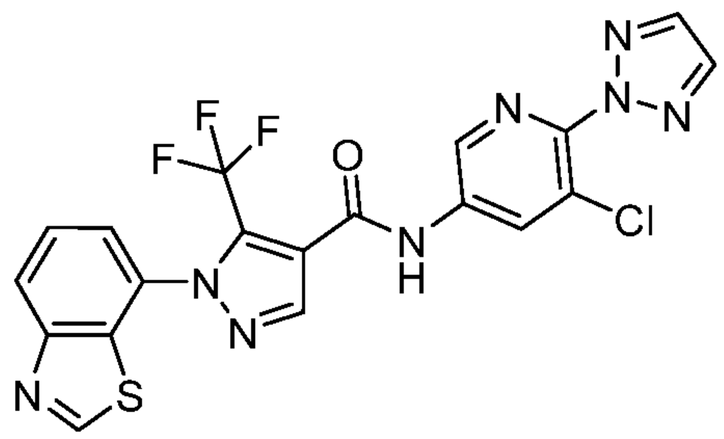
C. 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **153c**



, **153c**

A solution of ethyl 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **153b** (130 mg, 0.38 mmol), $LiOH.H_2O$ (23.98 mg, 0.57 mmol) in EtOH /H_2O (2/1, 2 mL) was stirred at room temperature overnight. 1N HCl solution was added to neutralize the reaction solution. The mixture was extracted with ethyl acetate (10 mL x 3). The separated organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated to afford the title product (100 mg, 83.8% yield) as a white solid.

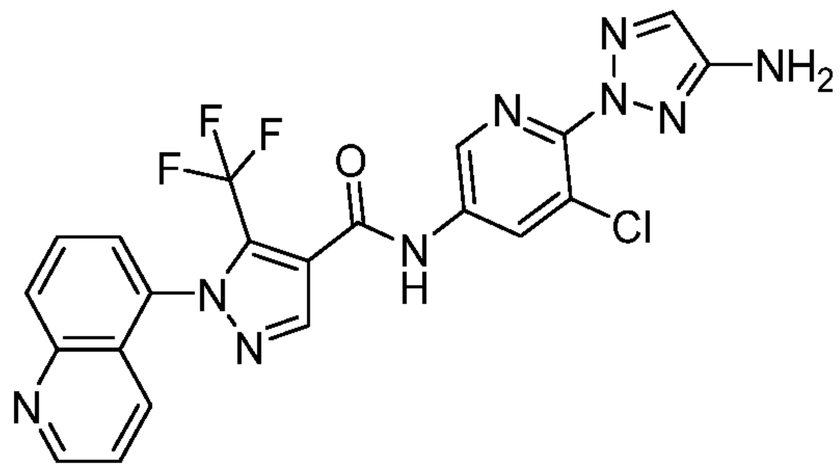
D. 1-(benzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 153**



Phosphorus oxychloride (39.71 uL, 0.43 mmol) was added to a solution of 1-(benzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **153c** (66.73 mg, 0.21 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (50 mg, 0.26 mmol), pyridine (172.28 uL, 2.13 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h and 5 mL H_2O was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (35% to 65% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (180 mg, 60.6%). LCMS (ESI) m/z M+1: 490.9. ^{1}H NMR (400 MHz, METHANOL-d4) δ ppm 7.69 (d, J=7.72 Hz, 1 H), 7.76 - 7.81 (m, 1 H), 8.06 (s, 2 H), 8.32 (d, J=8.16 Hz, 1 H), 8.38 (s, 1 H), 8.72 (d, J=1.76 Hz, 1 H), 8.80 (s, 1 H), 9.36 (s, 1 H).

Example 154

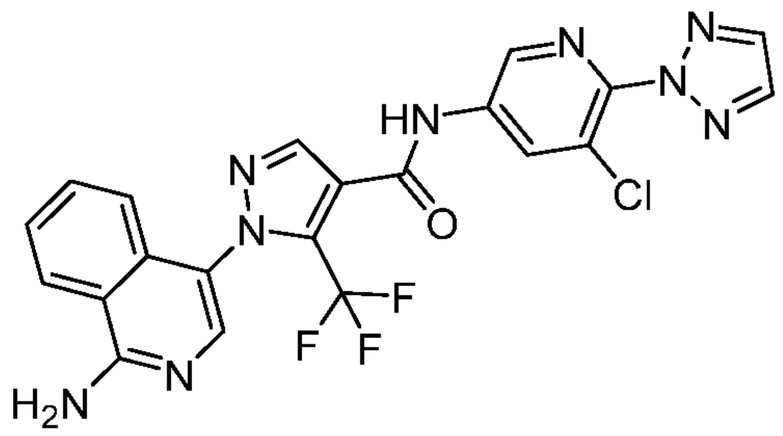
N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 154**



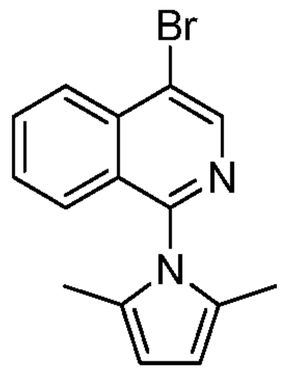
To a solution of 2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid, **Cpd 109** (160 mg, 0.29 mmol) in DMF (5 mL), DPPA (95.92 mg, 0.35 mmol) and TEA (118.83 ul, 0.87 mmol) were added under N_2 atmosphere. The mixture was stirred at 80 °C overnight. The mixture was concentrated to give a crude product, which was purified by preparative HPLC (40% to 70% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (45 mg, 30.8%). LCMS (ESI) m/z M+1: 499.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.51 (s, 2 H), 7.33 (s, 1 H), 7.59 - 7.64 (m, 1 H), 7.66 - 7.71 (m, 1 H), 7.91 - 8.01 (m, 2 H), 8.33 (d, J=8.60 Hz, 1 H), 8.58 - 8.62 (m, 2 H), 8.79 (d, J=2.21 Hz, 1 H), 9.06 (d, J=2.43 Hz, 1 H), 11.23 (br s, 1 H).

Example 155

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 155**

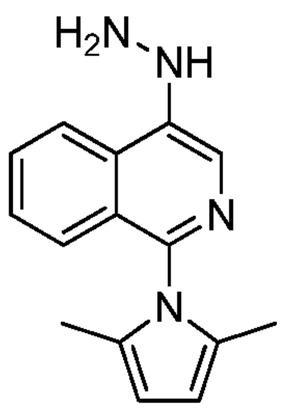


A. ethyl 1-(2-chloro-4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155a**


, **155a**

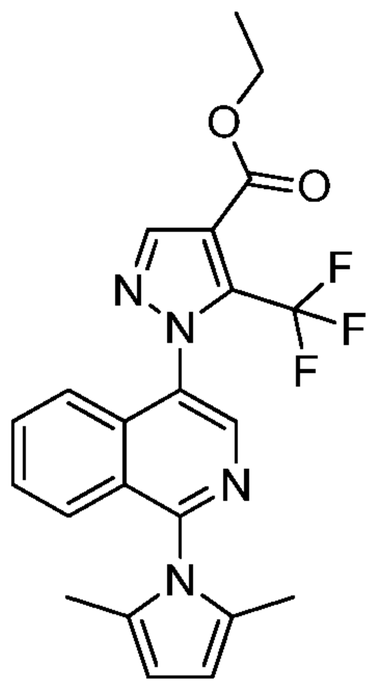
A solution of 4-bromoisoquinolin-1-amine (5.5 g, 24.656 mmol), hexane-2,5-dione (3.377 g, 29.59 mmol) and p-TSA (93.8 mg, 0.49 mmol) in toluene (50 mL) was heated to reflux for 36 h. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title product (3.3 g, 42.7% yield) as a white solid. LCMS (ESI) m/z M+1: 302.9.

B. 1-(2,5-dimethyl-1H-pyrrol-1-yl)-4-hydrazinylisoquinoline, **155b**


, **155b**

A mixture of ethyl 1-(2-chloro-4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155a** (2.6 g, 8.63 mmol), hydrazine (864.30 mg, 17.27 mmol), palladium(II)(pi-cinnamyl) chloride dimer (134.17 mg, 0.26 mmol) and N-[2-(di-1-adamantylphosphino)phenyl]morpholine (240.14 mg, 0.52 mmol) and t-BuONa (2486.21 mg, 25.90 mmol) in dioxane (50 mL) with N_2 atmosphere was stirred at 60 °C for 10 h. After filtering through diatomaceous earth, the mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (100 x 3 mL). The organic layer was separated, dried over $MgSO_4$, filtered and the filtrate concentrated to give the title product as a brown oil. LCMS (ESI) m/z M+1: 253.

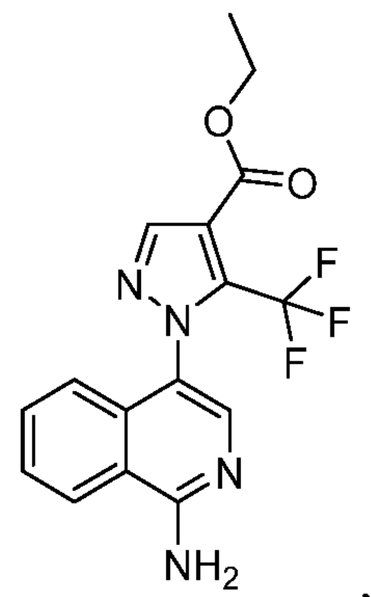
C. ethyl 1-(1-(2,5-dimethyl-1H-pyrrol-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155c**



, **155c**

A solution of 1-(2,5-dimethyl-1H-pyrrol-1-yl)-4-hydrazinylisoquinoline, **155b** (3.3 g, 8.63 mmol), ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (2.90 g, 12.09 mmol) in EtOH (50 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, the crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 50/50). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the product (3.5 g, 94.6% yield) as a yellow solid. LCMS (ESI) m/z M+1: 429.

D. ethyl 1-(1-(2,5-dimethyl-1H-pyrrol-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155d**

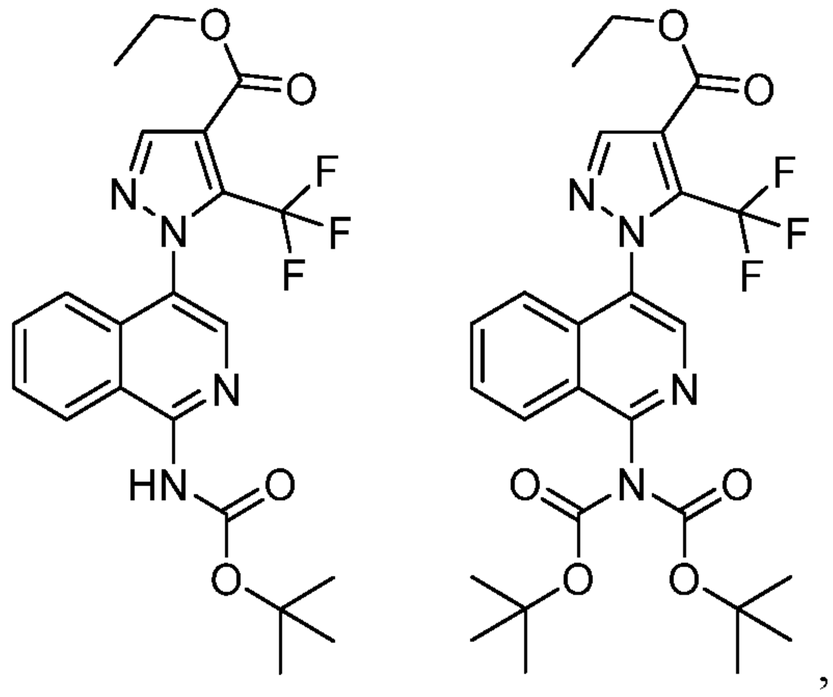


, **155d**

A solution of ethyl 1-(1-(2,5-dimethyl-1H-pyrrol-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **4c** (3.4 g, 7.94 mmol) and hydroxylamine

hydrochloride (13.24 g, 190.47 mmol) in EtOH (120 mL) was heated to reflux for 2 days. The solvent was removed and the residue was made basic by the addition of sat. $NaHCO_3$ solution (100 mL). The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were collected, dried over $MgSO_4$, filtered and the filtrate concentrated to give a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title product (1.6 g, 57.6% yield) as a brown solid. LCMS (ESI) m/z M+1: 350.9.

