IMIDAZO-PYRAZINE DERIVATIVES AND THEIR USE IN THE TREATMENT OF NEUROLOGIC DISORDERS

RELATED APPLICATIONS

[001] This application claims priority to U.S Provisional Application No. 63/554,888, filed February 16, 2024, the entire contents of which is incorporated herein by reference.

BACKGROUND

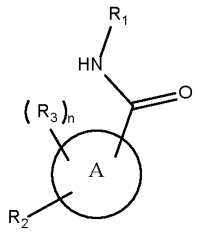
[002] Astrocytes are the most abundant glial cell type in the central nervous system (CNS). They play a role in CNS development and homeostasis associated with the control of synaptic activity, metabolism, and the maintaining the blood-brain barrier. Astrocytes also contribute to the pathology of neurologic disorders through both cell autonomous neurotoxic mechanisms, as well as cell non-autonomous neurotoxic mechanisms such as the recruitment of pro-inflammatory monocytes, the induction of microglial neurotoxic activity, the decreased support of neuron metabolism, the secretion of soluble neurotoxic molecules, and the direct uptake of synaptic and neuronal processes. Astrocytes and microglia are known to mutually regulate their activities through both secreted factors as well as contact-mediated mechanisms.

[003] Neurodegenerative diseases affect a significant segment of the global population and represent a tremendous healthcare burden with unmet medical need. For example, multiple sclerosis (MS) is one of the most common neurodegenerative disorders that affects approximately 2.3 million people world-wide with an estimated socioeconomic burden of more than $1 billion. Microglia and astrocytes establish cell contacts during CNS inflammation. For example, bi-directional signaling involving membrane-bound Ephrin receptor B3 (EphB3) in astrocytes and its membrane-bound ligand Ephrin-B3 in microglia promotes pathology in neurodegenerative disorders, such as autoimmune encephalomyelitis (AE) and in MS. EphB3 is a receptor in the ephrin receptor tyrosine kinase family. Ephrin receptors (Ephs) and their ligands, the ephrins, mediate numerous developmental processes, particularly in the nervous system and vascular systems. For example, EphB3 has been suggested to be neuroprotective in stroke and neurodegenerative disease. Upregulation of EphB3 expression after injury may also contribute to an environment in the spinal cord that is inhibitory to axonal regeneration. Therefore, compounds that may inhibit EphB3 signaling would be capable of ameliorating acute and chronic progressive AE and MS and other neurodegenerative diseases.

[004] This disclosure arises from the need to provide further compounds for the modulation of EphB3. In particular, compounds with improved physiochemical, pharmacological, and pharmaceutical properties to existing compounds are desirable.

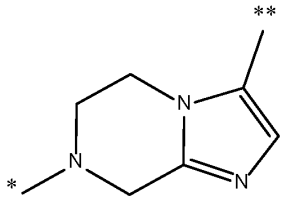
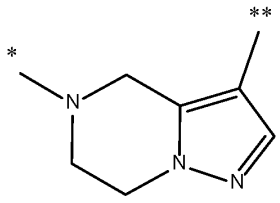
SUMMARY

[005] In some aspects, the present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, $-N(R_{2c})(R_{2d})$, $-OR_{2c}$, $-CO_2(R_{2c})$, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, C_1-C_7 alkoxy, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-CO(C_1$-C_6 alkyl), or $-CO_2(C_1$-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, $-NH$-$CO_2(C_1$-C_6 alkyl), or $-NH_2$;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-CO_2(R_{2g})$, $-CON(R_{2g})(R_{2h})$, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-C(O)$-$NH(C_1$-C_6 alkyl-C_1-C_6 alkoxy), $-(O(C_2$ alkyl$))_{1\text{-}6}$, or $-(O(C_2$ alkyl$))_{1\text{-}6}$-NH_2;

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

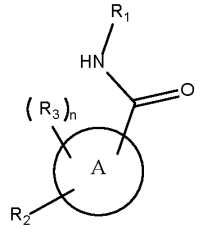
each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl, or

two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle; and

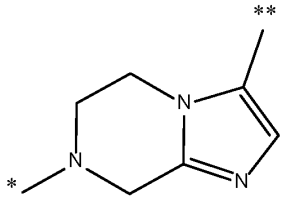
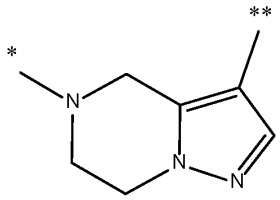
n is 0, 1, 2, 3, or 4.

[006] In some aspects, the present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-

membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-CO(C_1$-C_6 alkyl), or $-CO_2(C_1$-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, $-NH-CO_2(C_1$-C_6 alkyl), or $-NH_2$;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-CO_2(R_{2g})$, $-CON(R_{2g})(R_{2h})$, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $-C(O)-NH(C_1$-C_6 alkyl-C_1-C_6 alkoxy);

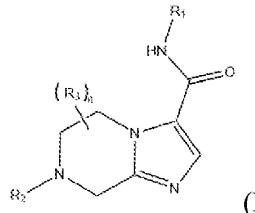
each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

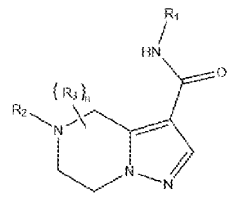
[007] In some aspects, the present disclosure relates to a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof.

[008] In some aspects, the present disclosure relates to a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof.

[009] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, a method for preparing a compound as described herein.

[010] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carriers or excipients.

[011] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein.

[012] In some aspects, the present disclosure provides a method of modulation of EphB3 activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure.

[013] In some aspects, the present disclosure provides a compound of the present disclosure for use in modulation of EphB3 activity (e.g., *in vitro* or *in vivo*).

[014] In some aspects, the present disclosure provides use of a compound of the present disclosure in the manufacture of a medicament for modulation of EphB3 activity (e.g., *in vitro* or *in vivo*).

[015] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutical composition of the present disclosure.

[016] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[017] In some aspects, the present disclosure provides use of a compound of the present disclosure in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[018] In some aspects, the disease or disorder is a neurodegenerative disease or disorder. In some aspects, the neurodegenerative disease or disorder is neuromyelitis optica ("NMO"),

transverse myelitis, myelin oligodendrocyte glycoprotein, acute disseminated encephalomyelitis ("ADEM"), optic neuritis, amyloidosis, Parkinson's disease, Alzheimer's disease, cerebral amyloid angiopathy, Pick's disease, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis ("ALS"), Huntington's disease, traumatic brain injury, stroke, fatty liver disease, endometriosis, paraneoplastic disorders, inflammatory demyelinating polyneuropathy, amyotrophy, fibromyalgia, multiple system atrophy, Friedrich's ataxia, or cerebellar ataxia.

[019] In some aspects, the disease or disorder is a psychiatric or neurodevelopmental disease or disorder. In some aspects, the psychiatric or neurodevelopmental disease or disorder is schizophrenia, major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia, post-traumatic stress disorder, autism spectrum disorder, cerebral palsy, Nasu Hakola disease, bipolar disorder, or substance abuse

[020] In some aspects, the disease or disorder is a viral or infectious disease or disorder. In some aspects, the viral or infectious disease or disorder is neuro-HIV, viral encephalitis, meningitis, neurocysticercosis, neurosyphilis, neuro-Lyme disease, infectious myelopathies, COVID-19 neuroinflammation, enteroviruses, poliovirus, Epstein-Barr virus (EBV), human herpesvirus, cytomegalovirus, rabies virus, herpes simplex virus, measles, progressive multifocal leukoencephalopathy John Cunningham ("PML JC") virus, bacterial meningitis, prion disease, or Creutzfeldt Jakob disease.

[021] In some aspects, the disease or disorder is an autoimmune disease or disorder. In some aspects, the autoimmune disease or disorder is antibody-mediated encephalitis, neurological complications of connective tissue damage, neurosarcoidosid, demyelinating diseases (non-MS), idiopathic autoimmune CNS and PNS syndromes, paraneoplastic neurological disease, CNS vasculitis, type 1 diabetes, type 2 diabetes, Crohn's disease, systemic lupus erythematous ("SLE"), irritable bowel disorders, asthma, chronic obstructive pulmonary disease ("COPD"), atopic dermatitis, obesity-associated inflammation, heart disease, ulcerative colitis, psoriasis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, Sjögren's syndrome, Reiter's disease, multiple sclerosis, autoimmune encephalitis, myasthenia gravis, idiopathic pulmonary fibrosis, ankylosing spondylitis, antiphospholipid antibody syndrome, osteomyelitis, gout, Henoch-Schonlein Purpura, dermatomyositis, idiopathic arthritis, scleroderma, Kawasaki disease, mixed connective tissue damage, myositis, spondyloarthritis, undifferentiated connective tissue disease, systemic sclerosis, or autoimmune hepatitis.

[022] In some aspects, the disease or disorder is an eye disease or disorder. In some aspects, the eye disease or disorder is uveitis, keratitis, conjunctivitis, thyroid eye disease, age-related

macular degeneration, glaucoma, diabetic retinopathy, diabetes-related macular edema, or scleritis.

[023] In some aspects, the disease or disorder is autoimmune encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, concentric sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, HTLV-I associated myelopathy ("HAM"), Schilder's disease, dementia, frontotemporal lobar dementia, accessory nerve disorder, autonomic dysreflexia, peripheral neuropathy, chemotherapy-induced peripheral neuropathies, mononeuropathy, polyneuropathy, radial neuropathy, ulnar neuropathy, Villaret's syndrome, diabetic neuropathy, nerve paralysis, progressive bulbar palsy, pseudobulbar palsy, spinal bulbar muscular atrophy, myotonic dystrophy, inclusion body myositis, seizure disorders, lysosomal storage disorders, transmissible spongiform encephalopathy, spinocerebellar ataxia, spinal muscular atrophy, Horner's syndrome, adrenoleukodystrophy, macular degeneration, or Lewy Body syndrome.

[024] In some aspects, the disease or disorder is an ocular inflammatory disease.

[025] In some aspects, the disease or disorder is autoimmune encephalomyelitis or multiple sclerosis.

[026] In some aspects, the disease or disorder is amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, or Huntington's disease.

[027] In some aspects, the Alzheimer's disease is Alzheimer's disease with APOE4.

[028] In some aspects, the multiple sclerosis is progression independent of relapses.

[029] In some aspects, the present disclosure provides a method of preparing a compound of the present disclosure.

[030] In some aspects, the present disclosure provides a method of preparing a compound, comprising one or more steps described herein.

[031] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. In the case of conflict between

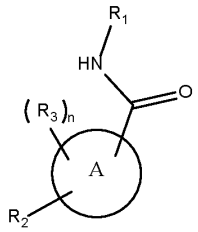
the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

DETAILED DESCRIPTION

[032] The disclosure relates to compounds useful for the modulation of EphB3. In particular, compounds with improved physicochemical, pharmacological and pharmaceutical properties to existing EphB3-modulating compounds are desired.

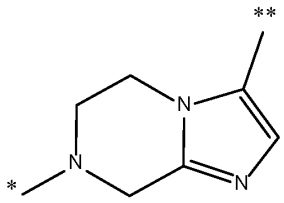
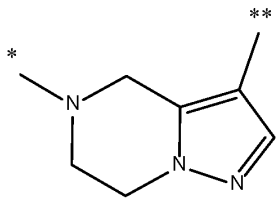
Compounds of the Present Disclosure

[033] In some aspects, the present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, C_1-C_7 alkoxy, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy), –(O(C_2 alkyl))$_{1\text{-}6}$, or –(O(C_2 alkyl))$_{1\text{-}6}$-NH_2;

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

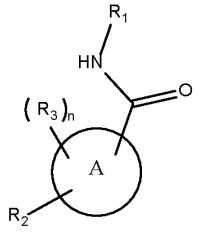
each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl, or

two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle; and

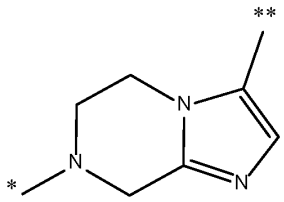
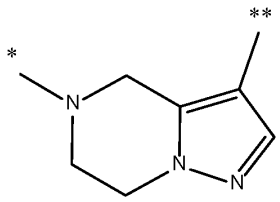
n is 0, 1, 2, 3, or 4.

[034] In some aspects, the present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-

membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or $-NH_2$;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy);

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

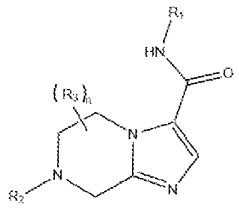
R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

[035] It is understood that, for a compound of Formula (I), R_1, R_{1a}, R_{1b}, R_{1c}, R_2, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_{2e}, R_{2f}, R_{2g}, R_{2h}, R_3, and n can each be, where applicable, selected from the groups described herein, and any group described herein for any of R_1, R_{1a}, R_{1b}, R_{1c}, R_2, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_{2e}, R_{2f}, R_{2g}, R_{2h}, R_3, and n can be combined, where applicable, with any group described herein for one or more of the remainder of R_1, R_{1a}, R_{1b}, R_{1c}, R_2, R_{2a}, R_{2b}, R_{2c}, R_{2d}, R_{2e}, R_{2f}, R_{2g}, R_{2h}, R_3, and n.

Formula (II)

[036] In some aspects, the present disclosure relates to a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- or 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, C_1-C_7 alkoxy, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy,

cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy), –(O(C_2 alkyl))$_{1\text{-}6}$, or –(O(C_2 alkyl))$_{1\text{-}6}$-NH_2;

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

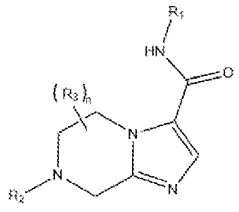
each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl, or

two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle; and

n is 0, 1, 2, 3, or 4.

[037] In some aspects, the present disclosure relates to a compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- or 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy);

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

[038] In some embodiments, R_1 is C_6-C_{10} aryl optionally substituted with one or more R_{1a}.

[039] In some embodiments, R_1 is C_6-C_{10} aryl substituted with one or more R_{1a}.

[040] In some embodiments, R_1 is C_6-C_{10} aryl.

[041] In some embodiments, R_1 is 5- to 10-membered heteroaryl optionally substituted with one or more R_{1a}.

[042] In some embodiments, R_1 is 5- to 10-membered heteroaryl substituted with one or more R_{1a}.

[043] In some embodiments, R_1 is 5- to 10-membered heteroaryl.

[044] In some embodiments, R_1 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{1a}.

[045] In some embodiments, R_1 is 5- or 6-membered heteroaryl substituted with one or more R_{1a}.

[046] In some embodiments, R_1 is 5- or 6-membered heteroaryl.

[047] In some embodiments, R_1 is phenyl optionally substituted with one or more R_{1a}.