E. mixture of ethyl 1-(1-((tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate and ethyl 1-(1-((di-tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155e**

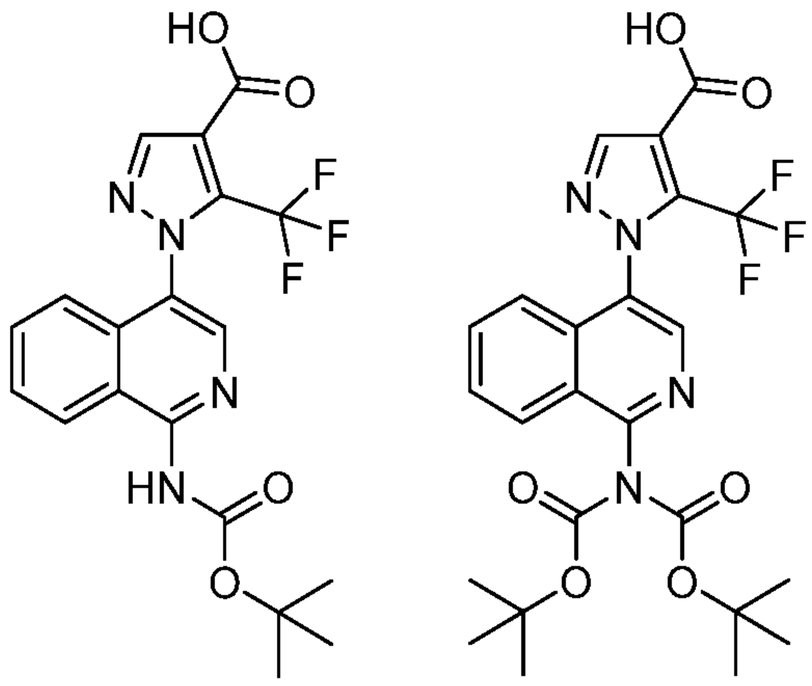


, **155e**

A solution of ethyl 1-(1-(2,5-dimethyl-1H-pyrrol-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **155d** (600 mg, 1.71 mmol) and Boc_2O (1121.47 mg, 5.14 mmol), DMAP (10.46 mg, 0.086 mmol) and TEA (715.22 ul, 5.14 mmol) in THF (5 mL) was stirred at room temperature overnight. The mixture was concentrated to give a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 50/50). The

desired fractions were collected and the solvent was concentrated under reduced pressure to afford the title product (650 mg, 68.9% yield) as a yellow solid.

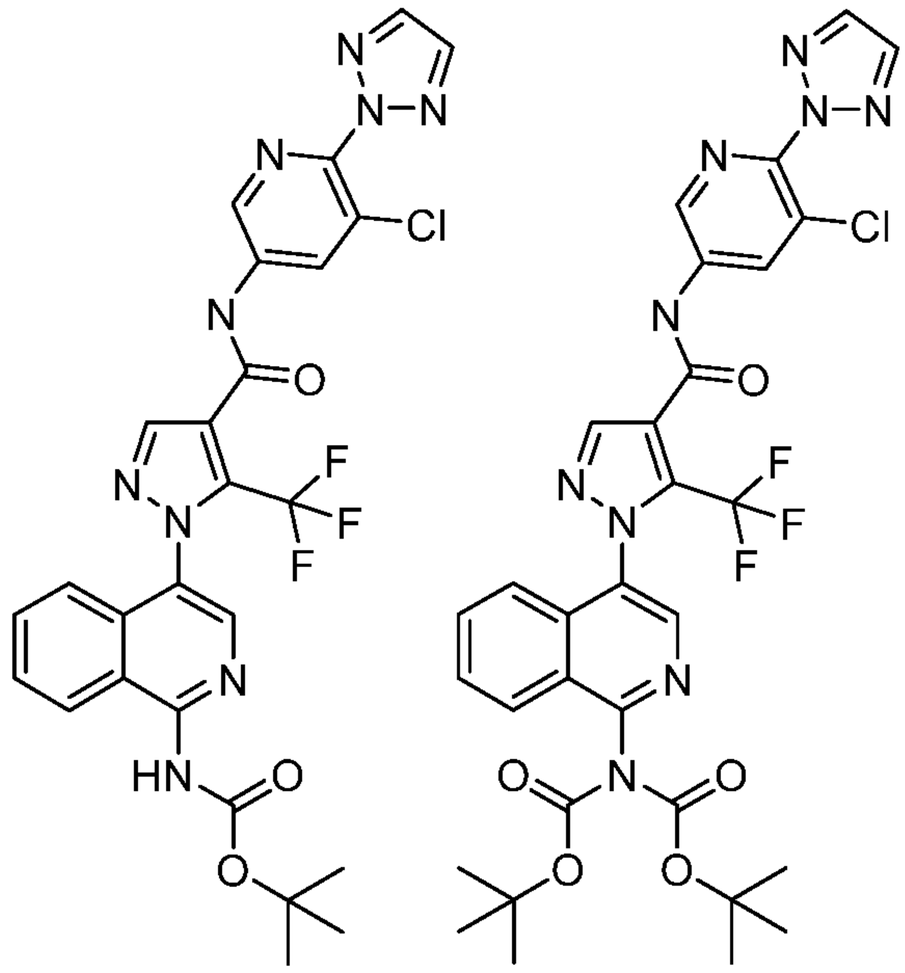
F. Mixture of 1-(1-((tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid; 1-(1-((di-tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **155f**



, **155f**

A solution of mixture of ethyl 1-(1-((tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate and ethyl 1-(1-((di-tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, 4e (420 mg, 0.42 mmol), LiOH (35.22 mg, 0.84 mmol) in THF /H_2O (2/1, 0.75 mL) was stirred at room temperature for 2 h. 1N HCl solution was added to neutralize the reaction solution. The mixture was extracted with ethyl acetate (10 mL x 3). The separated organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated to afford the title product (400 mg, crude product) as a white solid.

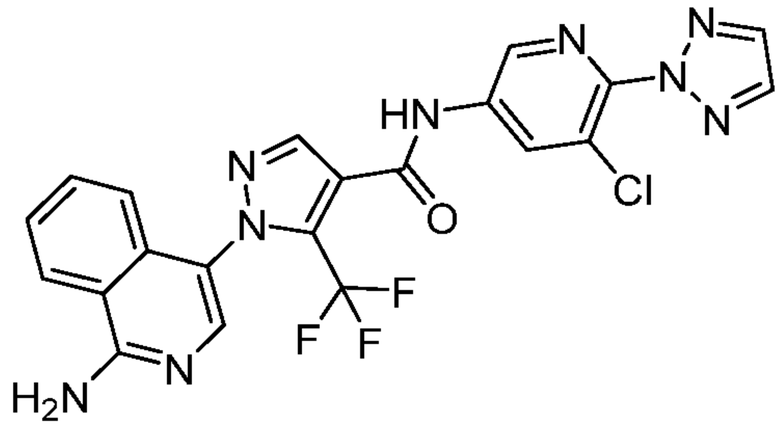
G. Mixture of *tert*-butyl (4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate and di-*tert*-butyl (4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate, **155g**



, **155g**

Phosphorus oxychloride (63.18 uL, 0.68 mmol) was added to a solution of mixture of 1-(1-((tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid; 1-(1-((di-tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **155f** (150 mg, 0.15 mmol), 5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (86.18 mg, 0.44 mmol), pyridine (274.09 uL, 3.39 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 1 h. 5 mL water was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product. LCMS (ESI) m/z M+1: 544.2.

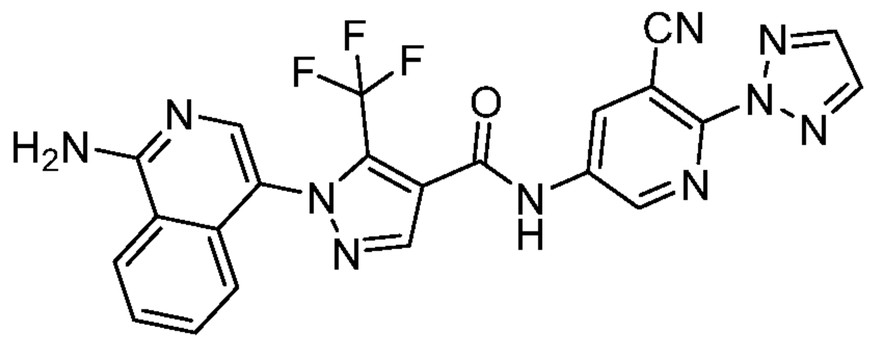
H. 1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 155**



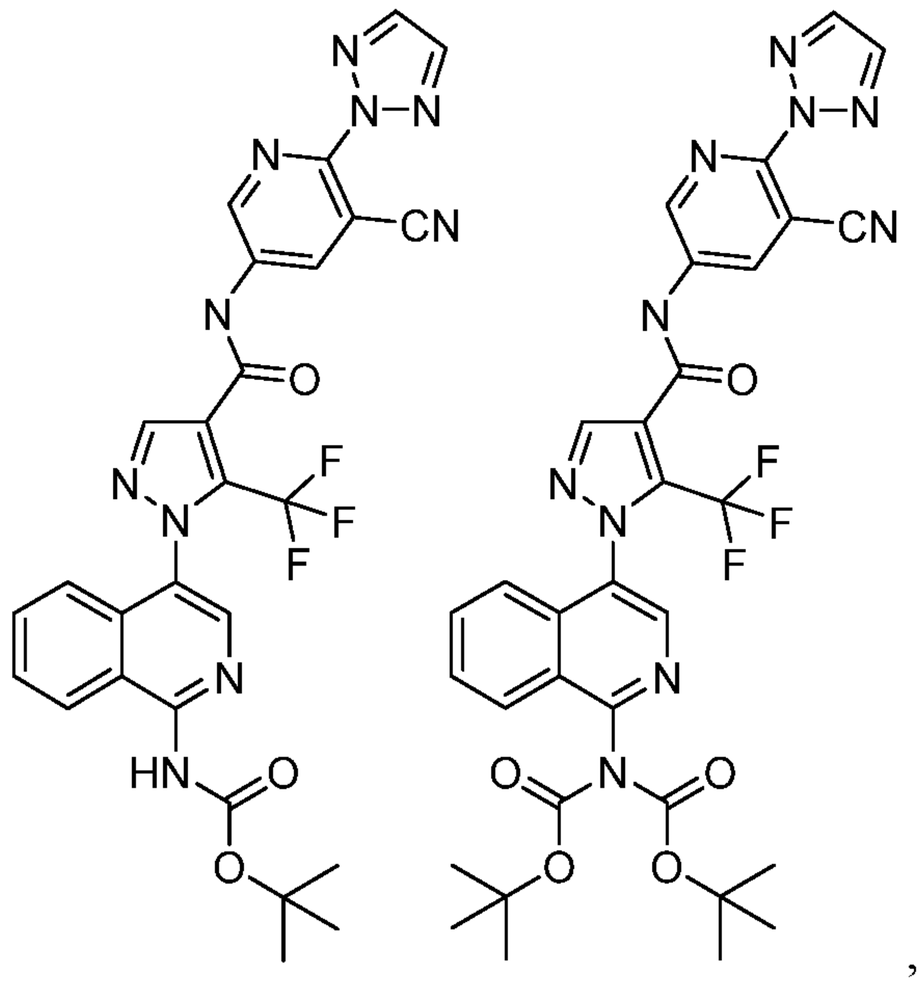
A mixture of mixture of *tert*-butyl (4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate and di-*tert*-butyl (4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate, **155g** (180 mg, 012 mmol) and HCl in dioxane (4N, 1.3 mL) in CH_2Cl_2 (2.6 mL) was stirred at room temperature for 2 h. Water (5 mL) was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (14% to 44% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (100 mg, 70.2%). LCMS (ESI) m/z M+1: 499.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 7.04 (d, J=8.16 Hz, 1 H), 7.87 (t, J=7.50 Hz, 1 H), 7.97 - 8.03 (m, 1 H), 8.16 (s, 2 H), 8.33 (s, 1 H), 8.64 - 8.75 (m, 3 H), 8.90 (d, J=2.20 Hz, 1 H), 9.57 (br s, 2 H), 11.48 (s, 1 H).

Example 156

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 156**



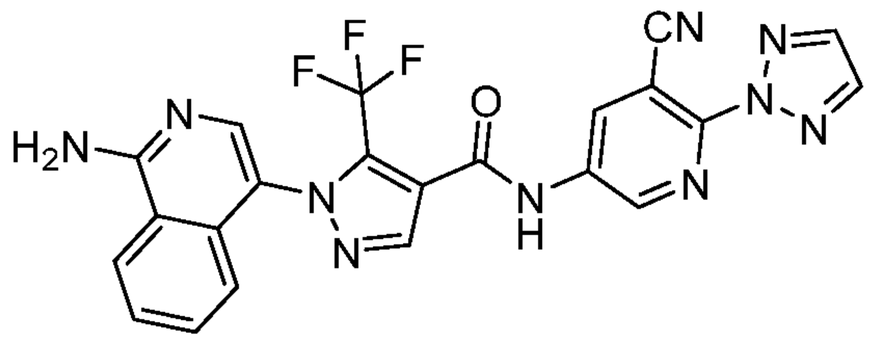
A. Mixture of *tert*-butyl (4-(4-((5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate and di-*tert*-butyl (4-(4-((5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate, **156a**



, **156a**

Phosphorus oxychloride (97.104 uL, 1.042 mmol) was added to a solution of mixture of 1-(1-((tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid and 1-(1-((di-tert-butoxycarbonyl)amino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **155f** (220 mg, 0.22 mmol), 5-amino-2-(2H-1,2,3-triazol-2-yl)nicotinonitrile (145.46 mg, 0.71 mmol), pyridine (421.29 uL, 5.21 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 1 h. Water (5 mL) was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product (300 mg). LCMS (ESI) m/z M+1: 535.1.