[048] In some embodiments, R_1 is phenyl substituted with one or more R_{1a}.

[049] In some embodiments, R_1 is phenyl substituted with one R_{1a}.

[050] In some embodiments, R_1 is phenyl substituted with two R_{1a}.

[051] In some embodiments, R_1 is phenyl substituted with three R_{1a}.

[052] In some embodiments, R_1 is 5-membered heteroaryl optionally substituted with one or more R_{1a}.

[053] In some embodiments, R_1 is 5-membered heteroaryl substituted with one or more R_{1a}.

[054] In some embodiments, R_1 is 5-membered heteroaryl substituted with one R_{1a}.

[055] In some embodiments, R_1 is 5-membered heteroaryl substituted with two R_{1a}.

[056] In some embodiments, R_1 is 5-membered heteroaryl substituted with three R_{1a}.

[057] In some embodiments, R_1 is 6-membered heteroaryl optionally substituted with one or more R_{1a}.

[058] In some embodiments, R_1 is 6-membered heteroaryl substituted with one or more R_{1a}.

[059] In some embodiments, R_1 is 6-membered heteroaryl substituted with one R_{1a}.

[060] In some embodiments, R_1 is 6-membered heteroaryl substituted with two R_{1a}.

[061] In some embodiments, R_1 is 6-membered heteroaryl substituted with three R_{1a}.

[062] In some embodiments, each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}).

[063] In some embodiments, each R_{1a} independently is halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}).

[064] In some embodiments, each R_{1a} independently is halo.

[065] In some embodiments, each R_{1a} independently is F, Cl, Br, or I.

[066] In some embodiments, each R_{1a} independently is F. In some embodiments, each R_{1a} independently is Cl. In some embodiments, each R_{1a} independently is Br. In some embodiments, each R_{1a} independently is I.

[067] In some embodiments, each R_{1a} independently is -OH.

[068] In some embodiments, each R_{1a} independently is C_1-C_6 alkyl.

[069] In some embodiments, each R_{1a} independently is methyl.

[070] In some embodiments, each R_{1a} independently is C_2-C_6 alkenyl.

[071] In some embodiments, each R_{1a} independently is C_2-C_6 alkynyl.

[072] In some embodiments, each R_{1a} independently is C_1-C_6 haloalkyl.

[073] In some embodiments, each R_{1a} independently is CH_2-CF_3 or CF_3.

[074] In some embodiments, each R_{1a} independently is CF_3.

[075] In some embodiments, each R_{1a} independently is C_1-C_6 alkoxyl.

[076] In some embodiments, each R_{1a} independently is methoxy.

[077] In some embodiments, each R_{1a} independently is -C(O)N(R_{1b})(R_{1c}).

[078] In some embodiments, each R_{1a} independently is Cl, F, CH_2-CF_3, CF_3, methyl, or methoxy.

[079] In some embodiments, each R_{1a} independently is Cl, F, CF_3, methyl, or methoxy.

[080] In some embodiments, each R_{1a} independently is Cl, F, methyl, or methoxy.

[081] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- or 6-membered heterocycle.

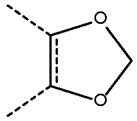
[082] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl.

[083] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form a 5- or 6-membered heterocycle.

[084] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form a 5-membered heterocycle.

[085] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form a 6-membered heterocycle.

[086] In some embodiments, two R_{1a}, together with the atoms to which they are attached, form



[087] In some embodiments, each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[088] In some embodiments, each R_{1b} independently is H.

[089] In some embodiments, each R_{1b} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[090] In some embodiments, each R_{1b} independently is C_1-C_6 alkyl.

[091] In some embodiments, each R_{1b} independently is C_2-C_6 alkenyl.

[092] In some embodiments, each R_{1b} independently is C_2-C_6 alkynyl.

[093] In some embodiments, each R_{1b} independently is C_1-C_6 haloalkyl.

[094] In some embodiments, each R_{1c} independently is C_6-C_{10} aryl.

[095] In some embodiments, each R_{1c} independently is C_6-C_{10} aryl substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

[096] In some embodiments, each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more C_1-C_6 haloalkyl.

[097] In some embodiments, each R_{1c} independently is C_6-C_{10} aryl substituted with one or more C_1-C_6 haloalkyl.

[098] In some embodiments, each R_{1c} independently is phenyl.

[099] In some embodiments, each R_{1c} independently is phenyl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

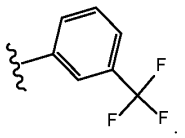
[0100] In some embodiments, each R_{1c} independently is phenyl substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

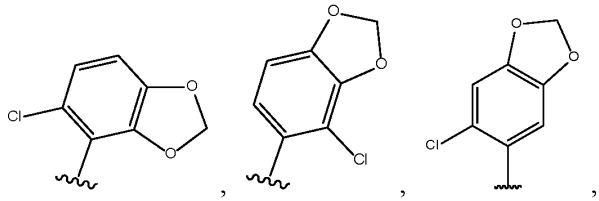
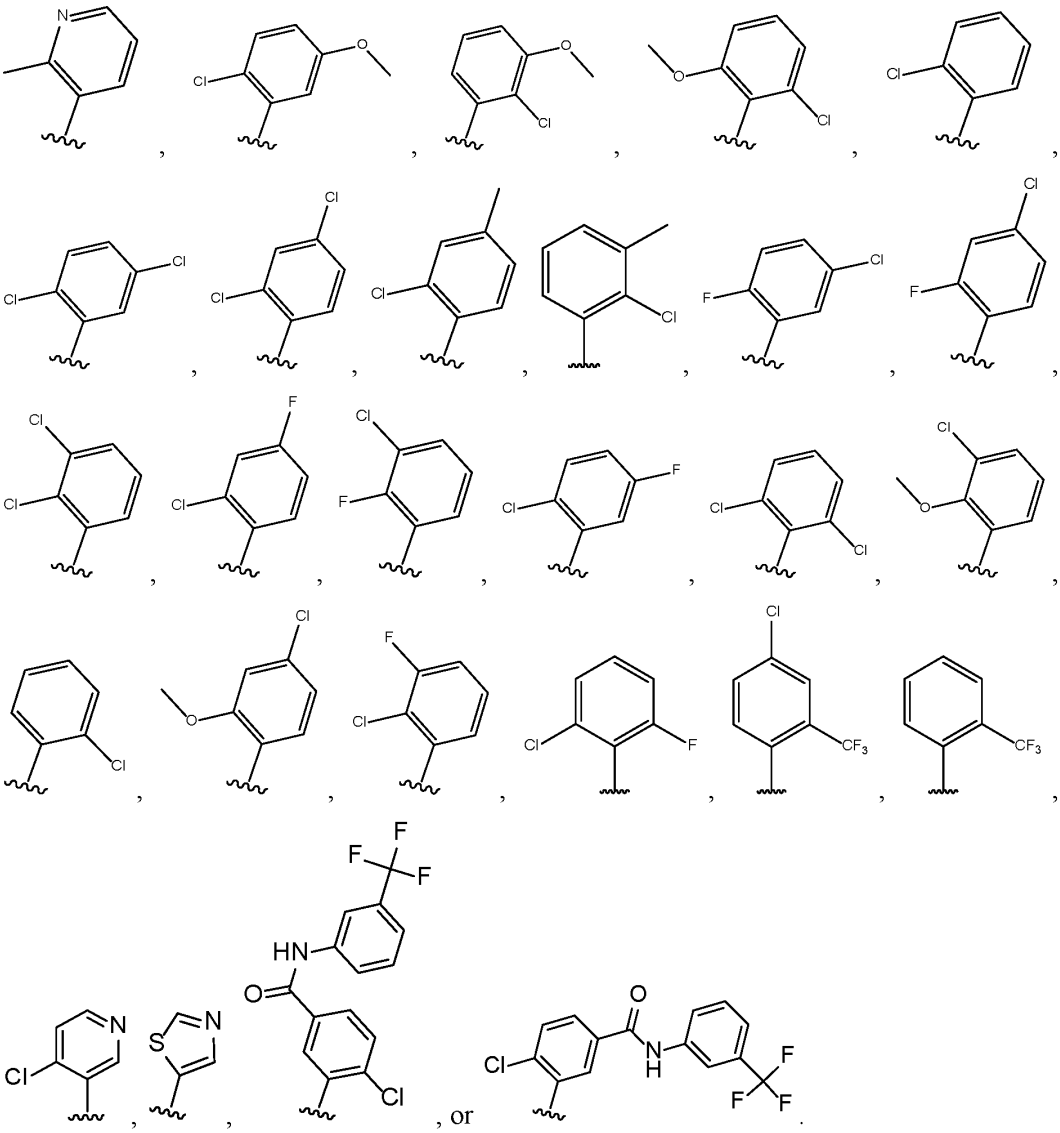
[0101] In some embodiments, each R_{1c} independently is phenyl optionally substituted with one or more C_1-C_6 haloalkyl.

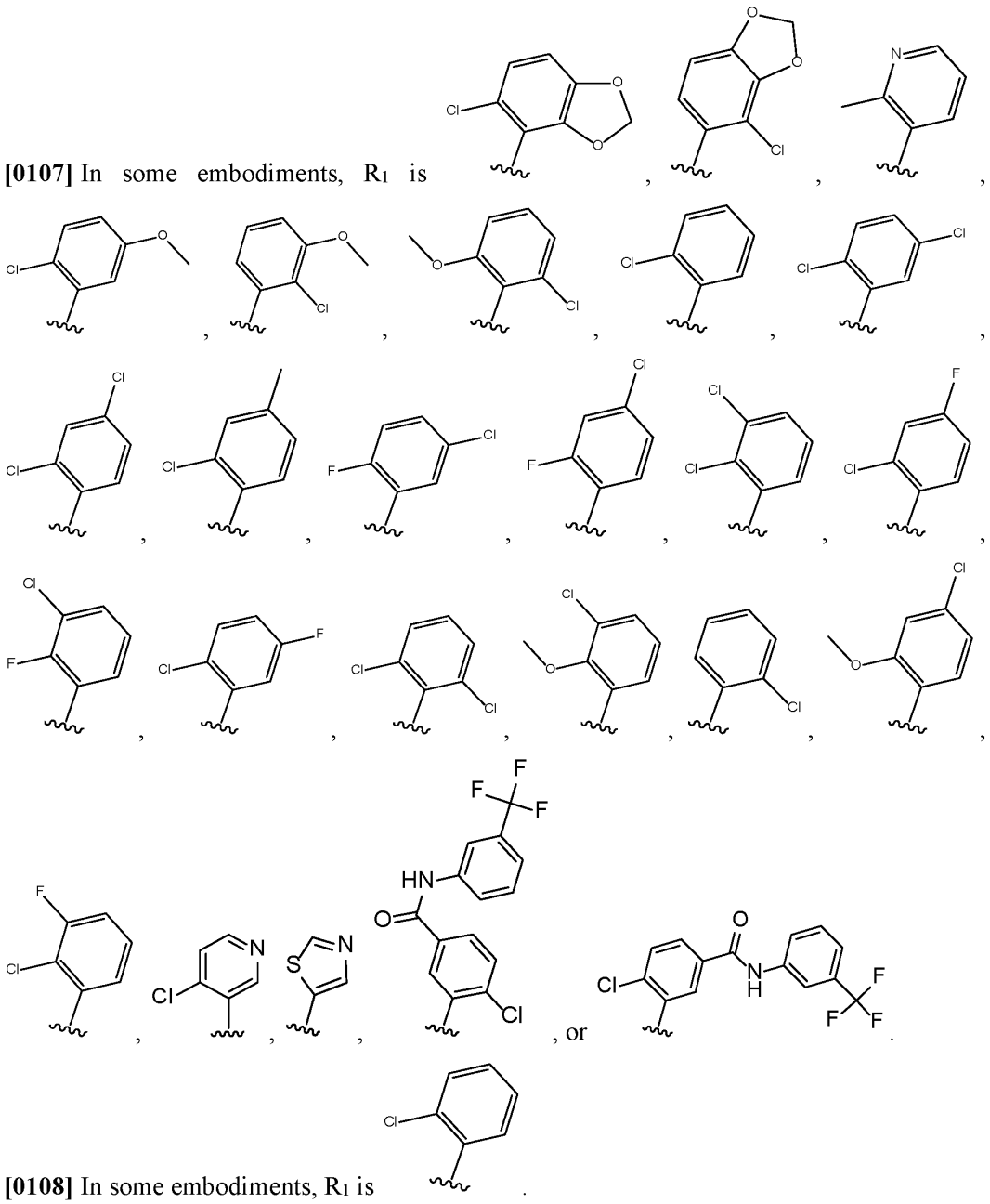
[0102] In some embodiments, each R_{1c} independently is phenyl substituted with one or more C_1-C_6 haloalkyl.

[0103] In some embodiments, each R_{1c} independently is phenyl optionally substituted with one or more -CF_3.

[0104] In some embodiments, each R_{1c} independently is phenyl substituted with one or more -CF_3.

[0105] In some embodiments, R_{1c} is .

[0106] In some embodiments, R_1 is , , or .

[0107] In some embodiments, R_1 is .

[0108] In some embodiments, R_1 is .

[0109] In some embodiments, R_2 is $-C(O)R_{2a}$.

[0110] In some embodiments, R_2 is C_2-C_6 alkenyl.

[0111] In some embodiments, R_2 is C_2-C_6 alkenyl optionally substituted with one or more R_{2b}.

[0112] In some embodiments, R_2 is C_2-C_6 alkenyl substituted with one or more R_{2b}.

[0113] In some embodiments, R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

[0114] In some embodiments, R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more R_{2b}.

[0115] In some embodiments, R_{2a} is C_1-C_6 alkyl.

[0116] In some embodiments, R_{2a} is C_1-C_6 alkyl optionally substituted with one or more R_{2b}.

[0117] In some embodiments, R_{2a} is C_1-C_6 alkyl substituted with one or more R_{2b}.

[0118] In some embodiments, R_{2a} is C_2-C_6 alkenyl.

[0119] In some embodiments, R_{2a} is C_2-C_6 alkenyl optionally substituted with one or more R_{2b}.

[0120] In some embodiments, R_{2a} is C_2-C_6 alkenyl substituted with one or more R_{2b}.

[0121] In some embodiments, R_{2a} is C_2-C_6 alkynyl.

[0122] In some embodiments, R_{2a} is C_2-C_6 alkynyl optionally substituted with one or more R_{2b}.

[0123] In some embodiments, R_{2a} is C_2-C_6 alkynyl substituted with one or more R_{2b}.

[0124] In some embodiments, R_{2a} is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}.

[0125] In some embodiments, each R_{2b} independently is halo.

[0126] In some embodiments, each R_{2b} independently is F, Cl, Br, or I.

[0127] In some embodiments, each R_{2b} independently is F. In some embodiments, each R_{2b} independently is Cl. In some embodiments, each R_{2b} independently is Br. In some embodiments, each R_{2b} independently is I.

[0128] In some embodiments, each R_{2b} independently is $-N(R_{2c})(R_{2d})$, $-OR_{2c}$, or $-CO_2(R_{2c})$.

[0129] In some embodiments, each R_{2b} independently is $-N(R_{2c})(R_{2d})$.

[0130] In some embodiments, each R_{2b} independently is $-OR_{2c}$.

[0131] In some embodiments, each R_{2b} independently is $-CO_2(R_{2c})$.

[0132] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0133] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e}.

[0134] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_{2e}.

[0135] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl.

[0136] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl optionally substituted with one or more R_{2e}.

[0137] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl substituted with one or more R_{2e}.

[0138] In some embodiments, each R_{2b} independently is 4- to 10-membered heterocyclyl.

[0139] In some embodiments, each R_{2b} independently is 4- to 10-membered heterocyclyl optionally substituted with one or more R_{2e}.

[0140] In some embodiments, each R_{2b} independently is 4- to 10-membered heterocyclyl substituted with one or more R_{2e}.

[0141] In some embodiments, each R_{2b} independently is C_6-C_{10} aryl.

[0142] In some embodiments, each R_{2b} independently is C_6-C_{10} aryl optionally substituted with one or more R_{2e}.

[0143] In some embodiments, each R_{2b} independently is C_6-C_{10} aryl substituted with one or more R_{2e}.

[0144] In some embodiments, each R_{2b} independently is 5- to 10-membered heteroaryl.

[0145] In some embodiments, each R_{2b} independently is 5- to 10-membered heteroaryl optionally substituted with one or more R_{2e}.

[0146] In some embodiments, each R_{2b} independently is 5- to 10-membered heteroaryl substituted with one or more R_{2e}.

[0147] In some embodiments, each R_{2b} independently is 4- to 10-membered heterocyclyl, -$N(R_{2c})(R_{2d})$, -OR_{2c}, C_6-C_{10} aryl, or -$CO_2(R_{2c})$, wherein the heterocyclyl or aryl is optionally substituted with one or more R_{2e}.

[0148] In some embodiments, each R_{2c} independently is H.

[0149] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0150] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f}.

[0151] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_{2f}.

[0152] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[0153] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl, wherein the alkyl, alkenyl, alkynyl, or haloalkyl is optionally substituted with one or more R_{2f}.

[0154] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl, wherein the alkyl, alkenyl, alkynyl, or haloalkyl is substituted with one or more R_{2f}.

[0155] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl.

[0156] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl optionally substituted with one or more R_{2f}.

[0157] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl substituted with one or more R_{2f}.

[0158] In some embodiments, each R_{2c} independently is C_2-C_6 alkenyl.

[0159] In some embodiments, each R_{2c} independently is C_2-C_6 alkenyl optionally substituted with one or more R_{2f}.

[0160] In some embodiments, each R_{2c} independently is C_2-C_6 alkenyl substituted with one or more R_{2f}.

[0161] In some embodiments, each R_{2c} independently is C_2-C_6 alkynyl.

[0162] In some embodiments, each R_{2c} independently is C_2-C_6 alkynyl optionally substituted with one or more R_{2f}.

[0163] In some embodiments, each R_{2c} independently is C_2-C_6 alkynyl substituted with one or more R_{2f}.

[0164] In some embodiments, each R_{2c} independently is C_1-C_6 haloalkyl.

[0165] In some embodiments, each R_{2c} independently is C_1-C_6 haloalkyl optionally substituted with one or more R_{2f}.

[0166] In some embodiments, each R_{2c} independently is C_1-C_6 haloalkyl substituted with one or more R_{2f}.

[0167] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0168] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f}.

[0169] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more R_{2f}.

[0170] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl.

[0171] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl optionally substituted with one or more R_{2f}.

[0172] In some embodiments, each R_{2c} independently is C_3-C_6 cycloalkyl substituted with one or more R_{2f}.

[0173] In some embodiments, each R_{2c} independently is 5- to 10-membered heterocyclyl.

[0174] In some embodiments, each R_{2c} independently is 5- to 10-membered heterocyclyl optionally substituted with one or more R_{2f}.

[0175] In some embodiments, each R_{2c} independently is 5- to 10-membered heterocyclyl substituted with one or more R_{2f}.

[0176] In some embodiments, each R_{2c} independently is C_6-C_{10} aryl.

[0177] In some embodiments, each R_{2c} independently is C_6-C_{10} aryl optionally substituted with one or more R_{2f}.

[0178] In some embodiments, each R_{2c} independently is C_6-C_{10} aryl substituted with one or more R_{2f}.

[0179] In some embodiments, each R_{2c} independently is 5- to 10-membered heteroaryl.

[0180] In some embodiments, each R_{2c} independently is 5- to 10-membered heteroaryl optionally substituted with one or more R_{2f}.

[0181] In some embodiments, each R_{2c} independently is 5- to 10-membered heteroaryl substituted with one or more R_{2f}.

[0182] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_6-C_{10} aryl, wherein the alkyl, cycloalkyl, or aryl is optionally substituted with one or more R_{2f}.

[0183] In some embodiments, each R_{2d} independently is H.

[0184] In some embodiments, each R_{2d} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[0185] In some embodiments, each R_{2d} independently is C_1-C_6 alkyl.

[0186] In some embodiments, each R_{2d} independently is methyl or ethyl.

[0187] In some embodiments, each R_{2d} independently is C_2-C_6 alkenyl.

[0188] In some embodiments, each R_{2d} independently is C_2-C_6 alkynyl.

[0189] In some embodiments, each R_{2d} independently is C_1-C_6 haloalkyl.

[0190] In some embodiments, each R_{2e} independently is halo, -CN, -OH, $-NH_2$, -NH(C_1-C_6 alkyl), or -N(C_1-C_6 alkyl)$_2$.

[0191] In some embodiments, each R_{2e} independently is halo.

[0192] In some embodiments, each R_{2e} independently is F, Cl, Br, or I.

[0193] In some embodiments, each R_{2e} independently is F. In some embodiments, each R_{2e} independently is Cl. In some embodiments, each R_{2e} independently is Br. In some embodiments, each R_{2e} independently is I.

[0194] In some embodiments, each R_{2e} independently is -CN.

[0195] In some embodiments, each R_{2e} independently is -OH.

[0196] In some embodiments, each R_{2e} independently is $-NH_2$.

[0197] In some embodiments, each R_{2e} independently is $-NH(C_1\text{-}C_6$ alkyl).

[0198] In some embodiments, each R_{2e} independently is $-N(C_1\text{-}C_6$ alkyl)$_2$.

[0199] In some embodiments, each R_{2e} independently is $C_1\text{-}C_7$ alkyl, $C_2\text{-}C_7$ alkenyl, $C_2\text{-}C_7$ alkynyl, $C_1\text{-}C_7$ haloalkyl, $C_1\text{-}C_7$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 4- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl).

[0200] In some embodiments, each R_{2e} independently is $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 5- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl).

[0201] In some embodiments, each R_{2e} independently is $C_1\text{-}C_7$ alkyl, $C_2\text{-}C_7$ alkenyl, $C_2\text{-}C_7$ alkynyl, $C_1\text{-}C_7$ haloalkyl, $C_1\text{-}C_7$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 4- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0202] In some embodiments, each R_{2e} independently is $C_1\text{-}C_7$ alkyl, $C_2\text{-}C_7$ alkenyl, $C_2\text{-}C_7$ alkynyl, $C_1\text{-}C_7$ haloalkyl, $C_1\text{-}C_7$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 4- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0203] In some embodiments, each R_{2e} independently is $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 5- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0204] In some embodiments, each R_{2e} independently is $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, $C_1\text{-}C_6$ alkoxy, $C_3\text{-}C_6$ cycloalkyl, 5- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, 5- to 10-membered heteroaryl, $-CO(C_1\text{-}C_6$ alkyl), or $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0205] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, or C_1-C_7 alkoxy.

[0206] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy.

[0207] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, or C_1-C_7 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0208] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, or C_1-C_7 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0209] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0210] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0211] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl.

[0212] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0213] In some embodiments, each R_{2e} independently is C_1-C_7 alkyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0214] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl.

[0215] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0216] In some embodiments, each R_{2e} independently is C_1-C_6 alkyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0217] In some embodiments, each R_{2e} independently is C_2-C_7 alkenyl.

[0218] In some embodiments, each R_{2e} independently is C_2-C_7 alkenyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0219] In some embodiments, each R_{2e} independently is C_2-C_7 alkenyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0220] In some embodiments, each R_{2e} independently is C_2-C_6 alkenyl.

[0221] In some embodiments, each R_{2e} independently is C_2-C_6 alkenyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0222] In some embodiments, each R_{2e} independently is C_2-C_6 alkenyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0223] In some embodiments, each R_{2e} independently is C_2-C_7 alkynyl.

[0224] In some embodiments, each R_{2e} independently is C_2-C_7 alkynyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0225] In some embodiments, each R_{2e} independently is C_2-C_7 alkynyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0226] In some embodiments, each R_{2e} independently is C_2-C_6 alkynyl.

[0227] In some embodiments, each R_{2e} independently is C_2-C_6 alkynyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0228] In some embodiments, each R_{2e} independently is C_2-C_6 alkynyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0229] In some embodiments, each R_{2e} independently is C_1-C_7 haloalkyl.

[0230] In some embodiments, each R_{2e} independently is C_1-C_7 haloalkyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0231] In some embodiments, each R_{2e} independently is C_1-C_7 haloalkyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0232] In some embodiments, each R_{2e} independently is C_1-C_6 haloalkyl.

[0233] In some embodiments, each R_{2e} independently is C_1-C_6 haloalkyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0234] In some embodiments, each R_{2e} independently is C_1-C_6 haloalkyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0235] In some embodiments, each R_{2e} independently is C_1-C_7 alkoxy.

[0236] In some embodiments, each R_{2e} independently is C_1-C_7 alkoxy optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0237] In some embodiments, each R_{2e} independently is C_1-C_7 alkoxy substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0238] In some embodiments, each R_{2e} independently is C_1-C_6 alkoxy.

[0239] In some embodiments, each R_{2e} independently is C_1-C_6 alkoxy optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0240] In some embodiments, each R_{2e} independently is C_1-C_6 alkoxy substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0241] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0242] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0243] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0244] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0245] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0246] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0247] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl.

[0248] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0249] In some embodiments, each R_{2e} independently is C_3-C_6 cycloalkyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0250] In some embodiments, each R_{2e} independently is 4- to 10-membered heterocyclyl.

[0251] In some embodiments, each R_{2e} independently is 4- to 10-membered heterocyclyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0252] In some embodiments, each R_{2e} independently is 4- to 10-membered heterocyclyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0253] In some embodiments, each R_{2e} independently is 5- to 10-membered heterocyclyl.

[0254] In some embodiments, each R_{2e} independently is 5- to 10-membered heterocyclyl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0255] In some embodiments, each R_{2e} independently is 5- to 10-membered heterocyclyl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0256] In some embodiments, each R_{2e} independently is C_6-C_{10} aryl.

[0257] In some embodiments, each R_{2e} independently is C_6-C_{10} aryl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0258] In some embodiments, each R_{2e} independently is C_6-C_{10} aryl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0259] In some embodiments, each R_{2e} independently is 5- to 10-membered heteroaryl.

[0260] In some embodiments, each R_{2e} independently is 5- to 10-membered heteroaryl optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0261] In some embodiments, each R_{2e} independently is 5- to 10-membered heteroaryl substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0262] In some embodiments, each R_{2e} independently is CO(C_1-C_6 alkyl) or -CO_2(C_1-C_6 alkyl).

[0263] In some embodiments, each R_{2e} independently is -CO(C_1-C_6 alkyl) or -CO_2(C_1-C_6 alkyl), wherein the alkyl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0264] In some embodiments, each R_{2e} independently is -CO(C_1-C_6 alkyl) or -CO_2(C_1-C_6 alkyl), wherein the alkyl is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0265] In some embodiments, each R_{2e} independently is CO(C_1-C_6 alkyl).

[0266] In some embodiments, each R_{2e} independently is -CO(C_1-C_6 alkyl), wherein the alkyl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0267] In some embodiments, each R_{2e} independently is -CO(C_1-C_6 alkyl), wherein the alkyl is substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2.

[0268] In some embodiments, each R_{2e} independently is -CO_2(C_1-C_6 alkyl).

[0269] In some embodiments, each R_{2e} independently is $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl is optionally substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0270] In some embodiments, each R_{2e} independently is $-CO_2(C_1\text{-}C_6$ alkyl), wherein the alkyl is substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl), or $-NH_2$.

[0271] In some embodiments, each R_{2e} independently is halo, -OH, -CN, $-CO(C_1\text{-}C_6$ alkyl), $-N(C_1\text{-}C_6$ alkyl)$_2$, or $-CO_2(C_1\text{-}C_6$ alkyl).

[0272] In some embodiments, each R_{2e} independently is F, -OH, -CN, $-CO(C_1\text{-}C_6$ alkyl), $-N(C_1\text{-}C_6$ alkyl)$_2$, or $-CO_2(C_1\text{-}C_6$ alkyl).

[0273] In some embodiments, each R_{2e} independently is $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ haloalkyl, $C_3\text{-}C_6$ cycloalkyl, or 5- to 10-membered heterocyclyl, wherein the alkyl, haloalkyl, alkoxy, cycloalkyl, or heterocyclyl, is optionally substituted with one or more -CN, -OH, $C_1\text{-}C_6$ alkoxy, or $-NH\text{-}CO_2(C_1\text{-}C_6$ alkyl).

[0274] In some embodiments, each R_{2f} independently is halo or -CN.

[0275] In some embodiments, each R_{2f} independently is halo.

[0276] In some embodiments, each R_{2f} independently is F, Cl, Br, or I.

[0277] In some embodiments, each R_{2f} independently is F. In some embodiments, each R_{2f} independently is Cl. In some embodiments, each R_{2f} independently is Br. In some embodiments, each R_{2f} independently is I.

[0278] In some embodiments, each R_{2f} independently is -CN.

[0279] In some embodiments, each R_{2f} independently is $C_1\text{-}C_6$ alkyl, $C_2\text{-}C_6$ alkenyl, $C_2\text{-}C_6$ alkynyl, $C_1\text{-}C_6$ haloalkyl, or $C_1\text{-}C_6$ alkoxy.

[0280] In some embodiments, each R_{2f} independently is $C_1\text{-}C_6$ alkyl.

[0281] In some embodiments, each R_{2f} independently is $C_2\text{-}C_6$ alkenyl.