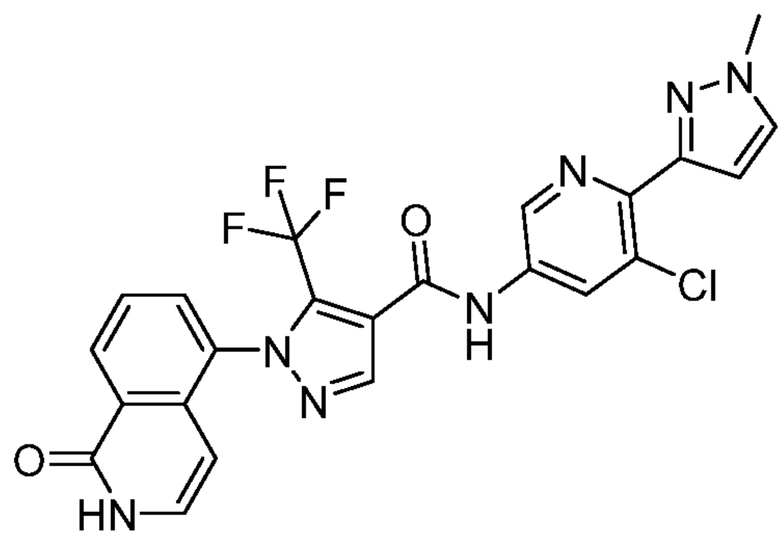
B. 1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 156**



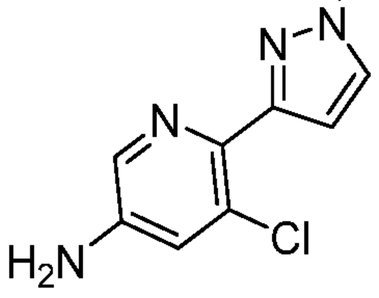
A mixture of *tert*-butyl (4-(4-((5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate and di-*tert*-butyl (4-(4-((5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)carbamate, **156a** (300 mg, 0.20 mmol) and HCl in dioxane (4N, 1.3 mL) in CH_2Cl_2 (2.6 mL) was stirred at room temperature for 2 h. Water (5 mL) was added to the mixture. Sat. $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (25% to 55% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (115 mg, 49.3%). LCMS (ESI) m/z M+1: 491.1; ^{1}H NMR (400 MHz, ACETONITRILE-d_3) δ ppm 9.06 (br s, 1 H), 8.83 (d, J=1.76 Hz, 1 H), 8.47 (d, J=8.38 Hz, 1 H), 8.38 (s, 1 H), 8.11 (br s, 2 H), 7.98 - 8.05 (m, 2 H), 7.86 - 7.95 (m, 1 H), 7.69 (s, 1 H), 7.21 (d, J=8.38 Hz, 1 H).

Example 157

N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 157**



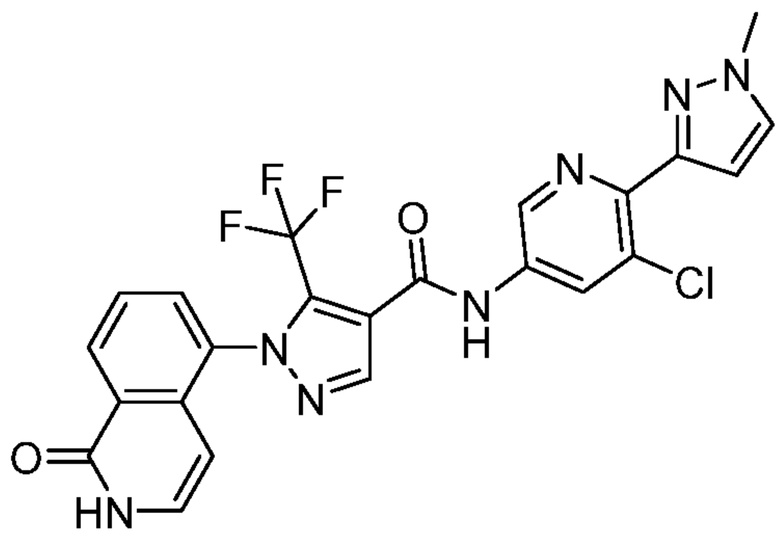
A. 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-amine, **157a**



, **157a**

$Pd_2(dba)_3$ (176.56 mg, 0.19 mmol) and Xphos (183.83 mg, 0.39 mmol) were added to a solution of 6-bromo-5-chloropyridin-3-amine (800 mg, 3.86 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1203.52 mg, 5.78 mmol) and K_3PO_4 (2.456 g, 11.57 mmol) in dioxane/H_2O (6/1, 20 mL) under an N_2 atmosphere. The mixture was stirred at 100 °C overnight. The reaction solution was filtered and the filtrate was concentrated to give a crude product. The crude product was purified by column chromatography over silica gel (petroleum ether/ ethyl acetate from 100/0 to 0/100). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford **157a** (530 mg, 59.0% yield) as a yellow solid. LCMS (ESI) m/z M+1: 209.1.

B. N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 157**

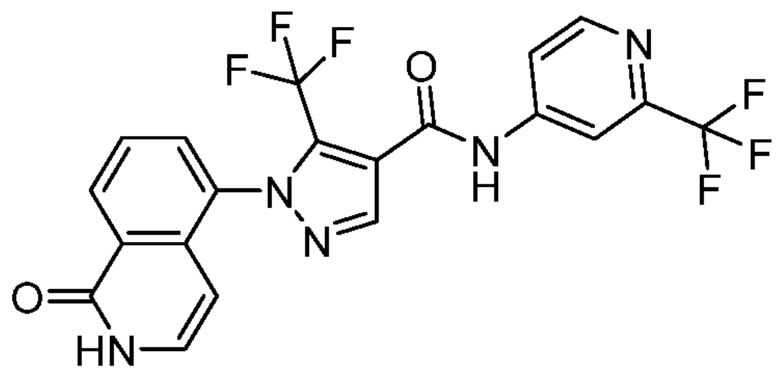


Phosphorus oxychloride (115.35 uL, 1.24 mmol) was added to a solution of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (400 mg, 1.24 mmol), 5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-amine (344.28 mg, 1.49 mmol), pyridine (1000.9 uL, 12.38 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 1 h. Water (5 mL) was added to the mixture and sat. $NaHCO_3$ was added to adjust the pH of the reaction mixture to 7~8. The mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over anhydrous Mg_2SO_4, filtered, and concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (29% to 59% (v/v) CH_3CN and H_2O with 0.05% HCl) and lyophilized to dryness to afford the title compound (190 mg, 29.0%). LCMS (ESI) m/z M+1: 513.9. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 3.94 (s, 3 H), 5.67 (d,

J=7.28 Hz, 1 H), 6.78 (d, J=2.21 Hz, 1 H), 7.30 (t, J=6.50 Hz, 1 H), 7.68 (t, J=7.83 Hz, 1 H), 7.80 (d, J=2.20 Hz, 1 H), 7.95 (d, J=7.28 Hz, 1 H), 8.42 - 8.48 (m, 2 H), 8.56 (s, 1 H), 8.88 (d, J=1.98 Hz, 1 H), 11.13 (s, 1 H), 11.64 (br d, J=5.51 Hz, 1 H).

Example 158

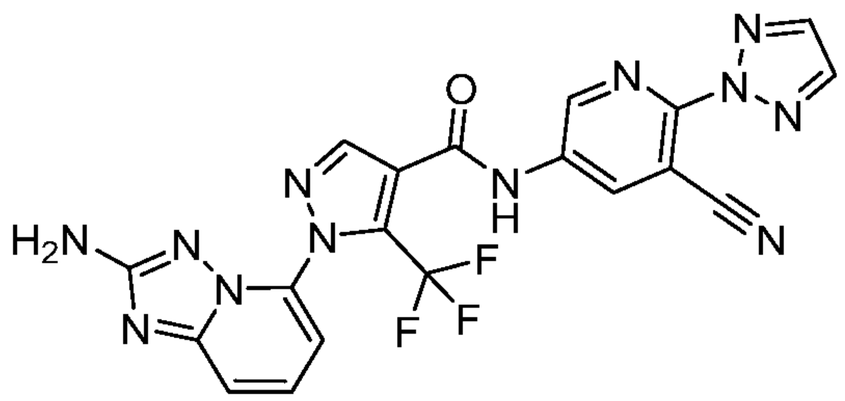
1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide, **Cpd 158**



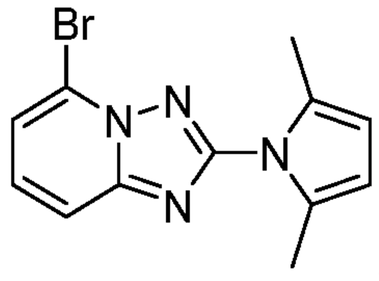
Phosphorus oxychloride (6.64 g, 43.3 mmol) was added to a solution of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (7.60 g, 21.7 mmol), 2-(trifluoromethyl)pyridin-4-amine (3.51 g, 21.7 mmol) in pyridine (50 mL). The mixture was stirred at room temperature for 2 h, sat. $NaHCO_3$ (500 mL) was added. The mixture was extracted with CH_2Cl_2 (500 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the filtrate concentrated to dryness under reduced pressure to afford the crude product, which was purified by preparative HPLC (5% to 60% (v/v) CH_3CN and H_2O with 0.05% HCl). The desired fraction was collected and adjusted to pH 7-8 with aqueous $NaHCO_3$ (10%). The organic solvent was concentrated under reduced pressure and a white solid was formed. The solid was collected and washed with water (3 x 300 mL) and dried to afford the title compound (5.90 g, 58.1%). LCMS (ESI) m/z M+1: 467.9; ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 5.66 (d, J=7.28 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.67 (t, J=7.83 Hz, 1 H), 7.94 (d, J=7.28 Hz, 1 H), 7.99 (dd, J=5.62, 1.65 Hz, 1 H), 8.26 (d, J=1.76 Hz, 1 H), 8.44 (d, J=8.16 Hz, 1 H), 8.56 (s, 1 H), 8.70 (d, J=5.51 Hz, 1 H), 11.35 (s, 1 H), 11.64 (br d, J=5.29 Hz, 1 H).

Example 159

1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 159**



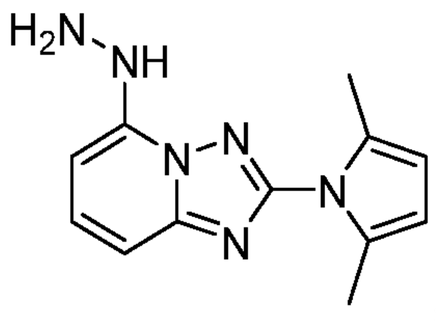
A. 5-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine, **159a**



, **159a**

Hexane-2,5-dione (428.6 mg, 3.76 mmol) was added to a solution of 5-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (400 mg, 1.88 mmol) and acetic acid (215 μL) in toluene (5 mL). The mixture was stirred at 155 °C for 12 h. The mixture was concentrated to give a crude product. The crude product was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). The eluant was collected and the solvent was concentrated under reduced pressure to give 5-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine as a yellow solid (500 mg, 91%). LC-MS: (ES, *m/z*): $[M+1]^+$ 292.9

B. 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-hydrazinyl-[1,2,4]triazolo[1,5-a]pyridine, **159b**

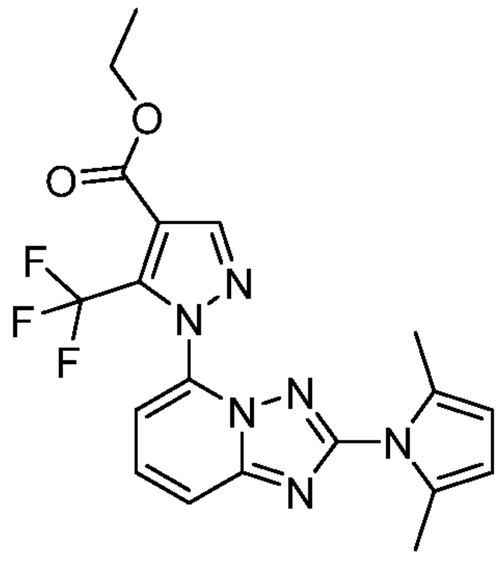


, **159b**

5-Bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (500 mg, 1.72 mmol) in hydrazine monohydrate (1 mL) was stirred at 80 °C overnight. The solid

was filtered and washed with water (2 mL x 3). The solid was collected and dried to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-hydrazinyl-[1,2,4]triazolo[1,5-a]pyridine as a white solid (416 mg, crude product).

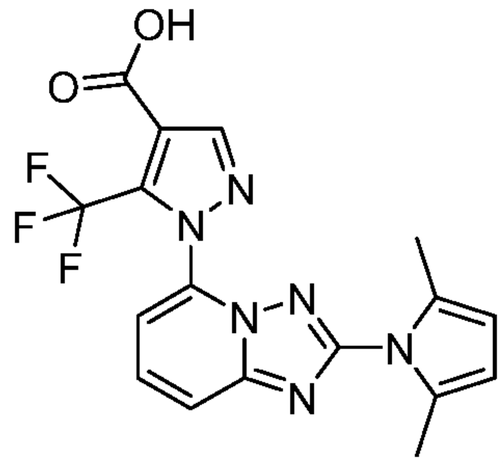
C. ethyl 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **159c**



, **159c**

Ethyl (*Z*)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **1f** (824.8 mg, 3.43 mmol) was added to a solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-hydrazinyl-[1,2,4]triazolo[1,5-a]pyridine (416 mg, 1.72 mmol) in ethanol (5 mL). The mixture was stirred at 80 °C overnight. The mixture was concentrated to give a crude product. The crude product was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 0/100). The eluent was collected and the solvent was concentrated under reduced pressure to give ethyl 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate as a yellow solid (650 mg, 90%). LC-MS: (ES, *m/z*): $[M+1]^+$ 419.1.

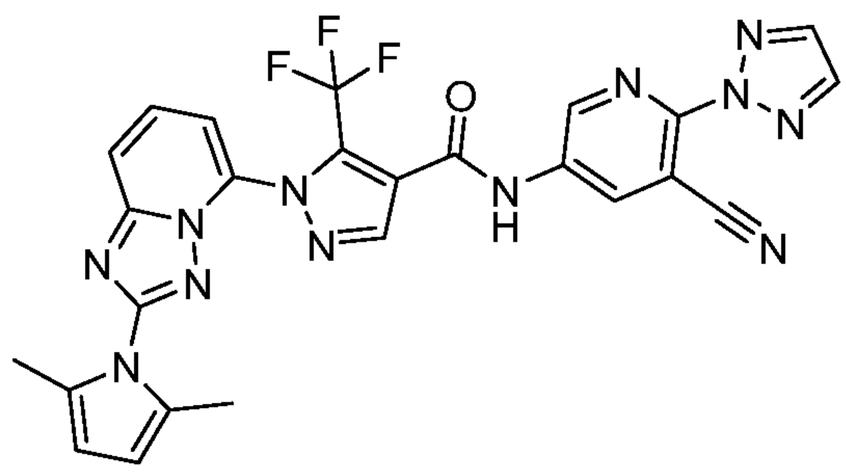
D. 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **159d**



, **159d**

Lithium hydroxide monohydrate (49.7 mg, 1.2 mmol) was added to ethyl 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (330 mg, 0.79 mmol) in ethanol/water (2:1, 3 mL) and the mixture was stirred at rt for 2 h. The mixture was concentrated to give a crude product. The crude product was dissolved in 2 mL water and 1M HCl was added to adjust the pH to 6~7. The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated to give 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid as a white solid (307 mg, crude product).

E. N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **159e**

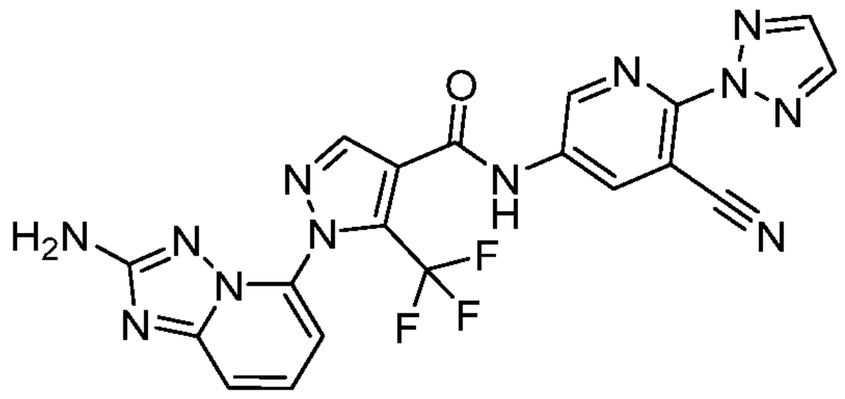


, **159e**

To a solution of 1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (300 mg, 0.77 mmol), 5-amino-2-(2*H*-1,2,3-triazol-2-yl)nicotinonitrile**,** 7**b** (172 mg, 0.922 mmol) and pyridine (622 μL, 7.69 mmol) in dichloromethane (2 mL) was added $POCl_3$ (143.3 μL, 1.54 mmol) dropwise. The reaction mixture was stirred at 20 °C for 1 h. Water (5 mL) was added to the mixture,

saturated aqueous $NaHCO_3$ (20 mL) was added and the pH was adjusted to 7-8. The mixture was extracted with dichloromethane (5 mL x 3). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the filtrates concentrated under reduced pressure to afford the crude product. The crude product was purified by column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 0/100) to afford N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (260 mg, 60 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 2.16 (s, 6 H), 5.86 (s, 2 H), 7.94 (d, J=6.61 Hz, 1 H), 8.03 (t, J=8.27 Hz, 1 H), 8.25 (d, J=9.04 Hz, 1 H), 8.31 (s, 2 H), 8.74 (s, 1 H), 8.89 (d, J=2.43 Hz, 1 H), 9.08 (d, J=2.43 Hz, 1 H). LC-MS: (ES, *m/z*): $[M+1]^+$ 558.9.

F. 1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 159**

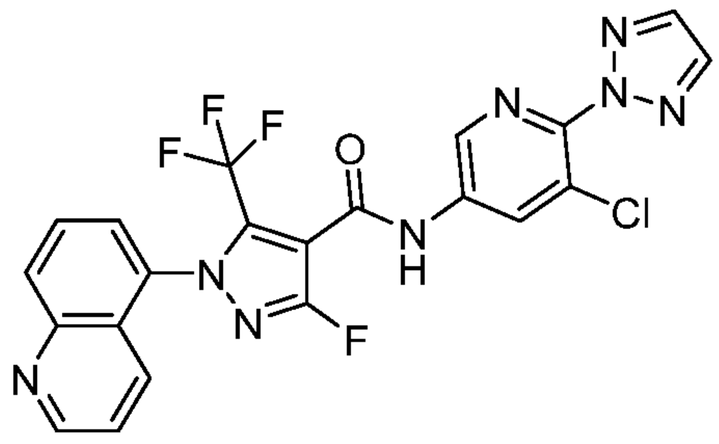


A solution of N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (200 mg, 0.357 mmol) in TFA (2 mL) and dioxane/water (4:1, 4 mL) was stirred at 70 °C for 5 h. Sat. $NaHCO_3$ was added to the mixture to adjust the pH to 7~8. The aqueous phase was extracted with ethyl acetate (5 mL x 3). The separated organic layer was dried ($MgSO_4$), filtered, and the filtrate concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (25% to 55% (v/v) CH_3CN and H_2O with 10 mM NH_4HCO_3) to give 1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (12 mg, 7% yield). ^{1}H NMR (400

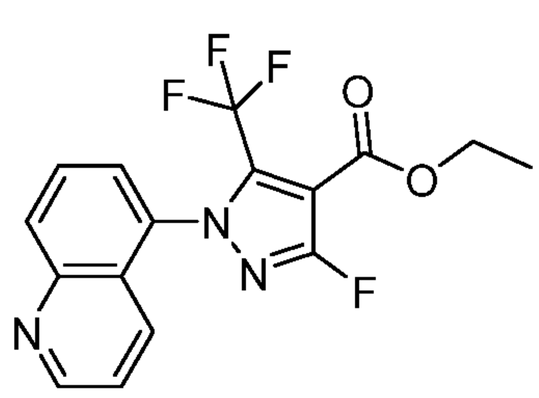
MHz, DMSO-d6) δ ppm 7.46 (dd, J=5.95, 2.20 Hz, 1 H), 7.65 - 7.74 (m, 2 H), 8.31 (s, 2 H), 8.77 (s, 1 H), 8.93 (d, J=2.20 Hz, 1 H), 9.17 (d, J=2.43 Hz, 1 H), 11.55 (s, 1 H). LC-MS: (ES, *m/z*): $[M+1]^+$ 558.9.

Example 160

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 160**



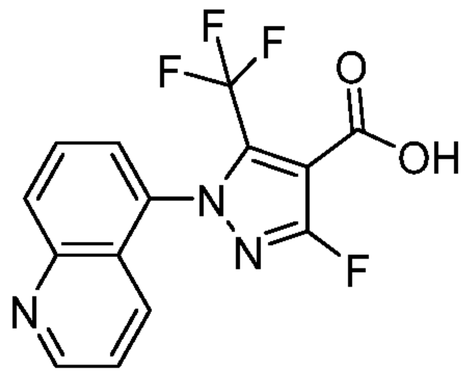
A. ethyl 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **160a**



, **160a**

Ethyl 1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate, **13b** (1 g, 2.98 mmol) was dissolved in acetonitrile (8 mL) and silver (II) fluoride (2.18 g, 14.9 mmol) was added. The reaction mixture was kept in a dark place with stirring at 60 °C for 16 h. The reaction was filtered though diatomaceous earth and washed with CH_3CN (200 mL), the filtrates were concentrated under reduced pressure to afford a crude product which was purified by preparative high-performance liquid chromatography. The pure fractions were collected and the solvent was concentrated under reduced pressure, lyophilized to dryness to give ethyl 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate as a yellow solid (30 mg). LC-MS: (ES, *m/z*): $[M+1]^+$ 354.0.

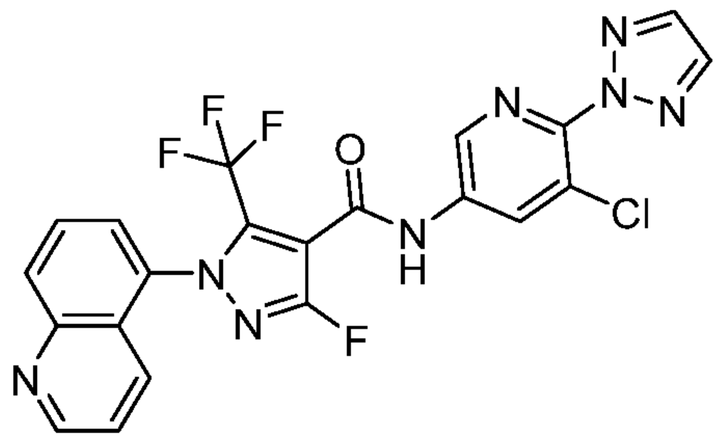
B. 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid, **160b**



, **160b**

Ethyl 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (30 mg, 0.035 mmol) was dissolved in THF (2 mL) and water (2 mL) and lithium hydroxide (8.41 mg, 0.35 mmol) were added. The reaction mixture was stirred at 30 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid as a white solid (30 mg, 73.5%). LC-MS: (ES, *m/z*): $[M+1]^+$ 325.9.

C. N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 160**

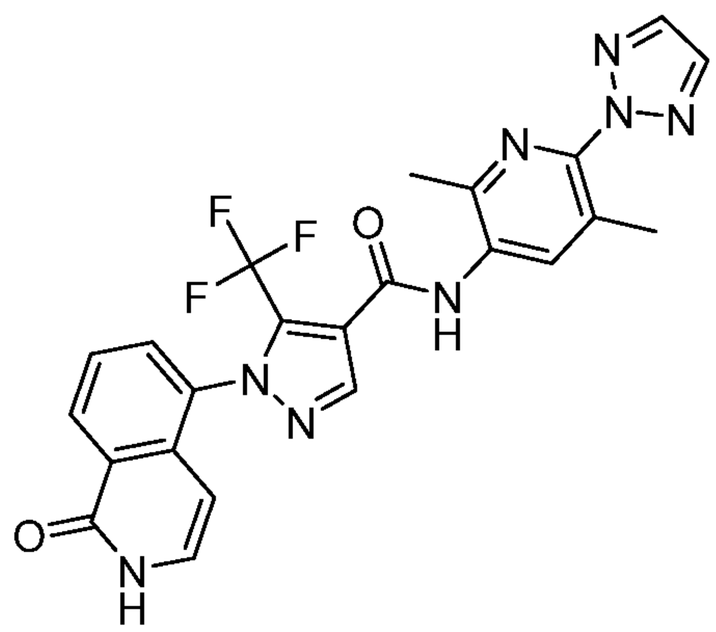


To a solution of 3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (30 mg, 30% pure by HPLC, 0.026 mmol), 5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-amine, **1j** (7.6 mg, 0.038 mmol), and pyridine (133.8 mg, 1.69 mmol) in dichloromethane (10 mL) was added $POCl_3$ (86.5 mg, 0.56 mmol) dropwise. The mixture was stirred at 25 °C for 3 h. Sat. $NaHCO_3$ (20 mL) was added and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude product as a yellow oil. The crude product was then purified by preparative HPLC (37% to 57% (v/v) CH_3CN and H_2O with 0.05%HCl) to afford N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide (2.5 mg, 18.7 %).

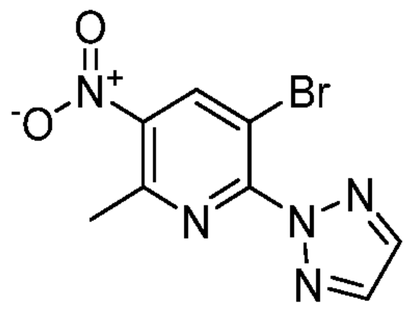
^{1}H NMR (400MHz, ACETONITRILE-d3) δ ppm 9.75 (br s, 1H), 9.06 (d, J=2.8 Hz, 1H), 8.82 (d, J=2.3 Hz, 1H), 8.63 (d, J=2.3 Hz, 1H), 8.37 (d, J=8.5 Hz, 1H), 8.02 (s, 2H), 7.96 - 7.91 (m, 1H), 7.90 - 7.84 (m, 2H), 7.63 (dd, J=4.1, 8.7 Hz, 1H). LC-MS: (ES, *m/z*): $[M+1]^+$ 502.9.