[0282] In some embodiments, each R_{2f} independently is $C_2\text{-}C_6$ alkynyl.

[0283] In some embodiments, each R_{2f} independently is $C_1\text{-}C_6$ haloalkyl.

[0284] In some embodiments, each R_{2f} independently is $C_1\text{-}C_6$ alkoxy.

[0285] In some embodiments, each R_{2f} independently is $-CO_2(R_{2g})$, $-CON(R_{2g})(R_{2h})$, or $-C(O)\text{-}NH(C_1\text{-}C_6$ alkyl-$C_1\text{-}C_6$ alkoxy).

[0286] In some embodiments, each R_{2f} independently is $-CO_2(R_{2g})$.

[0287] In some embodiments, each R_{2f} independently is $-CON(R_{2g})(R_{2h})$.

[0288] In some embodiments, each R_{2f} independently is $-C(O)\text{-}NH(C_1\text{-}C_6$ alkyl-$C_1\text{-}C_6$ alkoxy).

[0289] In some embodiments, each R_{2f} independently is $C_3\text{-}C_6$ cycloalkyl, 5- to 10-membered heterocyclyl, $C_6\text{-}C_{10}$ aryl, or 5- to 10-membered heteroaryl.

[0290] In some embodiments, each R_{2f} independently is C_3-C_6 cycloalkyl.

[0291] In some embodiments, each R_{2f} independently is 5- to 10-membered heterocyclyl.

[0292] In some embodiments, each R_{2f} independently is C_6-C_{10} aryl.

[0293] In some embodiments, each R_{2f} independently is 5- to 10-membered heteroaryl.

[0294] In some embodiments, each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), C_3-C_6 cycloalkyl, C_6-C_{10} aryl, C_1-C_6 haloalkyl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy).

[0295] In some embodiments, each R_{2f} independently is F, -CN, methyl, methoxy, phenoxy, -CO_2(R_{2g}), cyclopropyl, phenyl, -CF_3, or -C(O)-NH(ethyl-methoxy).

[0296] In some embodiments, each R_{2g} independently is H.

[0297] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0298] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0299] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0300] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy.

[0301] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0302] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxy, wherein the alkyl, alkenyl, alkynyl, haloalkyl, or alkoxy is substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0303] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl.

[0304] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0305] In some embodiments, each R_{2g} independently is C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0306] In some embodiments, each R_{2g} independently is C_2-C_6 alkenyl.

[0307] In some embodiments, each R_{2g} independently is C_2-C_6 alkenyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0308] In some embodiments, each R_{2g} independently is C_2-C_6 alkenyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0309] In some embodiments, each R_{2g} independently is C_2-C_6 alkynyl.

[0310] In some embodiments, each R_{2g} independently is C_2-C_6 alkynyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0311] In some embodiments, each R_{2g} independently is C_2-C_6 alkynyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0312] In some embodiments, each R_{2g} independently is C_1-C_6 haloalkyl.

[0313] In some embodiments, each R_{2g} independently is C_1-C_6 haloalkyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0314] In some embodiments, each R_{2g} independently is C_1-C_6 haloalkyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0315] In some embodiments, each R_{2g} independently is C_1-C_6 alkoxy.

[0316] In some embodiments, each R_{2g} independently is C_1-C_6 alkoxy optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0317] In some embodiments, each R_{2g} independently is C_1-C_6 alkoxy substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0318] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

[0319] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0320] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0321] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl.

[0322] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0323] In some embodiments, each R_{2g} independently is C_3-C_6 cycloalkyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0324] In some embodiments, each R_{2g} independently is 5- to 10-membered heterocyclyl.

[0325] In some embodiments, each R_{2g} independently is 5- to 10-membered heterocyclyl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0326] In some embodiments, each R_{2g} independently is 5- to 10-membered heterocyclyl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0327] In some embodiments, each R_{2g} independently is C_6-C_{10} aryl.

[0328] In some embodiments, each R_{2g} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0329] In some embodiments, each R_{2g} independently is C_6-C_{10} aryl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0330] In some embodiments, each R_{2g} independently is 5- to 10-membered heteroaryl.

[0331] In some embodiments, each R_{2g} independently is 5- to 10-membered heteroaryl optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0332] In some embodiments, each R_{2g} independently is 5- to 10-membered heteroaryl substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl.

[0333] In some embodiments, each R_{2g} independently is H or C_1-C_6 alkyl.

[0334] In some embodiments, each R_{2g} independently is H or tert-butyl.

[0335] In some embodiments, each R_{2h} independently is H.

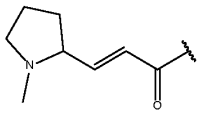
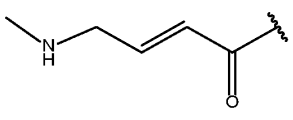
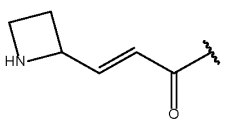
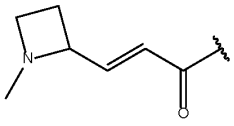
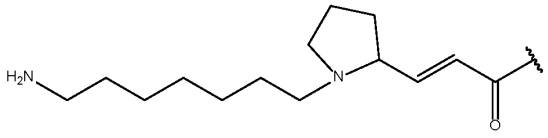
[0336] In some embodiments, each R_{2h} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

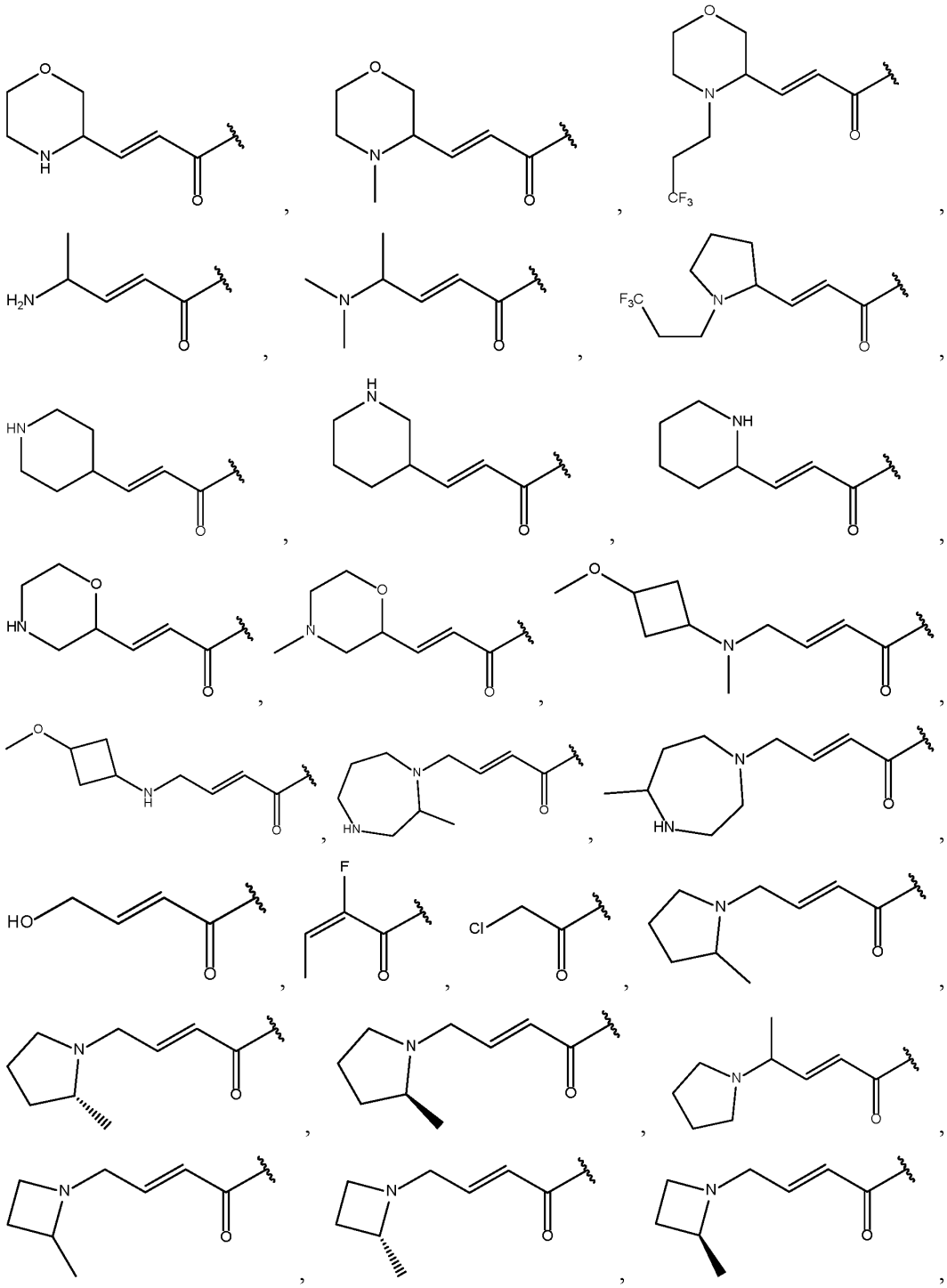
[0337] In some embodiments, each R_{2h} independently is C_1-C_6 alkyl.

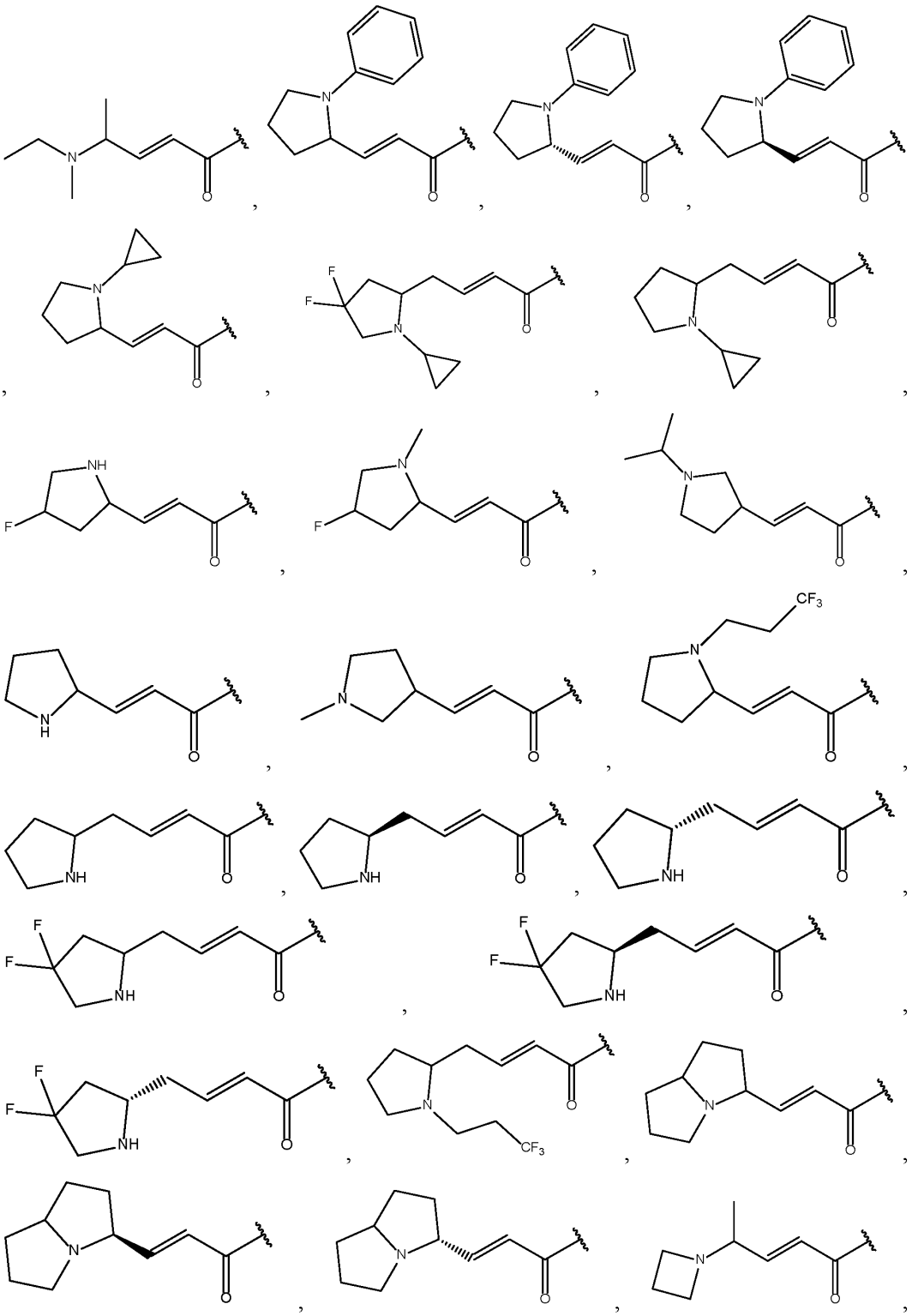
[0338] In some embodiments, each R_{2h} independently is C_2-C_6 alkenyl.

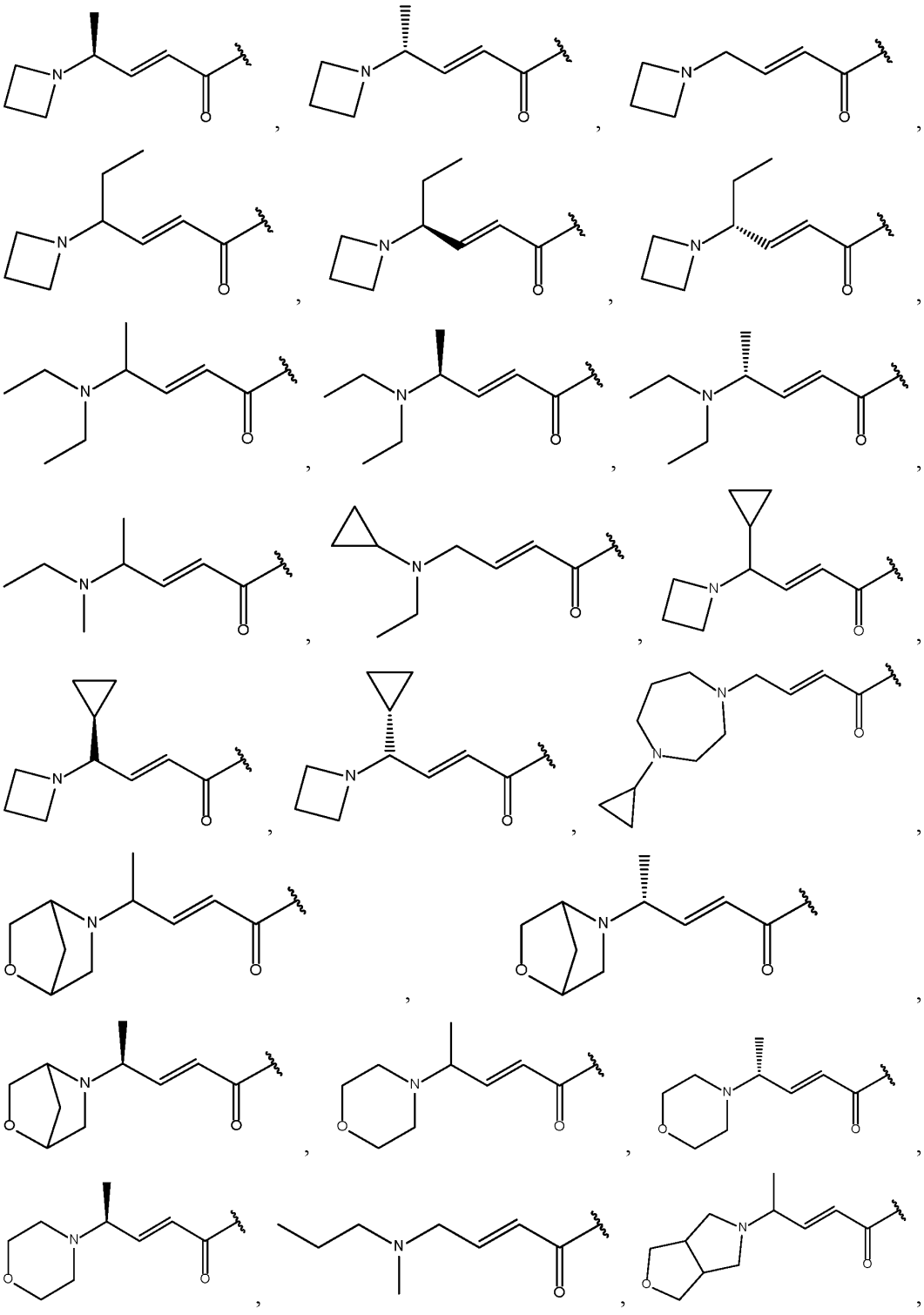
[0339] In some embodiments, each R_{2h} independently is C_2-C_6 alkynyl.

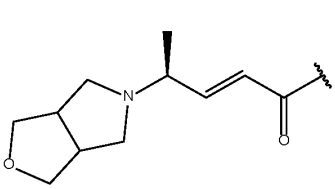
[0340] In some embodiments, each R_{2h} independently is C_1-C_6 haloalkyl.

[0341] In some embodiments, R_2 is , , , , ,





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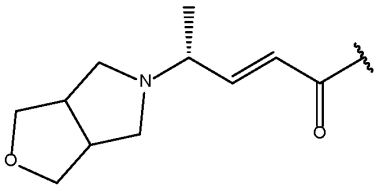
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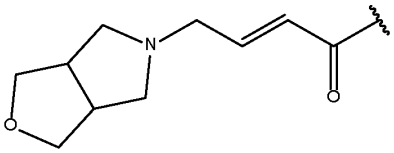
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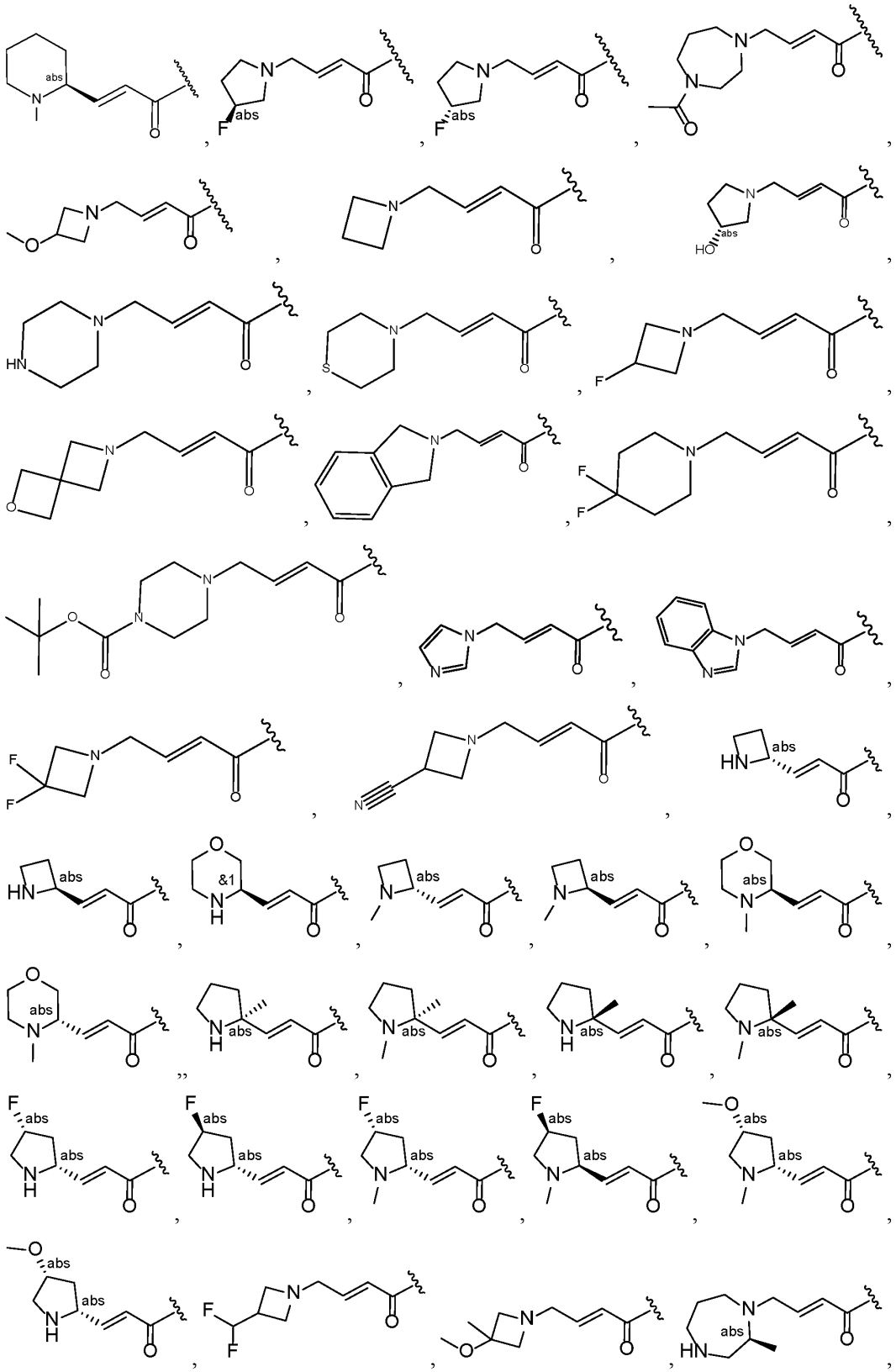

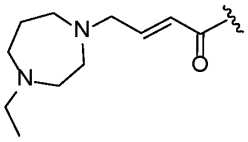
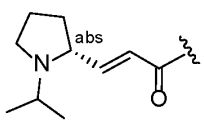
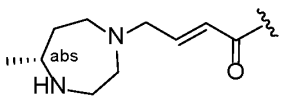

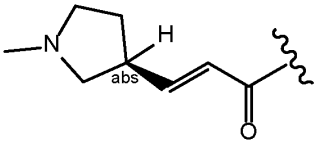
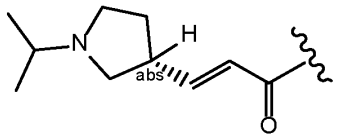
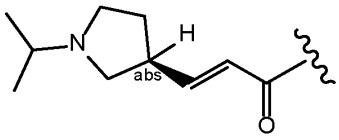
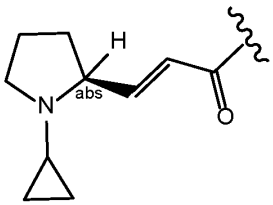
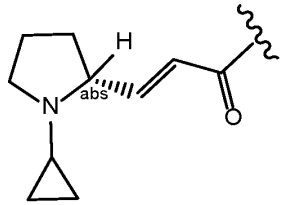
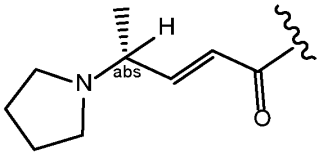
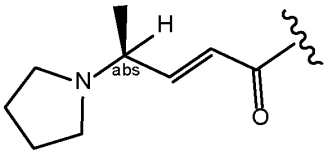
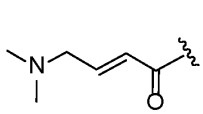
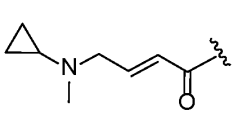
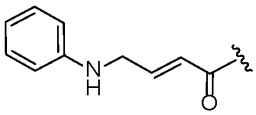
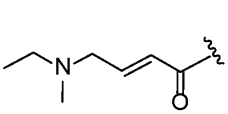
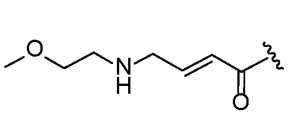
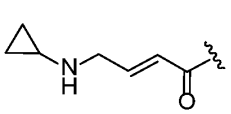
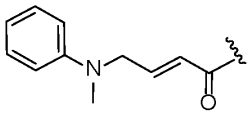
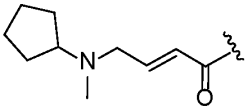
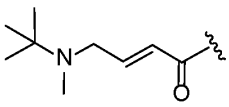
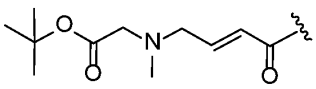
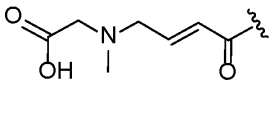
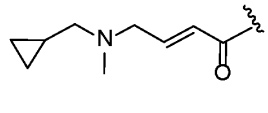
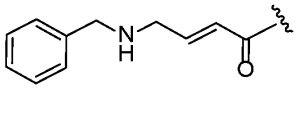
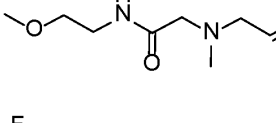
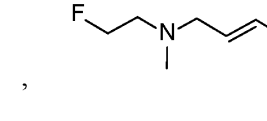
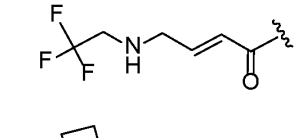
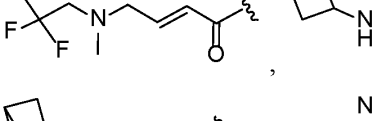
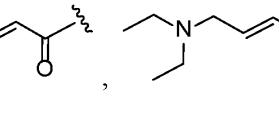
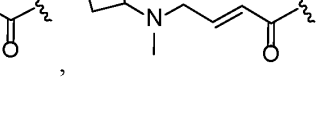
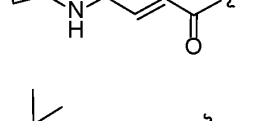
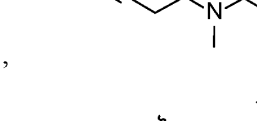
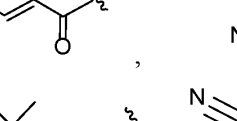
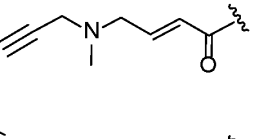
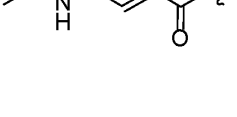
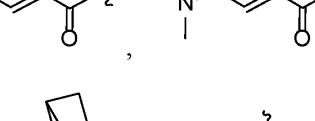
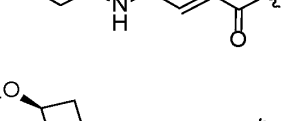
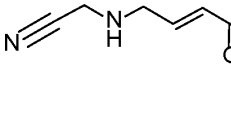
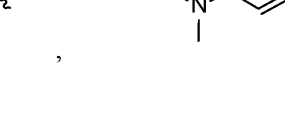
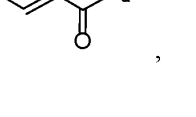
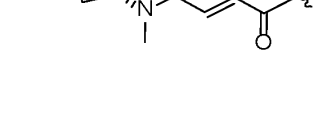