Example 161

N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 161**



A. 3-bromo-6-methyl-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine, **161a**

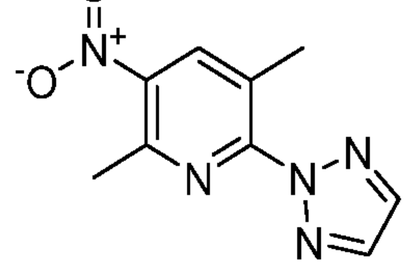


, **161a**

3-Bromo-2-chloro-6-methyl-5-nitropyridine (4.0 g, 15.9 mmol) and 1H-1,2,3-triazole (1.43 g, 20.7 mmol) were dissolved in acetonitrile (30 mL) and potassium carbonate (3.30 g, 23.9 mmol) was added. The reaction mixture was stirred at 60 °C for 2 h. Sat. NH_4Cl (100 mL) was added and the reaction mixture extracted with EtOAc (200 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford the crude product as a purple oil. The oil was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 85/15). The desired fractions were collected and the

solvent was concentrated under reduced pressure to afford product as purple solid (2.5 g, 55.3%, yield).

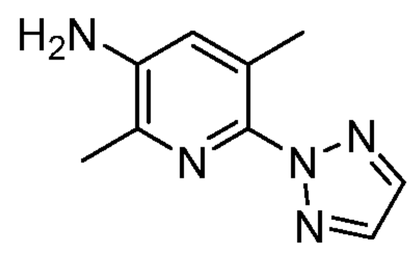
B. 2,5-dimethyl-3-nitro-6-(2H-1,2,3-triazol-2-yl)pyridine, **161b**



, **161b**

3-Bromo-6-methyl-5-nitro-2-(2H-1,2,3-triazol-2-yl)pyridine (1.0 g, 3.52 mmol) and methylboronic acid (316.1 mg, 5.28 mmol) were dissolved in dioxane (20 mL), palladium diacetate (79.0 mg, 0.35 mmol), Xantphos (407.4 mg, 0.70 mmol) and potassium carbonate (973 mg, 7.04 mmol) were added and the reaction mixture purged with N_2 for 1 min. The reaction mixture was stirred at 100 °C for 16 h, then filtered, and the residue was washed with EtOAc (50 mL x 3). The combined filtrates were concentrated under reduced pressure to afford crude product as a brown oil. The crude product was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford the product as a yellow solid (700 mg, 90.7%).

C. 2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine, **161c**

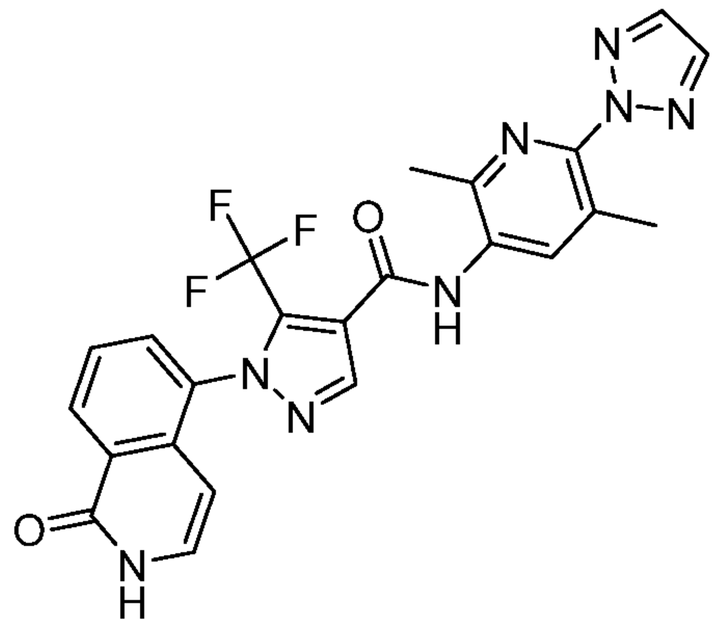


, **161c**

2,5-Dimethyl-3-nitro-6-(2H-1,2,3-triazol-2-yl)pyridine (200 mg. 3.19 mmol), iron (1.07 g, 19.2 mmol), NH_4Cl (1.03 g, 19.2 mmol) were added to the mixture of THF (20 mL) and water (20 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was filtered though a pad of diatomaceous earth and the pad was washed with EtOAc (50 mL x 3). The combined filtrates were concentrated to dryness to give the crude

product as a yellow oil. The crude product was purified by flash column chromatography over silica gel (eluent: petroleum ether/ethyl acetate from 100/0 to 40/60). The desired fractions were collected and the solvent was concentrated under reduced pressure to afford product as a yellow oil (360 mg, 59.6%). ^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.82 (s, 2H), 6.91 (s, 1H), 3.78 (br s, 2H), 2.42 (s, 3H), 2.20 (s, 3H).

D. N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide, **Cpd 161**



To a solution of 1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (213.2 mg, 0.66 mmol), 2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-amine (150 mg, 0.79 mmol) and pyridine (522.5 mg, 6.61 mmol) in CH_2Cl_2 (15 mL) was added $POCl_3$ (304 mg, 1.98 mmol) dropwise. The mixture was stirred at 25 °C for 4 h and at 40 °C for 3 h. 30 mL sat.$NaHCO_3$ was added and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the filtrates were concentrated under reduced pressure to afford crude product as a yellow oil. The crude product was then purified by preparative HPLC (33% to 63% (v/v) CH_3CN and H_2O with 0.05%HCl) to afford product (190 mg, 57.4 %). ^{1}H NMR (400MHz, DMSO-d6) δ ppm 11.60 (br d, J=5.7 Hz, 1H), 10.44 (s, 1H), 8.50 (s, 1H), 8.42 (d, J=7.9 Hz, 1H), 8.11 (s, 2H), 8.02 (s, 1H), 7.95 - 7.89 (m, 1H), 7.65 (t, J=7.9 Hz, 1H), 7.28 (dd, J=6.1, 7.2 Hz, 1H), 5.67 (d, J=7.3 Hz, 1H), 2.47 (br s, 3H), 2.19 (s, 3H). LC-MS: (ES, *m/z*): $[M+1]^+$ 495.0.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	459

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JUMBO APPLICATIONS/PATENTS

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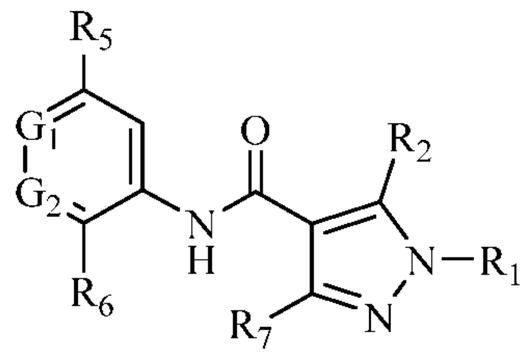
NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

We claim:

1. A compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, , cyclopropyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, 1-ethoxyethyl, hydroxy, methoxy, ethoxy, fluoro, chloro, bromo, methylthio, cyano, amino, methylamino, dimethylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylcarbonyl, methylaminocarbonyl, oxo, 1-(t-butoxycarbonyl)azetidin-2-yl, N-(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of C_{1-4}alkyl, 1-methoxy-ethyl, difluoromethyl, fluoro, chloro, bromo, cyano, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 are N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, C_{1-4}alkyl, fluoro, chloro, bromo, methylcarbonyl, methylthio, methylsulfinyl, and methanesulfonyl; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

R_4 is selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyrrolyl, thiazolyl, tetrazolyl, oxadiazolyl, imidazolyl, 2-amino-pyrimidin-4-yl, 2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl, 1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from oxo, C_{1-4}alkyl, carboxy, methoxycarbonyl, aminocarbonyl, hydroxymethyl, aminomethyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, or cyano;

vi) 1-methyl-piperidin-4-yloxy;

vii) 4-methyl-piperazin-1-ylcarbonyl;

viii) (4-aminobutyl)aminocarbonyl;

ix) (4-amino)butoxy;

x) 4-(4-aminobutyl)-piperazin-1-ylcarbonyl;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

xiv) 3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl;

xv) 2-oxopyrrolidin-1-yl;

xvi) (*E*)- (4-aminobut-1-en-1-yl-aminocarbonyl;

xvii) difluoromethoxy;

and

xviii) morpholin-4-ylcarbonyl;

R_5 is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, methoxy, methylsulfonyl, cyano, C_{1-4}alkyl, ethynyl, morpholin-4-yl, trifluoromethyl, hydroxyethyl, methylcarbonyl, methylsulfinyl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, azetidin-2-yl, methylthio, and 1,1-difluoroethyl;

or R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl, 4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-5-yl, 1,3-dioxolo[4,5]pyridine-5-yl, 1-oxo-1,3-dihydroisobenzofuran-5-yl, 2,2-dimethylbenzo[d][1,3]dioxol-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 1-oxoisoindolin-5-yl, or 2-methyl-1-oxoisoindolin-5-yl, 1*H*-indazol-5-yl;

R_6 is hydrogen, C_{1-4}alkyl, fluoro, 2-methoxy-ethoxy, chloro, cyano, or trifluoromethyl;

R_7 is hydrogen or fluoro;

provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is C(R_4) wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

2. The compound according to claim 1 wherein R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, methoxy, fluoro, chloro, bromo, cyano, amino, methylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylaminocarbonyl, oxo, N-

(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl.

3. The compound according to claim 1 wherein R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, difluoromethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, aminocarbonyl, methylaminocarbonyl, oxo, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl.

4. The compound according to claim 1 wherein R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, or oxo.

5. The compound according to claim 4 wherein R_1 is selected from the group consisting of

i) naphthalen-1-yl, 4-amino-naphthalen-1-yl, 4-fluoronaphthalen-1-yl, or 5-fluoronaphthalenen-1-yl;

and

ii) a heteroaryl selected from the group consisting of isoquinolin-1-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-7-yl, cinnolin-4-yl, imidazo[1,2-a]pyrazin-8-yl, phthalazin-1-yl, naphthyridin-5-yl, thieno[3,2-c]pyridin-4-yl, furo[3,2-c]pyridin-4-yl, furo[2,3-c]pyridin-7-yl, quinoxalin-5-yl, 1*H*-indazolylfuro[3,2-b]pyridin-7-yl, pyrazolo[1,5-a]pyrazin-4-yl, quinolin-4-yl, quinolin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-5-yl, benzo[d]thiazol-7-yl, 1-hydroxyisoquinolin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, thieno[2,3-c]pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl, thieno[3,2-b]pyridin-7-yl, 2-oxo-1,2-dihydroquinolin-4-yl, 1-amino-8-fluoroisoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 1-cyanoisoquinolin-5-yl, pyrrolo[2,1-f][1,2,4]triazin-4-yl, 7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl, thieno[2,3-d]pyrimidin-4-yl, thieno[2,3-c]pyridin-7-yl, 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl,

imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-(hydroxyethyl)quinolin-4-yl, 1-(methoxymethyl)isoquinolin-4-yl, 1-fluoroisoquinolin-4-yl, 1-(difluoromethyl)isoquinolin-4-yl, 8-fluoroquinolin-4-yl, 8-fluoroquinolin-5-yl, 1-(tetrahydrofuran-2(*R*)-yl)isoquinolin-4-yl, 2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 2-(aminocarbonyl)quinolin-4-yl, 1H-indazol-7-yl, 1-(1,4-dioxan-2-yl)isoquinolin-4-yl, 2-methylimidazo[1,2-a]pyridin-5-yl, 1-chloroisoquinolin-4-yl, 2-cyanoquinolin-4-yl, 8-fluoro-1-(methylamino)isoquinolin-4-yl, benzo[d]isoxazol-3-yl, 2-aminobenzo[d]thiazol-7-yl, 2-fluoroquinolin-5-yl, 1,7-naphthyridin-4-yl, imidazo[1,2-a]pyrazin-5-yl, (N-(methyl)formamido)methyl)isoquinolin-4-yl, [1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methylbenzo[d]oxazol-7-yl, 1,5-naphthyridin-4-yl, 5-oxopyrrolidin-2-ylisoquinolin-4-yl, 1-methyl-1H-indazol-3-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(1,1-difluoroethyl)isoquinolin-4-yl, 1-(1(^{x}S)-hydroxyethyl)isoquinolin-4-yl, 1-(methylamino)isoquinolin-4-yl, 4-fluoroisoquinolin-1-yl, 1H-pyrazolo[4,3-b]pyridin-7-yl, 5-fluoroquinolin-8-yl, 6-fluoroimidazo[1,2-a]pyridin-5-yl, 2-methylfuro[3,2-b]pyridin-7-yl, 8-(difluoromethyl)quinolin-5-yl, 1-(4-oxotetrahydrofuran-2*R*-yl)isoquinolin-4-yl, 1-(dimethylamino)isoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methoxyquinolin-4-yl, imidazo[1,2-a]pyrimidin-5-yl, 2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, quinolin-5-yl, 1-(1-ethoxyethyl)isoquinolin-4-yl, 2-(azetidin-2-yl)quinolin-4-yl, 2-methylbenzo[d]thiazol-7-yl, 2-acetylquinolin-4-yl, 1-(methylthio)isoquinolin-4-yl, 2-aminoquinolin-5-yl, 1-methoxyisoquinolin-5-yl, imidazo[1,2-b]pyridazin-6-yl, 1-(pyrrolidin-2-yl)isoquinolin-4-yl, 4-

(difluoromethyl)quinolin-5-yl, 1-acetylisoquinolin-5-yl, 2-aminoquinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-4-yl, 1-ethoxyisoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl, 1-aminoisoquinolin-5-yl, 1-methyl-1H-indazol-4-yl, 2-aminoquinolin-4-yl, 2-oxo-1,2-dihydroquinolin-5-yl, 1-(azetidin-3-yl)isoquinolin-4-yl, 2-methylthieno[3,2-b]pyridin-7-yl, benzo[d][1,2,3]thiadiazol-4-yl, 1-(1(*S*)-hydroxyethyl)isoquinolin-5-yl, imidazo[1,2-a]pyridin-8-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl, 2-(tetrahydrofuran-2-yl)quinolin-5-yl, , 1-(1(*R*)-hydroxyethyl)isoquinolin-5-yl, 1,6-naphthyridin-4-yl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 2-aminocarbonyl-quinolin-5-yl, 2-chloroquinolin-5-yl, 2-chloroquinolin-4-yl, 2-cyanoquinolin-5-yl, 1-aminoisoquinolin-5-yl, 2-methoxyquinolin-5-yl, 2-methylbenzo[d]oxazol-4-yl, 2-(difluoromethyl)quinolin-5-yl, 2-(azetidin-2-yl)quinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-5-yl, 1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-5-yl, and 1-(1-t-butoxycarbonylazetidin-2-yl)isoquinolin-5-yl.