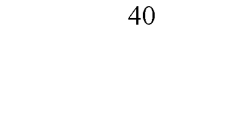

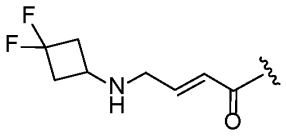
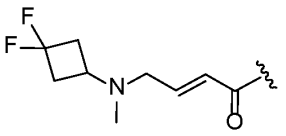
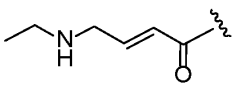
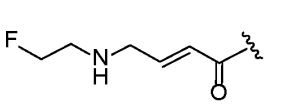
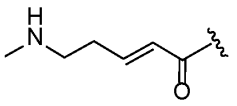
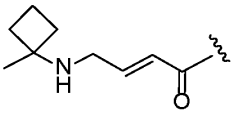
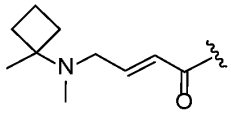
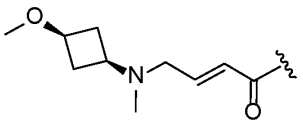
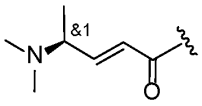
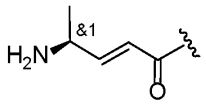
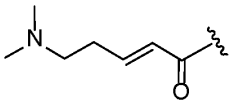
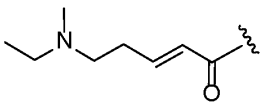
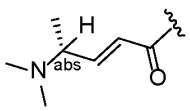
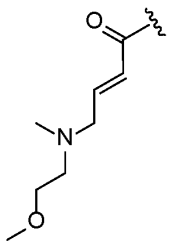
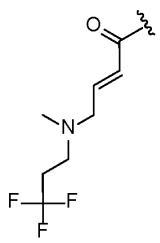
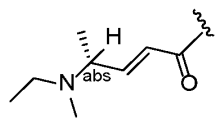
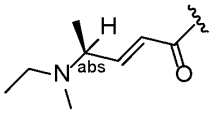
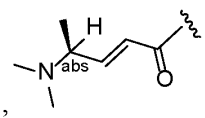
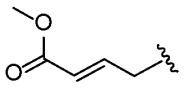
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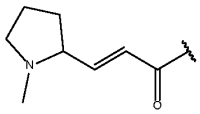
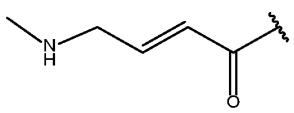
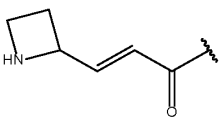
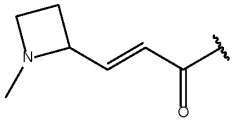
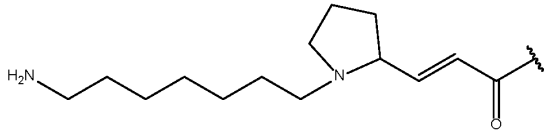
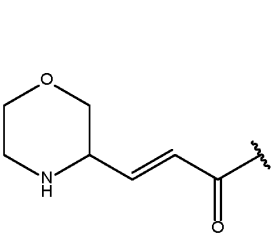
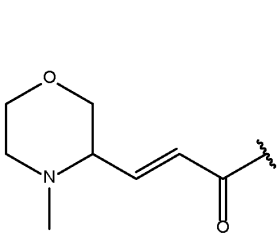
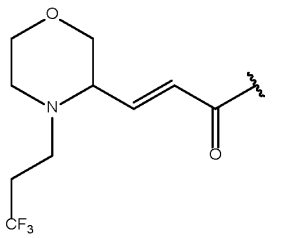
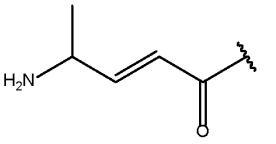
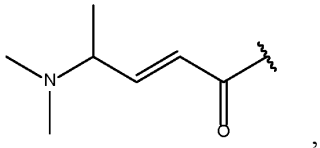
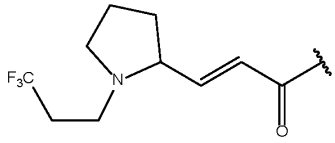
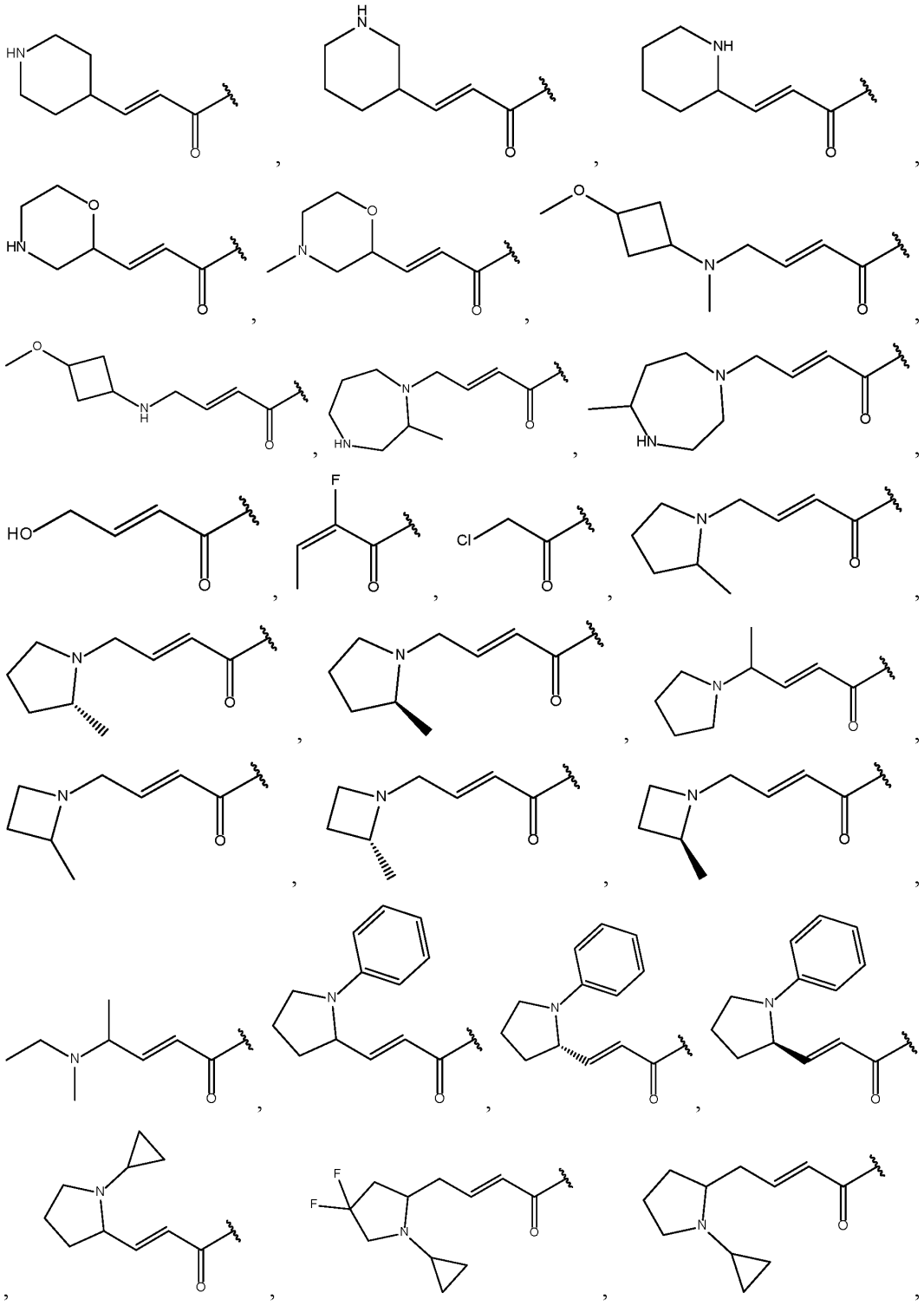
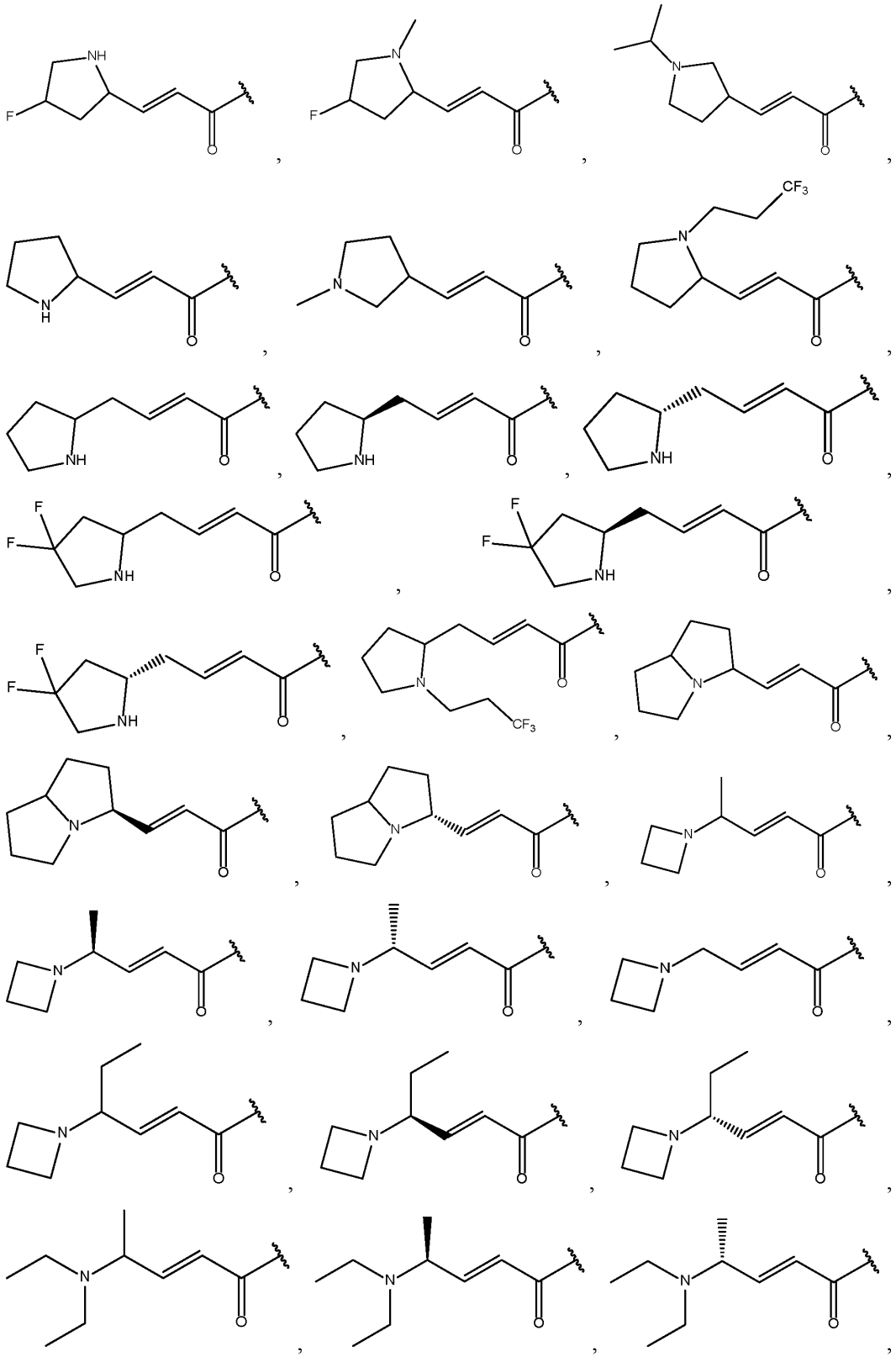
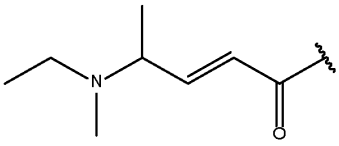
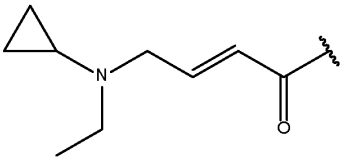
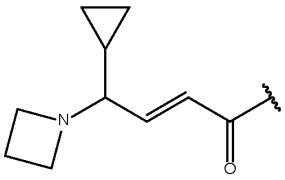
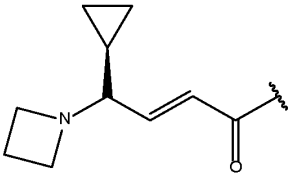
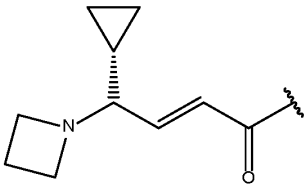
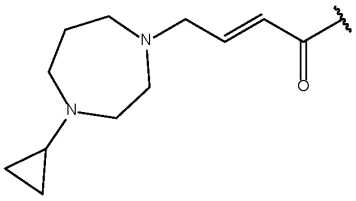
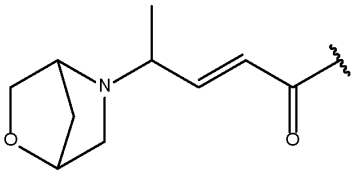
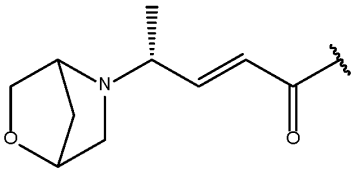
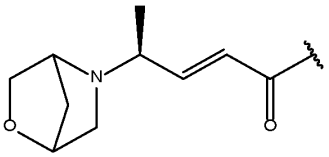
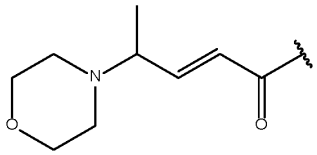
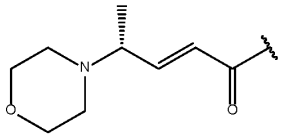
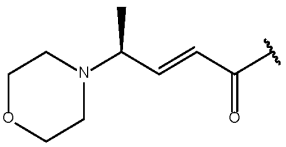
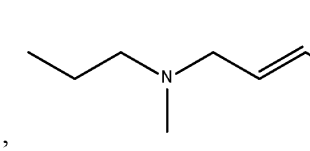
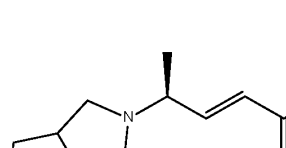
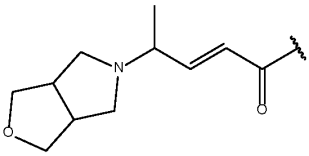
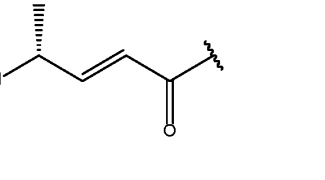
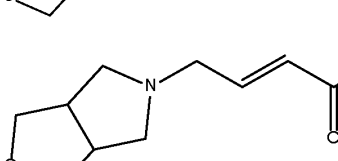
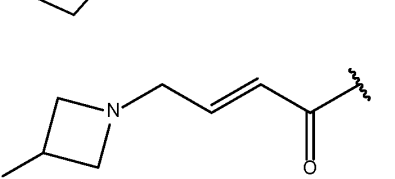
[0342] In some embodiments, R_2 is , , , , , , , , , , .





, , ,
, , ,
, ,
, , ,
, ,
, , ,
, , ,
, ,
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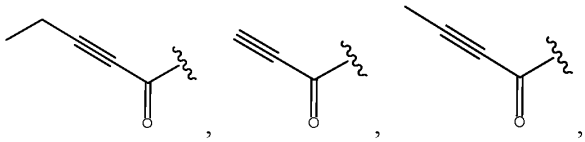
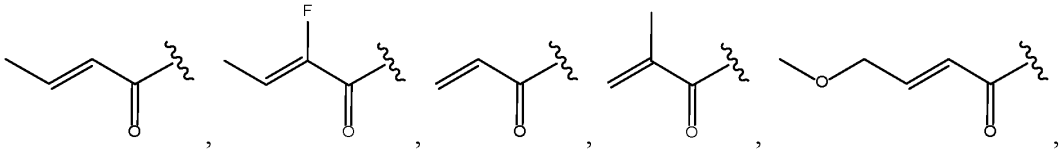
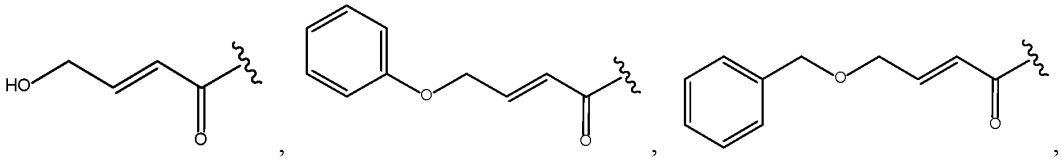
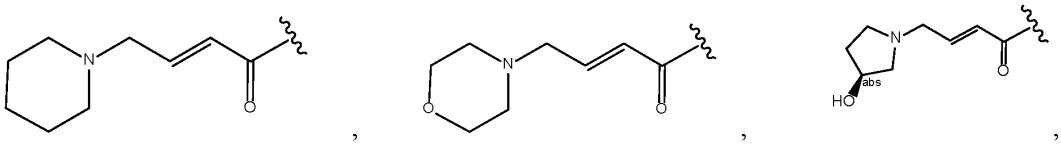
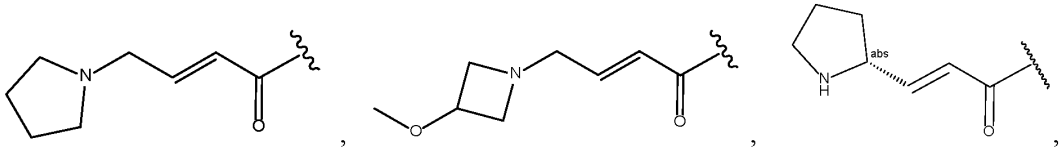
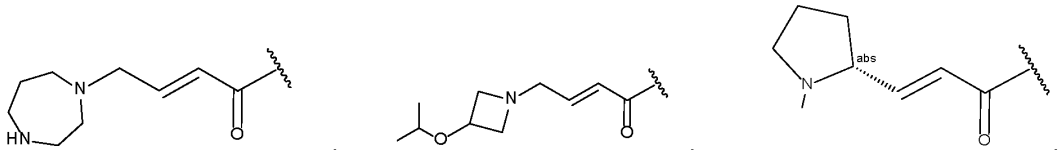
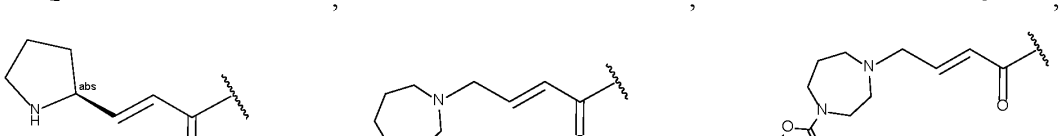
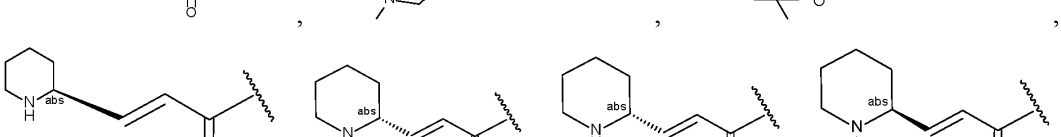
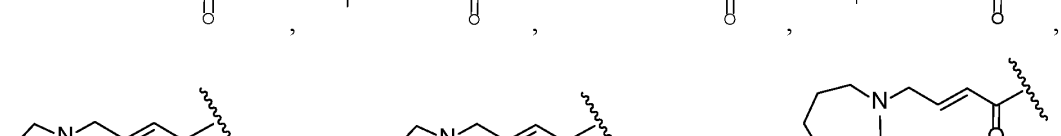
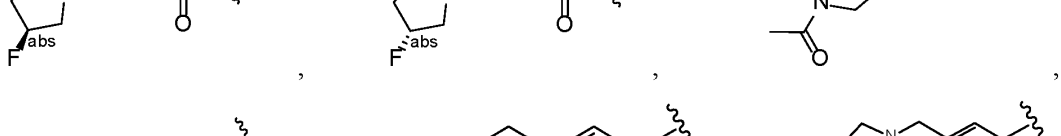
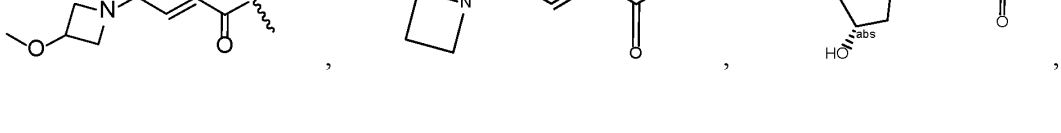
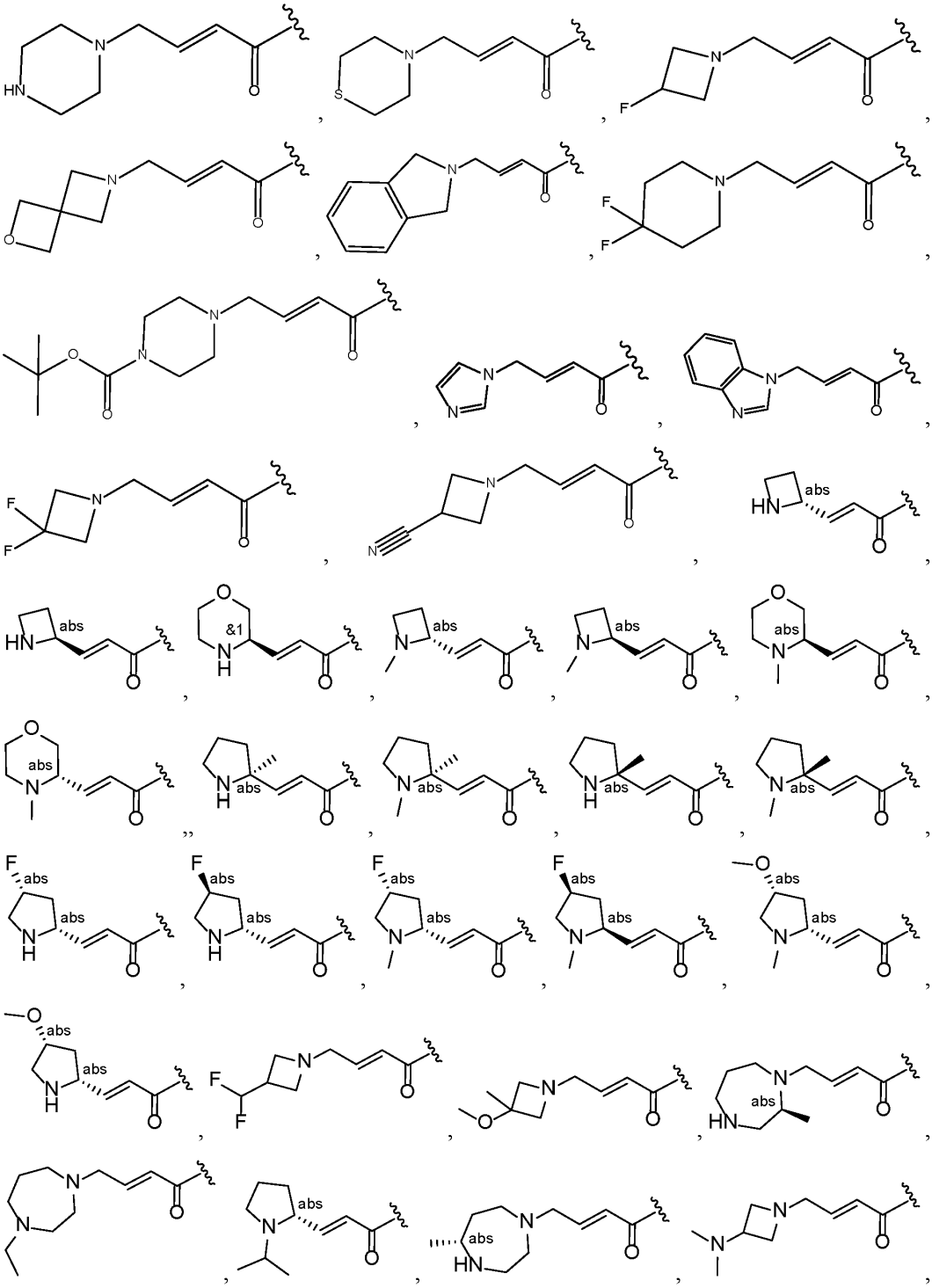
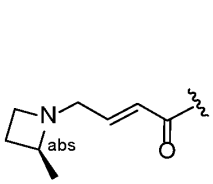
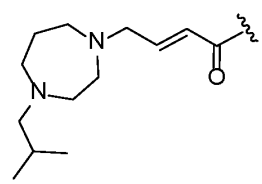
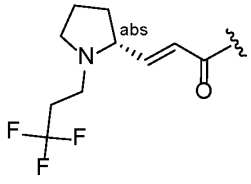
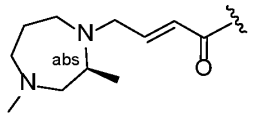
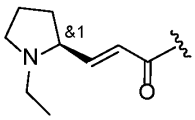
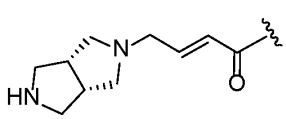
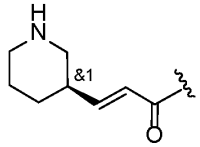
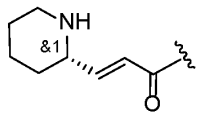
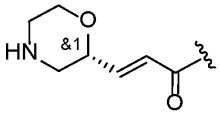
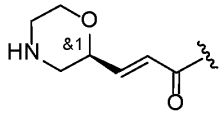
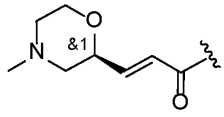
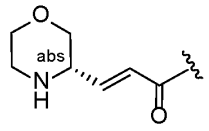
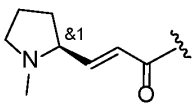
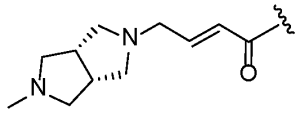
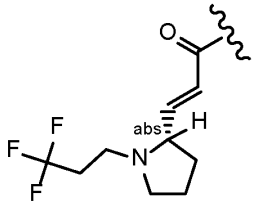
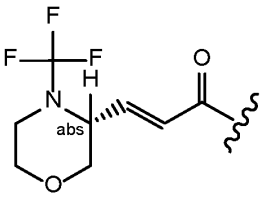
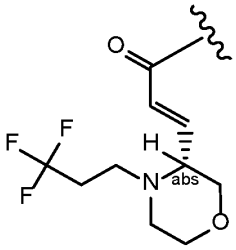
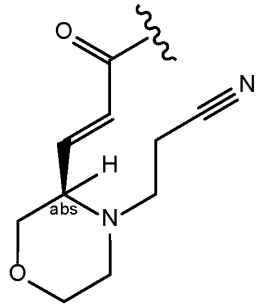
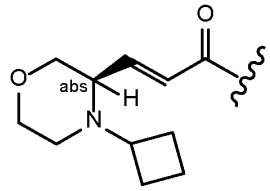
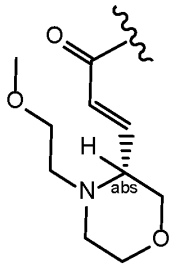
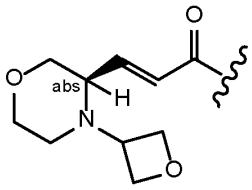
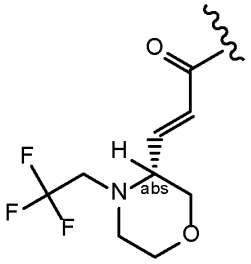
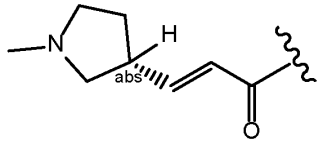
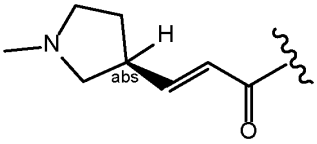
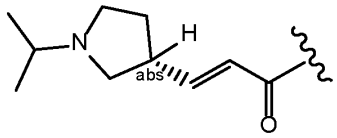
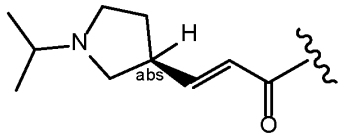
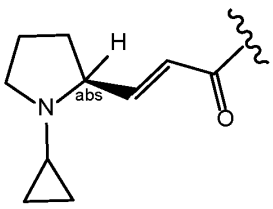
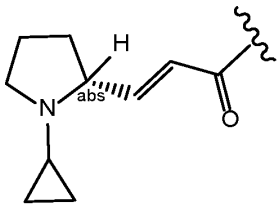
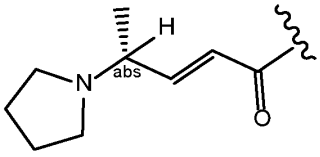
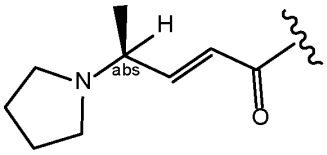
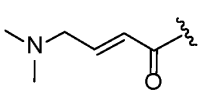
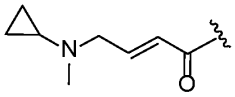
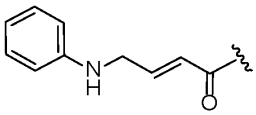
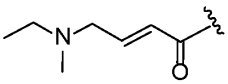
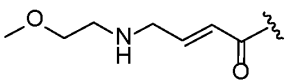
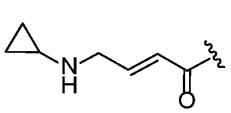
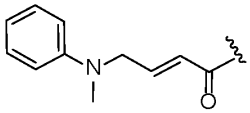
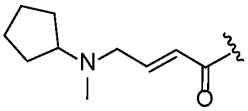
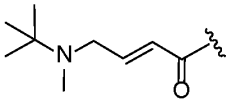
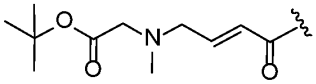
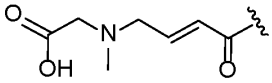
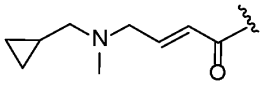
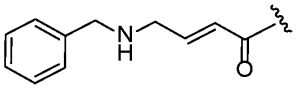
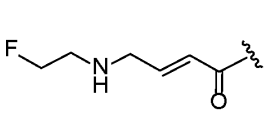
[0343] In some embodiments, R_2 is , , , , , , , , , , , ,

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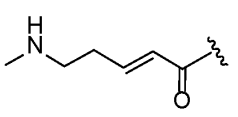
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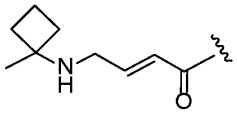
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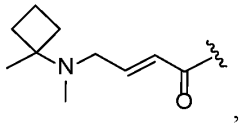
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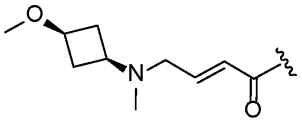
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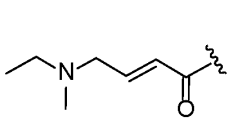
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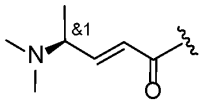
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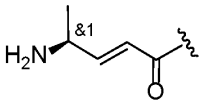
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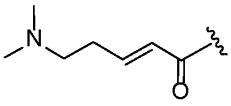
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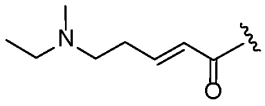
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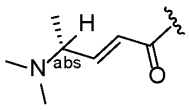
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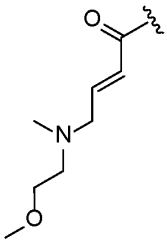
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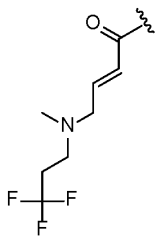
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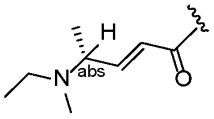
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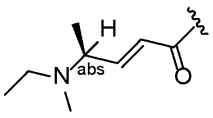
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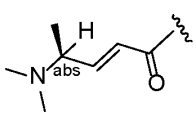
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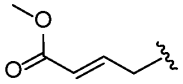
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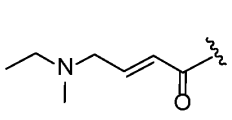
[0344] In some embodiments, R_2 is

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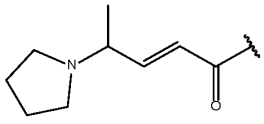
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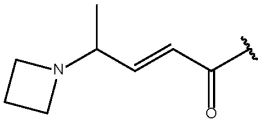
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[0345] In some embodiments, R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[0346] In some embodiments, R_3 is C_1-C_6 alkyl.