6. The compound according to claim 1 wherein R_1 is

i) napthalen-1-yl, 4-fluoronaphthalen-1-yl, 5-fluoronaphthalen-1-yl, or 4-aminonaphthalen-1-yl;

and

ii) a heteroaryl selected from the group consisting of thieno[3,2-c]pyridin-4-yl, isoquinolin-4-yl, 8-fluoroquinolin-4-yl, furo[3,2-c]pyridin-4-yl, quinolin-5-yl, furo[2,3-c]pyridin-7-yl, benzofuran-4-yl 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, pyrrolo[1,2-a]pyrazin-1-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, benzo[d]thiazol-4-yl, 1-aminoisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, imidazo[1,2-a]pyridin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, and 1-(hydroxyethyl)quinolin-4-yl.

7. The compound according to claim 1 wherein R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, bromo, chloro, and trifluoromethyl.

8. The compound according to claim 7 wherein R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl.

9. The compound according to claim 8 wherein R_2 is trifluoromethyl.

10. The compound according to claim 1 wherein R_3 is independently selected from the group consisting of trifluoromethyl, cyano, methylcarbonyl, methylthio, methylsulfinyl, methanesulfonyl, and chloro; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl.

11. The compound according to claim 1 wherein R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro.

12. The compound according to claim 1 wherein G_2 is N or C(R_3), and wherein R_3 is chloro.

13. The compound according to claim 11 wherein G_2 is N.

14. The compound according to claim 1 wherein R_4 is selected from the group consisting of

i) hydrogen, when G_2 is N;
ii) C_{1-4}alkoxy;
iii) cyano;
iv) cyclopropyloxy;
v) carboxy;

vi) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, imidazolyl, and pyrimidin-4-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of C_{1-4}alkyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, and cyano;

vii) 1-methyl-piperidin-4-yloxy;

viii) 4-methyl-piperazin-1-ylcarbonyl;

ix) (4-aminobutyl)aminocarbonyl;

x) (4-amino)butoxy;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

and

xiv) morpholin-4-ylcarbonyl.

15. The compound according to claim 14 wherein R_4 is selected from the group consisting of

i) hydrogen;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, and imidazolyl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of methyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, and amino, methoxymethyl;

vi) (4-amino)butoxy;

vii) methoxycarbonyl;

viii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;
and

ix) 1,1-dioxo-isothiazolidin-2-yl.

16. The compound according to claim 15 wherein R_4 is selected from the group consisting of

i) methoxy;

ii) a heteroaryl independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, 1,3,4-oxadiazol-2-yl, 2-methyl-2H-tetrazol-5-yl, 5-amino-1-methyl-1H-pyrazol-3-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-cyano-2H-1,2,3-triazol-2-yl, 5-amino-1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-4-yl, 2H-tetrazol-5-yl, 4-(aminomethyl)-1H-pyrazol-1-yl, 4-(methoxymethyl)-2H-1,2,3-triazol-2-yl, 2-methyl-2H-tetrazol-5-yl, and 4-methyl-1H-1,2,3-triazol-1-yl;
and

iii) methoxycarbonyl.

17. The compound according to claim 16 wherein R_4 is selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 1*H*-imidazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-

triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, and 1,3,4-oxadiazol-2-yl.

18. The compound according to claim 1 wherein R_5 is hydrogen, chloro, fluoro, bromo, cyano, methyl, ethyl, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl.

19. The compound according to claim 18 wherein R_5 is hydrogen, chloro, bromo, cyano, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl.

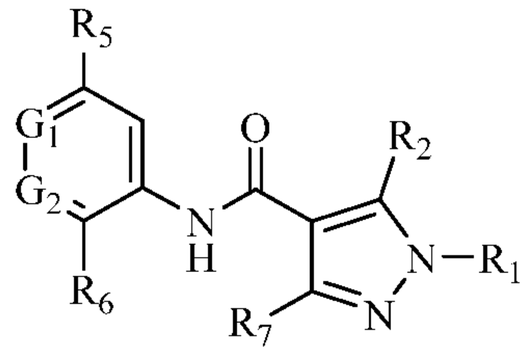
20. The compound according to claim 19 wherein R_5 is hydrogen, chloro, fluoro, or cyano.

21. The compound according to claim 20 wherein R_5 is hydrogen, chloro, or cyano.

22. The compound according to claim 1 wherein R_6 is hydrogen or methyl.

23. The compound according to claim 1 wherein R_7 is hydrogen.

24. A compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, 4-fluoronaphthalen-1-yl, 5-fluoronaphthalen-1-yl, or 4-aminonaphthalen-1-yl;

and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, hydroxy, methoxy, fluoro, chloro, bromo, cyano, amino, methylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylaminocarbonyl, oxo, N-(methyl)formamidomethyl, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is independently selected from the group consisting of methyl, isopropyl, cyano, bromo, chloro, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, methylcarbonyl, methylthio, methylsulfinyl, methanesulfonyl, and chloro; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

R_4 is independently selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) carboxy;

vi) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, imidazolyl, and pyrimidin-4-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of C_{1-4}alkyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, and cyano;

vii) 1-methyl-piperidin-4-yloxy;

viii) 4-methyl-piperazin-1-ylcarbonyl;

ix) (4-aminobutyl)aminocarbonyl;

x) (4-amino)butoxy;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

and

xiv) morpholin-4-ylcarbonyl;

R_5 is hydrogen, chloro, fluoro, bromo, cyano, methyl, ethyl, or trifluoromethyl; or, R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl or 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

and provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

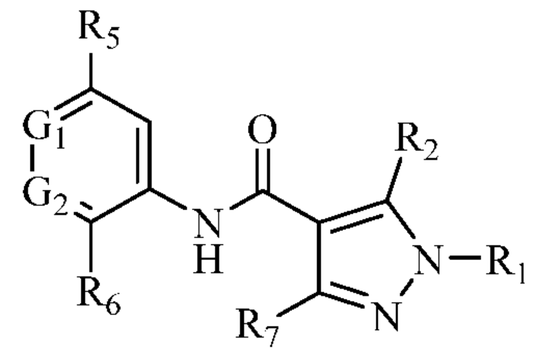
a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is C(R_4) wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

25. A compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, difluoromethyl, hydroxymethyl, 1-hydroxyethyl,

hydroxy, fluoro, cyano, amino, aminocarbonyl, methylaminocarbonyl, oxo, tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is independently selected from the group consisting of

i) hydrogen;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, pyrazolyl, thiazolyl, oxadiazolyl, and imidazolyl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from the group consisting of methyl, carboxy, methoxycarbonyl, hydroxymethyl, aminocarbonyl, (dimethylamino)methyl, and amino, methoxymethyl;

vi) (4-amino)butoxy;

vii) methoxycarbonyl;

viii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl; and

ix) 1,1-dioxo-isothiazolidin-2-yl;

R_5 is hydrogen, chloro, bromo, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

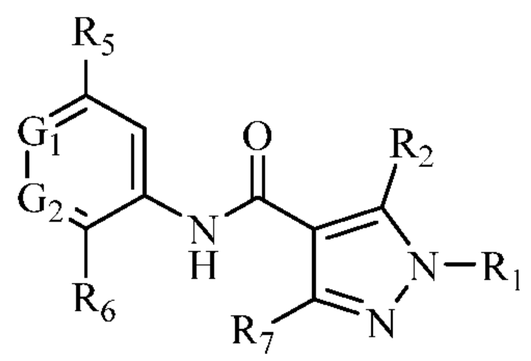
a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is $C(R_4)$ wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is $C(R_4)$ wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

26. A compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with an amino or fluoro substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from hydroxymethyl, 1-hydroxyethyl, hydroxy, fluoro, cyano, amino, oxo, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of methyl, isopropyl, cyano, and trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is selected from the group consisting of

i) methoxy;

ii) a heteroaryl selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-

pyrazol-3-yl, 1,3,4-oxadiazol-2-yl, 2-methyl-2H-tetrazol-5-yl, 5-amino-1-methyl-1H-pyrazol-3-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-cyano-2H-1,2,3-triazol-2-yl, 5-amino-1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-4-yl, 2H-tetrazol-5-yl, 4-(aminomethyl)-1H-pyrazol-1-yl, 4-(methoxymethyl)-2H-1,2,3-triazol-2-yl, 2-methyl-2H-tetrazol-5-yl, and 4-methyl-1H-1,2,3-triazol-1-yl;

and

iii) methoxycarbonyl;

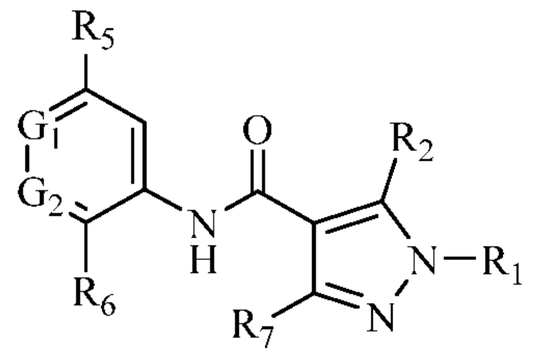
R_5 is hydrogen, chloro, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

27. A compound of Formula (I)



Formula (I)

wherein

R_1 is independently selected from the group consisting of

i) naphthalen-1-yl, 4-amino-naphthalen-1-yl, 4-fluoronaphthalen-1-yl, or 5-fluoronaphthalen-1-yl;

and

ii) a heteroaryl selected from the group consisting of isoquinolin-1-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-7-yl, cinnolin-4-yl, imidazo[1,2-a]pyrazin-8-yl, phthalazin-1-yl, naphthyridin-5-yl, thieno[3,2-c]pyridin-4-yl, furo[3,2-c]pyridin-4-yl, furo[2,3-c]pyridin-7-yl, quinoxalin-5-yl, 1*H*-indazolylfuro[3,2-b]pyridin-7-yl, pyrazolo[1,5-a]pyrazin-4-yl, quinolin-4-yl, quinolin-5-yl, 1-aminoisoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-5-yl, benzo[d]thiazol-7-yl, 1-hydroxyisoquinolin-5-yl, benzo[d][1,2,3]thiadiazol-7-yl, thieno[2,3-c]pyridin-4-yl, pyrazolo[1,5-a]pyridin-4-yl, thieno[3,2-b]pyridin-7-yl, 2-oxo-1,2-dihydroquinolin-4-yl, 1-amino-8-fluoroisoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 1-cyanoisoquinolin-5-yl, pyrrolo[2,1-f][1,2,4]triazin-4-yl, 7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl, thieno[2,3-d]pyrimidin-4-yl, thieno[2,3-c]pyridin-7-yl, 1,7-naphthyridin-5-yl, pyrrolo[1,2-a]pyrazin-1-yl, imidazo[1,2-a]pyridin-5-yl, 1-aminocarbonyl-isoquinolin-4-yl, benzo[d]thiazol-4-yl, 8-fluoro-1-hydroxyisoquinolin-4-yl, thieno[3,2-d]pyrimidin-4-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 3-methylimidazo[1,2-a]pyridin-5-yl, 1-oxo-quinolin-4-yl, 8-aminoquinolin-5-yl, benzo[d]oxazol-4-yl, 3-methylthieno[3,2-b]pyridin-7-yl, 1-(hydroxymethyl)isoquinolin-4-yl, (3*R*-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (1-hydroxyethyl)isoquinolin-4-yl, 8-fluoroisoquinolin-4-yl, 2-(difluoromethyl)quinolin-4-yl, 8-fluoroquinolin-5-yl, 1-hydroxyisoquinolin-4-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, 1-(1-hydroxyethyl)isoquinolin-4-yl, 1-cyanoisoquinolin-4-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-4-yl, quinazolin-4-yl, 2-methylimidazo[1,2-a]pyridin-3-yl, thiazolo[5,4-d]pyrimidin-7-yl, 6-*N*-oxido-1H-pyrazol-1-yl)thieno[2,3-c]pyridin-4-yl, imidazo[1,2-a]pyridin-3-yl, furo[2,3-d]pyrimidin-4-yl, 2-fluoroquinolin-5-yl, isoquinolin-5-yl, benzo[d]isothiazol-3-yl, 7-methylpyrazolo[1,5-a]pyridin-4-yl, 1-(hydroxyethyl)quinolin-4-yl, 1-

(methoxymethyl)isoquinolin-4-yl, 1-fluoroisoquinolin-4-yl, 1-(difluoromethyl)isoquinolin-4-yl, 8-fluoroquinolin-4-yl, 8-fluoroquinolin-5-yl, 1-(tetrahydrofuran-2(*R*)-yl)isoquinolin-4-yl, 2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 2-(aminocarbonyl)quinolin-4-yl, 1H-indazol-7-yl, 1-(1,4-dioxan-2-yl)isoquinolin-4-yl, 2-methylimidazo[1,2-a]pyridin-5-yl, 1-chloroisoquinolin-4-yl, 2-cyanoquinolin-4-yl, 8-fluoro-1-(methylamino)isoquinolin-4-yl, benzo[d]isoxazol-3-yl, 2-aminobenzo[d]thiazol-7-yl, 2-fluoroquinolin-5-yl, 1,7-naphthyridin-4-yl, imidazo[1,2-a]pyrazin-5-yl, (N-(methyl)formamido)methyl)isoquinolin-4-yl, [1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methylbenzo[d]oxazol-7-yl, 1,5-naphthyridin-4-yl, 5-oxopyrrolidin-2-ylisoquinolin-4-yl, 1-methyl-1H-indazol-3-yl, 8-fluoroimidazo[1,2-a]pyridin-5-yl, 1-(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl, 1-(1,1-difluoroethyl)isoquinolin-4-yl, 1-(1(*xS*)-hydroxyethyl)isoquinolin-4-yl, 1-(methylamino)isoquinolin-4-yl, 4-fluoroisoquinolin-1-yl, 1H-pyrazolo[4,3-b]pyridin-7-yl, 5-fluoroquinolin-8-yl, 6-fluoroimidazo[1,2-a]pyridin-5-yl, 2-methylfuro[3,2-b]pyridin-7-yl, 8-(difluoromethyl)quinolin-5-yl, 1-(4-oxotetrahydrofuran-2*R*-yl)isoquinolin-4-yl, 1-(dimethylamino)isoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl, 2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl, 2-methoxyquinolin-4-yl, imidazo[1,2-a]pyrimidin-5-yl, 2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl, quinolin-5-yl, 1-(1-ethoxyethyl)isoquinolin-4-yl, 2-(azetidin-2-yl)quinolin-4-yl, 2-methylbenzo[d]thiazol-7-yl, 2-acetylquinolin-4-yl, 1-(methylthio)isoquinolin-4-yl, 2-aminoquinolin-5-yl, 1-methoxyisoquinolin-5-yl, imidazo[1,2-b]pyridazin-6-yl, 1-(pyrrolidin-2-yl)isoquinolin-4-yl, 4-(difluoromethyl)quinolin-5-yl, 1-acetylisoquinolin-5-yl, 2-aminoquinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-4-yl, 1-ethoxyisoquinolin-4-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl, 1-aminoisoquinolin-5-yl, 1-methyl-1H-

indazol-4-yl, 2-aminoquinolin-4-yl, 2-oxo-1,2-dihydroquinolin-5-yl, 1-(azetidin-3-yl)isoquinolin-4-yl, 2-methylthieno[3,2-b]pyridin-7-yl, benzo[d][1,2,3]thiadiazol-4-yl, 1-(1(*S*)-hydroxyethyl)isoquinolin-5-yl, imidazo[1,2-a]pyridin-8-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl, 2-(tetrahydrofuran-2-yl)quinolin-5-yl, 1-(1(*R*)-hydroxyethyl)isoquinolin-5-yl, 1,6-naphthyridin-4-yl, 1H-pyrazolo[3,4-d]pyrimidin-4-yl, 2-aminocarbonyl-quinolin-5-yl, 2-chloroquinolin-5-yl, 2-chloroquinolin-4-yl, 2-cyanoquinolin-5-yl, 1-aminoisoquinolin-5-yl, 2-methoxyquinolin-5-yl, 2-methylbenzo[d]oxazol-4-yl, 2-(difluoromethyl)quinolin-5-yl, 2-(azetidin-2-yl)quinolin-5-yl, 1-(azetidin-2-yl)isoquinolin-5-yl, 1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl, 1-oxo-1,2-dihydroisoquinolin-4-yl, 2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, 8-fluoro-1-(3-hydroxyazetidin-1-yl)isoquinolin-4-yl, (R)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, (S)-8-fluoro-1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl, 3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl, 8-(3-hydroxyazetidin-1-yl)imidazo[1,2-a]pyridin-5-yl, 7-(3-hydroxyazetidin-1-yl)pyrazolo[1,5-a]pyridin-4-yl, 1-(3-hydroxyazetidin-1-yl)isoquinolin-5-yl, and 1-(1-t-butoxycarbonylazetidin-2-yl)isoquinolin-5-yl;

R_2 is trifluoromethyl;

G_1 is N or C(R_4);

G_2 is N or C(R_3); such that only one of G_1 and G_2 is N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, and chloro;

R_4 is independently selected from the group consisting of 2H-1,2,3-triazol-2-yl, 4-carboxy-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-methyl-2H-1,2,3-triazol-2-yl, oxazol-2-yl, 1*H*-imidazol-2-yl, 4-amino-2H-1,2,3-triazol-2-yl, 4-(hydroxymethyl)-1H-pyrazol-1-yl, 4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl, 4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl, 4-methoxycarbonyl-2H-1,2,3-triazol-2-yl, 4-aminocarbonyl-2H-1,2,3-triazol-2-yl,1-methyl-1H-pyrazol-3-yl, and 1,3,4-oxadiazol-2-yl;

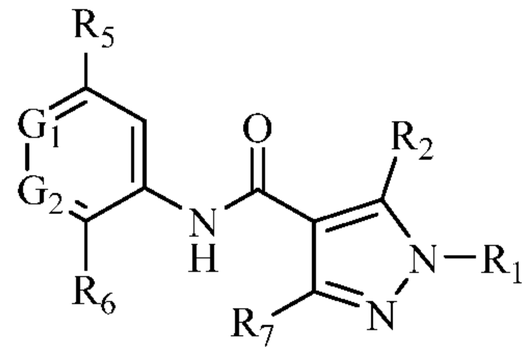
R_5 is hydrogen, chloro, bromo, or cyano;

R_6 is hydrogen or methyl;

R_7 is hydrogen;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

28. A compound of Formula (I)



Formula (I)

selected from the group consisting of

N-(2-cyanopyridin-4-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide;

1-(naphthalen-1-yl)-5-(trifluoromethyl)-*N*-(5-(trifluoromethyl)pyridin-3-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(naphthalen-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(quinolin-5-yl)-5-(trifluoromethyl)-*N*-(2-(trifluoromethyl)pyridin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylisoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-methoxyphenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-pyrazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isobutyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-ethyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-isopropyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-methylisoquinolin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(benzofuran-4-yl)-*N*-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(1-methoxyethyl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-fluoropyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,1-dioxidoisothiazolidin-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

methyl 3-chloro-5-(3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamido)picolinate;

N-(5-chloro-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-pyrazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(3-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-methyl-*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-chloro-4-(3-methyl-*1H*-1,2,4-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(difluoromethyl)-1-(isoquinolin-1-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-(2-aminopyrimidin-4-yl)-3-chlorophenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-cyano-4-(*2H*-1,2,3-triazol-2-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-fluoro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(3-cyano-4-(*1H*-1,2,3-triazol-1-yl)phenyl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(thiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-methyl-1-(quinolin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylquinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methylisoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroquinolin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(*1H*-indazol-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-imidazol-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(4-aminobutyl)-3-chloro-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinamide;

1-(isoquinolin-4-yl)-*N*-(2-methyl-6-(trifluoromethyl)pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

methyl 6-chloro-4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate;

methyl 4-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamido)picolinate

N-(5-chloro-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-*1H*-pyrazole-4-carboxamide;

N-(2-cyanopyridin-4-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-ethoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(4-aminobutoxy)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*1H*-1,2,4-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-cyclopropoxypyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(1-methyl-*1H*-pyrazol-3-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

1-(cinnolin-4-yl)-*N*-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-c]pyridin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(4-methylpiperazine-1-carbonyl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[b][1,4]oxazin-6-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(6-(4-(4-aminobutyl)piperazine-1-carbonyl)-5-cyanopyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(phthalazin-1-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-8-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-chloro-6-(*1H*-imidazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(5-cyano-6-(*2H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinoxalin-5-yl)-5-(trifluoromethyl)-*1H*-pyrazole-4-carboxamide;

N-(2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

tert-butyl 2-(5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinolin-1-yl)azetidine-1-carboxylate;

N -(3-(methylsulfonyl)-4-(1H-1,2,3-triazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1,5-bis(tetrahydrofuran-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-2-yl)isoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(3-(methylsulfonyl)-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N -(2-methyl-1-oxo-1,2-dihydroisoquinolin-7-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-(azetidin-2-yl)quinolin-5-yl)- *N* -(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methyl-6-(3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2,5-diethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

1-(2-chloroquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-chloroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[3,4-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,6-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

(**R*)-N-(5-chloro-6-(2*H*-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(**R*)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2-oxopyrrolidin-1-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-cyano-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylic acid;

N-(1H-pyrazolo[3,4-b]pyridin-5-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-methylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-3-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylic acid;

N-(5-methoxy-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-aminobutyl)-3-cyano-5-(1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide;

2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoic acid

N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-methylphenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methyl-6-(1-methyl-1H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-ethoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-(azetidin-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-acetylisoquinolin-5-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(pyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(difluoromethoxy)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-b]pyridazin-6-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylthio)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-3-fluoro-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-cyano-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-acetylquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]thiazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-(aminomethyl)-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-(azetidin-2-yl)quinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-ethoxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 1-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1H-1,2,3-triazole-4-carboxylate

1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-ethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrimidin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methoxy-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methoxyquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2,5-dimethyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-(methoxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylic acid;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

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

N-(6-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 2-(2-chloro-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)phenyl)-2H-1,2,3-triazole-4-carboxylate;

N-(5-cyano-6-(2-methyl-2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate;

N-(6-(1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyanopyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

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

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(dimethylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-(difluoromethyl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylfuro[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(6-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoroquinolin-8-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-pyrazolo[4,3-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoroisoquinolin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1,1-difluoroethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-chloro-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-1H-indazol-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(5-oxopyrrolidin-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-(3-cyano-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxylate;

N-(5-cyano-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,5-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(5-((dimethylamino)methyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylbenzo[d]oxazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-(aminomethyl)-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-([1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-((N-methylformamido)methyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyrazin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isothiazolo[5,4-b]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(1H-pyrrol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methoxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-aminobenzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(1H-1,2,3-triazol-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]isoxazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

5-bromo-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-cyanoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-chloroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide;

1-(1-(1,4-dioxan-2-yl)isoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1H-indazol-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline-2-carboxamide;

N-(5-chloro-6-(5-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(4-oxotetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(benzo[d]thiazol-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-6-(1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(difluoromethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(methoxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(1-hydroxyethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylpyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]isothiazol-3-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine 6-oxide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thiazolo[5,4-d]pyrimidin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methylimidazo[1,2-a]pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-methoxypyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinazolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(1-hydroxyethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-methyl-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(difluoromethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(tetrahydrofuran-2-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(methoxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(4-(4-(aminomethyl)-1H-pyrazol-1-yl)-3-chlorophenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(difluoromethyl)quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-(methylamino)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-4-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(3-hydroxypyrrolidin-1-yl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-(hydroxymethyl)isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylthieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]oxazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(4-(hydroxymethyl)-1H-pyrazol-1-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(8-aminoquinolin-5-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)quinoline 1-oxide;

N-(5-cyano-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 2-cyano-4-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)benzoate;

N-(6-(5-amino-1H-1,2,3-triazol-1-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-cyano-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-cyanopyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(isoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(3-methylimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(5-amino-1-methyl-1H-pyrazol-3-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoro-1-hydroxyisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(2H-1,2,3-triazol-2-yl)-5-(trifluoromethyl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)isoquinoline-1-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(imidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[1,2-a]pyrazin-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1,7-naphthyridin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-d]pyrimidin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1,3,4-oxadiazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(1-hydroxyethyl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrrolo[2,1-f][1,2,4]triazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylate;

N-(5-chloro-6-(4-((dimethylamino)methyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-cyanoisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-1H-pyrazol-1-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyrazin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(6-(4-amino-2H-1,2,3-triazol-2-yl)-5-chloropyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-cyano-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(4-aminonaphthalen-1-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(4-fluoro-2-methoxyphenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-Dquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-D-quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(3-chloro-4-(2H-1,2,3-triazol-2-yl)phenyl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(pyrazolo[1,5-a]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(oxazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-b]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d][1,2,3]thiadiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(5-fluoronaphthalen-1-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-hydroxyisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-7-yl)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(4-(hydroxymethyl)-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(benzo[d]thiazol-7-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-amino-8-fluoroisoquinolin-4-yl)-N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

2-(3-chloro-5-(1-(quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)pyridin-2-yl)-2H-1,2,3-triazole-4-carboxylic acid;

N-(5-cyano-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(furo[3,2-b]pyridin-7-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide;

1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(5-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-bromo-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(4-methyl-1H-1,2,3-triazol-1-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-morpholinopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-methoxypyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(5-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-ethynyl-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*R)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxypyrrolidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)thieno[2,3-c]pyridine-7-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyclopropylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-methylthieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-cyanothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

4-(4-((5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)carbamoyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-methylthieno[2,3-c]pyridine-7-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-(3-hydroxyazetidin-1-yl)thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(7-chlorothieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-aminoisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-methyl-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-N-(pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-cyclopropylpyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N,N-dimethyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide

1-(1-aminoisoquinolin-4-yl)-N-(2-cyanopyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-methyl-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinamide;

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

N-(5-chloropyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

1-(8-fluoroimidazo[1,2-a]pyridin-5-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(6-cyano-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

methyl 3-chloro-5-(1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamido)picolinate;

1-(8-fluoroisoquinolin-4-yl)-5-(trifluoromethyl)-N-(2-(trifluoromethyl)pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-(2-cyanopyridin-4-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(2-(2-methoxyethoxy)-5-(trifluoromethyl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(thieno[2,3-c]pyridin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-oxo-1,2-dihydroquinolin-4-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-(5-chloro-2-methyl-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(1-oxo-1,2-dihydroisoquinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

(*S)-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-1-(2-(tetrahydrofuran-2-yl)quinolin-5-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

or a pharmaceutically acceptable salt form thereof.

29. A pharmaceutical composition comprising a compound of claim 1 to 28 and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.

30. The pharmaceutical composition of claim 29, wherein the composition is a solid oral dosage form.

31. The pharmaceutical composition of claim 29, wherein the composition is a syrup, an elixir or a suspension.

32. A method of treating a disease, syndrome, condition, or disorder, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1, comprising administering to a subject in need thereof a therapeutically effective amount of the compound of claim 1.

33. The method of claim 32 wherein said disease, syndrome, condition, or disorder is selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma rheumatoid arthitis (RA), psoritic arthitis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chonic obstructive pulmonary disease (COPD).

34. A method of treating a disease, syndrome, condition, or disorder selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma rheumatoid arthitis (RA), psoritic arthitis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chonic obstructive pulmonary disease (COPD), comprising administering to a subject in need thereof a therapeutically effective amount of the composition of claim 1.

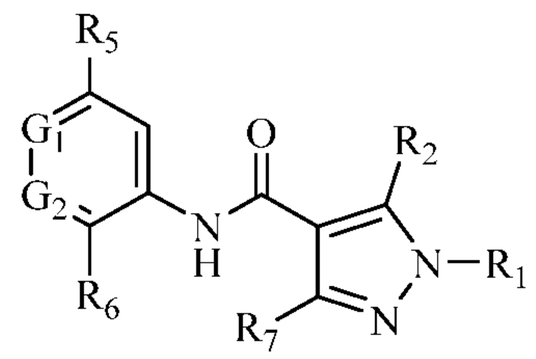
35. The use of a compound as in claim 1 for the preparation of a medicament for treating a disease, syndrome, syndrome, disorder or condition selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma rheumatoid arthitis (RA), psoritic arthitis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chonic obstructive pulmonary disease (COPD), in a subject in need thereof.

36. The use of a compound as in claim 1, for use in a method for treating a disorder selected from the group consisting of diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL), and mucosa-associated lymphoid tissue (MALT) lymphoma rheumatoid arthitis (RA), psoritic arthitis (PsA), psorisis (Pso), ulcerative colitis (UC), Crohn's disease, systemic lupus erythematosus (SLE), asthma, and chonic obstructive pulmonary disease (COPD), in a subject in need thereof.

37. A method of treating a disease, syndrome, condition, or disorder, wherein said disease, syndrome, condition, or disorder is affected by the inhibition of MALT1,

comprising administering to a subject in need thereof a therapeutically effective amount of (a) a MALT1 inhibitor, and (b) a pharmaceutical agent selected from the group consisting of a BTK inhibitor, a SYK inhibitor, a PKC inhibitor, a PI3K pathway inhibitor, a BCL family inhibitor, a JAK inhibitor, a PIM kinase inhibitor, a B cell antigen-binding antibody, an immune cell redirection agent, an immunomodulatory agent, an anti-PD1 antibody, and an anti-PD-L1 antibody;

wherein said MALT1 inhibitor is a compound of Formula (I)



Formula (I)

wherein

R_1 is selected from the group consisting of

i) naphthalen-1-yl, optionally substituted with a fluoro or amino substituent; and

ii) a heteroaryl of nine to ten members containing one to four heteroatoms selected from the group consisting of O, N, and S; such that no more than one heteroatom is O or S; wherein said heteroaryl of ii) is optionally independently substituted with one or two substituents selected from deuterium, methyl, ethyl, propyl, isopropyl, trifluoromethyl, , cyclopropyl, methoxymethyl, difluoromethyl, 1,1-difluoroethyl, hydroxymethyl, 1-hydroxyethyl, 1-ethoxyethyl, hydroxy, methoxy, ethoxy, fluoro, chloro, bromo, methylthio, cyano, amino, methylamino, dimethylamino, 4-oxotetrahydrofuran-2-yl, 5-oxopyrrolidin-2-yl, 1,4-dioxanyl, aminocarbonyl, methylcarbonyl, methylaminocarbonyl, oxo, 1-(t-butoxycarbonyl)azetidin-2-yl, N-(methyl)formamidomethyl,

tetrahydrofuran-2-yl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, or azetidin-2-yl;

R_2 is selected from the group consisting of C_{1-4}alkyl, 1-methoxy-ethyl, difluoromethyl, fluoro, chloro, bromo, cyano, and trifluoromethyl;

G_1 is N or $C(R_4)$;

G_2 is N or $C(R_3)$; such that only one of G_1 and G_2 are N in any instance;

R_3 is independently selected from the group consisting of trifluoromethyl, cyano, C_{1-4}alkyl, fluoro, chloro, bromo, methylcarbonyl, methylthio, methylsulfinyl, and methanesulfonyl; or, when G_1 is N, R_3 is further selected from C_{1-4}alkoxycarbonyl;

R_4 is selected from the group consisting of

i) hydrogen, when G_2 is N;

ii) C_{1-4}alkoxy;

iii) cyano;

iv) cyclopropyloxy;

v) a heteroaryl selected from the group consisting of triazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyrrolyl, thiazolyl, tetrazolyl, oxadiazolyl, imidazolyl, 2-amino-pyrimidin-4-yl, 2H-[1,2,3]triazolo[4,5-c]pyridin-2-yl, 2H-[1,2,3]triazolo[4,5-b]pyridin-2-yl, 3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl, 1H-[1,2,3]triazolo[4,5-c]pyridin-1-yl, wherein the heteroaryl is optionally substituted with one or two substituents independently selected from oxo, C_{1-4}alkyl, carboxy, methoxycarbonyl, aminocarbonyl, hydroxymethyl, aminomethyl, (dimethylamino)methyl, amino, methoxymethyl, trifluoromethyl, amino(C_{2-4}alkyl)amino, or cyano;

vi) 1-methyl-piperidin-4-yloxy;

vii) 4-methyl-piperazin-1-ylcarbonyl;

viii) (4-aminobutyl)aminocarbonyl;

ix) (4-amino)butoxy;

x) 4-(4-aminobutyl)-piperazin-1-ylcarbonyl;

xi) methoxycarbonyl;

xii) 5-chloro-6-(methoxycarbonyl)pyridin-3-ylaminocarbonyl;

xiii) 1,1-dioxo-isothiazolidin-2-yl;

xiv) 3-methyl-2-oxo-2,3-dihydro-1H-imidazol-1-yl;

xv) 2-oxopyrrolidin-1-yl;

xvi) (*E*)- (4-aminobut-1-en-1-yl-aminocarbonyl;

xvii) difluoromethoxy;

and

xviii) morpholin-4-ylcarbonyl;

R_5 is independently selected from the group consisting of hydrogen, chloro, fluoro, bromo, methoxy, methylsulfonyl, cyano, C_{1-4}alkyl, ethynyl, morpholin-4-yl, trifluoromethyl, hydroxyethyl, methylcarbonyl, methylsulfinyl, 3-hydroxy-pyrrolidin-1-yl, pyrrolidin-2-yl, 3-hydroxyazetidinyl, azetidin-3-yl, azetidin-2-yl, methylthio, and 1,1-difluoroethyl;

or R_4 and R_5 may be taken together to form 8-chloro-4-methyl-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 8-chloro-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazin-6-yl, 2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl, 4-methyl-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl, 1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl, 1H-pyrazolo[3,4-b]pyridin-5-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-5-yl, 1,3-dioxolo[4,5]pyridine-5-yl, 1-oxo-1,3-dihydroisobenzofuran-5-yl, 2,2-

dimethylbenzo[d][1,3]dioxol-5-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 1-oxoisoindolin-5-yl, or 2-methyl-1-oxoisoindolin-5-yl, 1*H*-indazol-5-yl;

R_6 is hydrogen, C_{1-4}alkyl, fluoro, 2-methoxy-ethoxy, chloro, cyano, or trifluoromethyl;

R_7 is hydrogen or fluoro;

provided that a compound of Formula (I) is other than

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *2H*-1,2,3-triazol-2-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-imidazol-1-yl, G_2 is N, and R_5 is chloro;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is *1H*-1,2,3-triazol-1-yl, G_2 is N, and R_5 is hydrogen;

a compound wherein R_1 is isoquinolin-8-yl, R_2 is trifluoromethyl, G_1 is C(R_4) wherein R_4 is hydrogen, G_2 is N, and R_5 is fluoro;

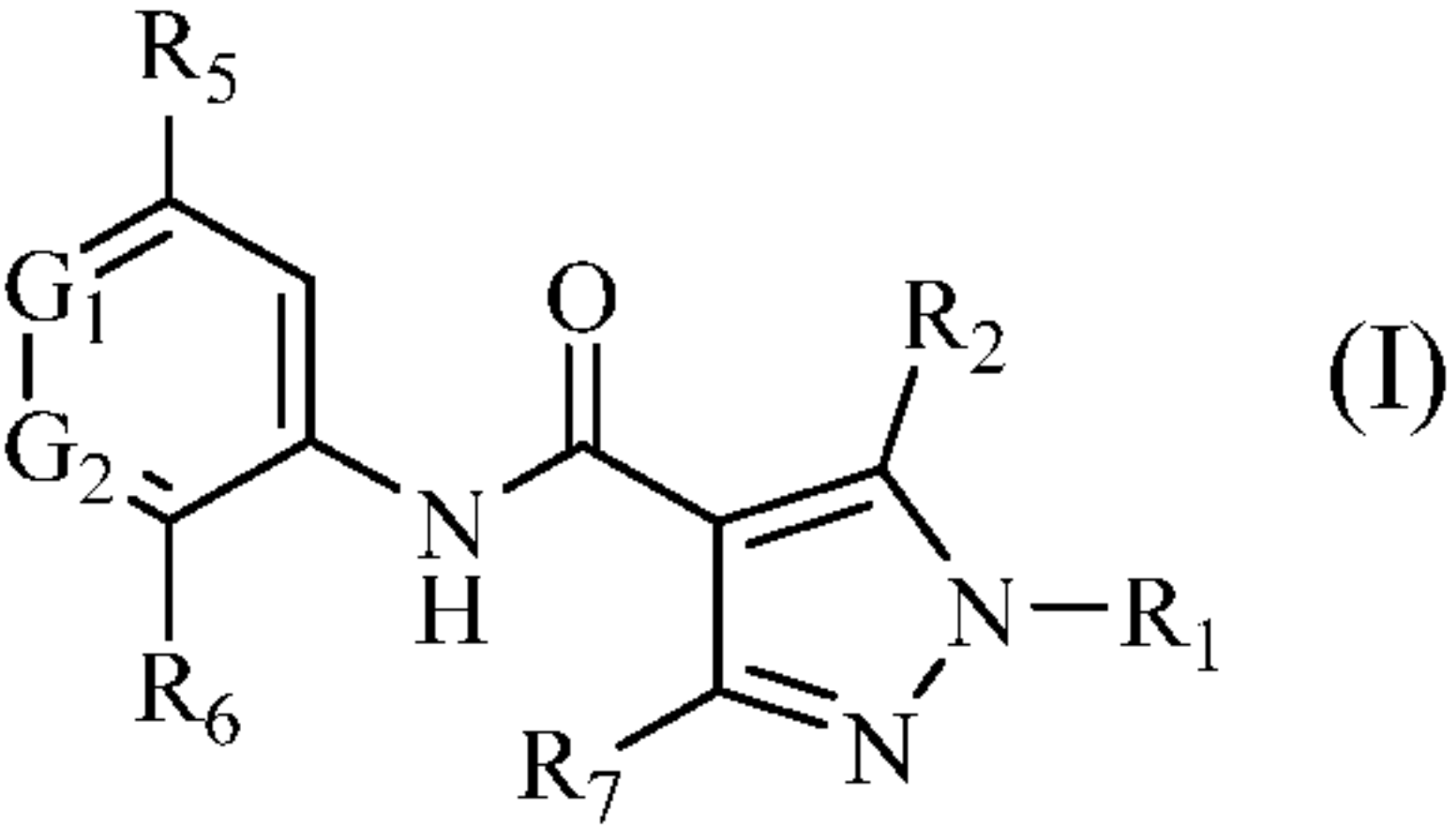
a compound wherein R_1 quinolin-4-yl, R_2 is hydrogen, G_1 is C(R_4) wherein R_4 is (*2H*)-1,2,3-triazol-2-yl, G_2 is N, and R_5 is chloro;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt form thereof.

38. The method of claim 37 wherein the BTK inhibitor is ibrutinib.

39. The method of claim 37 wherein the B cell antigen-binding antibody is rituximab.

40. The method of claim 37 wherein the immunomodulatory agent is daratumumab.



(I)