[0347] In some embodiments, R_3 is C_2-C_6 alkenyl.

[0348] In some embodiments, R_3 is C_2-C_6 alkynyl.

[0349] In some embodiments, R_3 is C_1-C_6 haloalkyl.

[0350] In some embodiments, R_3 is C_3-C_{10} cycloalkyl or 5- to 10-membered heterocyclyl.

[0351] In some embodiments, R_3 is C_3-C_{10} cycloalkyl.

[0352] In some embodiments, R_3 is 5- to 10-membered heterocyclyl.

[0353] In some embodiments, R_3 is C_1-C_6 alkyl or C_3-C_{10} cycloalkyl.

[0354] In some embodiments, R_3 is $-CH_2-CF_3$, methyl, or cyclopropyl.

[0355] In some embodiments, R_3 is methyl or cyclopropyl.

[0356] In some embodiments, two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle.

[0357] In some embodiments, two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl.

[0358] In some embodiments, two R_3, together with the atoms to which they are attached, form a cyclopentyl.

[0359] In some embodiments, two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl.

[0360] In some embodiments, R_3 is $-CH_2-CF_3$, methyl, or cyclopropyl, or two R_3, together with the atoms to which they are attached, form a cyclopentyl.

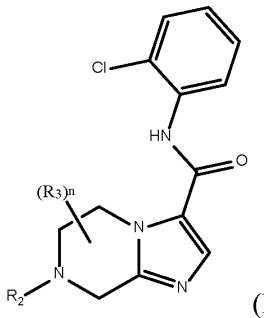
[0361] In some embodiments, R_3 is methyl or cyclopropyl, or two R_3, together with the atoms to which they are attached, form a cyclopentyl.

[0362] In some embodiments, n is 0 or 1.

[0363] In some embodiments, n is 0, 1, or 2.

[0364] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

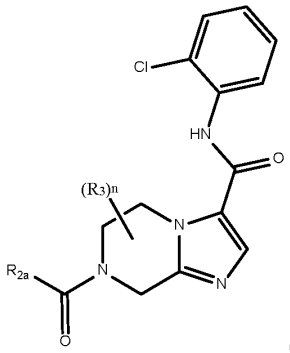
[0365] In some embodiments, the compound of Formula (II) is of Formula (II-a):



(II-a),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

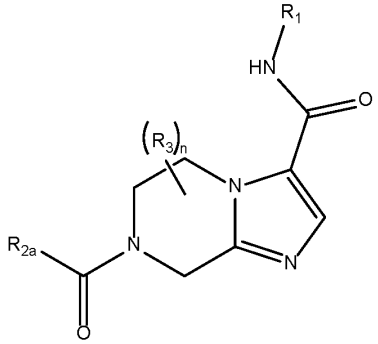
[0366] In some embodiments, the compound of Formula (II) is of Formula (II-b):



(II-b),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

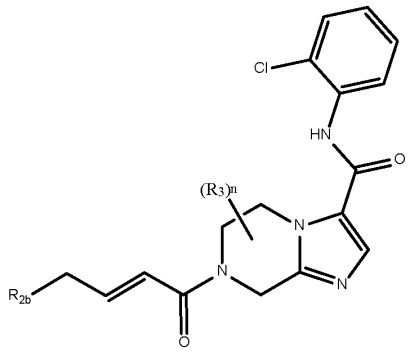
[0367] In some embodiments, the compound of Formula (II) is of Formula (II-b'):



(II-b'),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

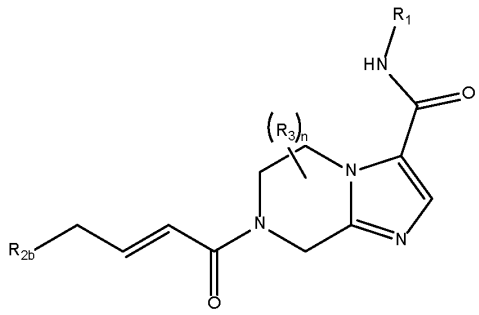
[0368] In some embodiments, the compound of Formula (II) is of Formula (II-c):



(II-c),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

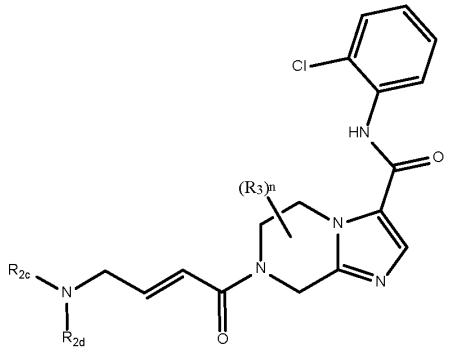
[0369] In some embodiments, the compound of Formula (II) is of Formula (II-c'):



(II-c'),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

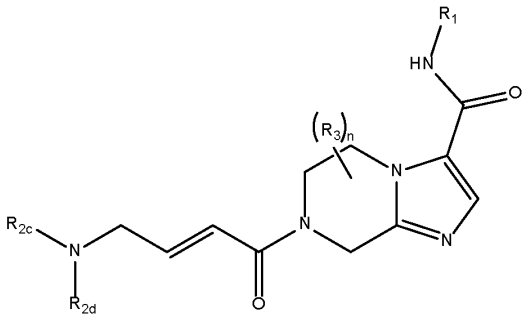
[0370] In some embodiments, the compound of Formula (II) is of Formula (II-d):



(II-d),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0371] In some embodiments, the compound of Formula (II) is of Formula (II-d'):

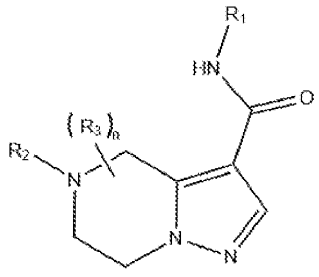


(II-d'),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

Formula (III)

[0372] In some aspects, the present disclosure relates to a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is -C(O)R_{2a};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -$N(R_{2c})(R_{2d})$, -OR_{2c}, -$CO_2(R_{2c})$, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

[0373] In some embodiments, R_1 is C_6-C_{10} aryl substituted with one or more R_{1a}.

[0374] In some embodiments, R_1 is C_6-C_{10} aryl.

[0375] In some embodiments, R_1 is phenyl optionally substituted with one or more R_{1a}.

[0376] In some embodiments, R_1 is phenyl substituted with one or more R_{1a}.

[0377] In some embodiments, R_1 is phenyl substituted with one R_{1a}.

[0378] In some embodiments, R_1 is phenyl substituted with two R_{1a}.

[0379] In some embodiments, R_1 is phenyl substituted with three R_{1a}.

[0380] In some embodiments, each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl.

[0381] In some embodiments, each R_{1a} independently is halo.

[0382] In some embodiments, each R_{1a} independently is F, Cl, Br, or I.

[0383] In some embodiments, each R_{1a} independently is F. In some embodiments, each R_{1a} independently is Cl. In some embodiments, each R_{1a} independently is Br. In some embodiments, each R_{1a} independently is I.

[0384] In some embodiments, each R_{1a} independently is -OH.

[0385] In some embodiments, each R_{1a} independently is C_1-C_6 alkyl.

[0386] In some embodiments, each R_{1a} independently is methyl.

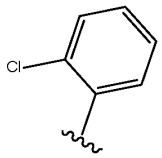
[0387] In some embodiments, each R_{1a} independently is C_2-C_6 alkenyl.

[0388] In some embodiments, each R_{1a} independently is C_2-C_6 alkynyl.

[0389] In some embodiments, each R_{1a} independently is C_1-C_6 haloalkyl.

[0390] In some embodiments, each R_{1a} independently is C_1-C_6 alkoxyl.

[0391] In some embodiments, each R_{1a} independently is methoxy.



[0392] In some embodiments, R_1 is .

[0393] In some embodiments, R_2 is $-C(O)R_{2a}$.

[0394] In some embodiments, R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

[0395] In some embodiments, R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is substituted with one or more R_{2b}.

[0396] In some embodiments, R_{2a} is C_1-C_6 alkyl.

[0397] In some embodiments, R_{2a} is C_1-C_6 alkyl optionally substituted with one or more R_{2b}.

[0398] In some embodiments, R_{2a} is C_1-C_6 alkyl substituted with one or more R_{2b}.

[0399] In some embodiments, R_{2a} is C_2-C_6 alkenyl.

[0400] In some embodiments, R_{2a} is C_2-C_6 alkenyl optionally substituted with one or more R_{2b}.

[0401] In some embodiments, R_{2a} is C_2-C_6 alkenyl substituted with one or more R_{2b}.

[0402] In some embodiments, R_{2a} is C_2-C_6 alkynyl.

[0403] In some embodiments, R_{2a} is C_2-C_6 alkynyl optionally substituted with one or more R_{2b}.

[0404] In some embodiments, R_{2a} is C_2-C_6 alkynyl substituted with one or more R_{2b}.

[0405] In some embodiments, R_{2a} is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}.

[0406] In some embodiments, R_{2a} is , , , , or .

[0407] In some embodiments, each R_{2b} independently is halo.

[0408] In some embodiments, each R_{2b} independently is F, Cl, Br, or I.

[0409] In some embodiments, each R_{2b} independently is F. In some embodiments, each R_{2b} independently is Cl. In some embodiments, each R_{2b} independently is Br. In some embodiments, each R_{2b} independently is I.

[0410] In some embodiments, each R_{2b} independently is $-N(R_{2c})(R_{2d})$, $-OR_{2c}$, or $-CO_2(R_{2c})$.

[0411] In some embodiments, each R_{2b} independently is $-N(R_{2c})(R_{2d})$.

[0412] In some embodiments, each R_{2b} independently is $-OR_{2c}$.

[0413] In some embodiments, each R_{2b} independently is $-CO_2(R_{2c})$.

[0414] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl.

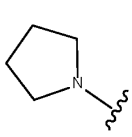
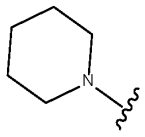
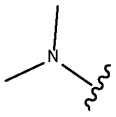
[0415] In some embodiments, each R_{2b} independently is C_3-C_6 cycloalkyl.

[0416] In some embodiments, each R_{2b} independently is 4- to 10-membered heterocyclyl.

[0417] In some embodiments, each R_{2b} independently is C_6-C_{10} aryl.

[0418] In some embodiments, each R_{2b} independently is 5- to 10-membered heteroaryl.

[0419] In some embodiments, each R_{2b} independently is $-N(R_{2c})(R_{2d})$ or 4- to 10-membered heterocyclyl.

[0420] In some embodiments, each R_{2b} independently is , , or .

[0421] In some embodiments, each R_{2c} independently is H.

[0422] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[0423] In some embodiments, each R_{2c} independently is C_1-C_6 alkyl.

[0424] In some embodiments, each R_{2c} independently is methyl.

[0425] In some embodiments, each R_{2c} independently is C_2-C_6 alkenyl.

[0426] In some embodiments, each R_{2c} independently is C_2-C_6 alkynyl.

[0427] In some embodiments, each R_{2c} independently is C_1-C_6 haloalkyl.

[0428] In some embodiments, each R_{2d} independently is H.

[0429] In some embodiments, each R_{2d} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

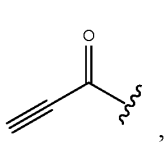
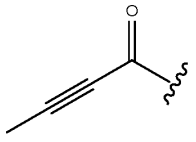
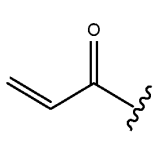
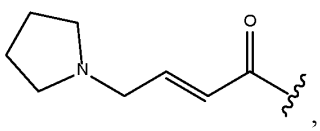
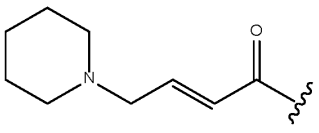
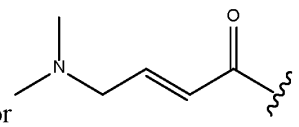
[0430] In some embodiments, each R_{2d} independently is C_1-C_6 alkyl.

[0431] In some embodiments, each R_{2d} independently is methyl.

[0432] In some embodiments, each R_{2d} independently is C_2-C_6 alkenyl.

[0433] In some embodiments, each R_{2d} independently is C_2-C_6 alkynyl.

[0434] In some embodiments, each R_{2d} independently is C_1-C_6 haloalkyl.

[0435] In some embodiments, R_2 is , , , , , or .

[0436] In some embodiments, R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl.

[0437] In some embodiments, R_3 is C_1-C_6 alkyl.

[0438] In some embodiments, R_3 is C_2-C_6 alkenyl.

[0439] In some embodiments, R_3 is C_2-C_6 alkynyl.

[0440] In some embodiments, R_3 is C_1-C_6 haloalkyl.

[0441] In some embodiments, R_3 is C_3-C_{10} cycloalkyl or 5- to 10-membered heterocyclyl.

[0442] In some embodiments, R_3 is C_3-C_{10} cycloalkyl.

[0443] In some embodiments, R_3 is 5- to 10-membered heterocyclyl.

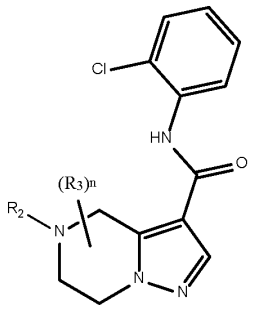
[0444] In some embodiments, R_3 is C_1-C_6 alkyl or C_3-C_{10} cycloalkyl.

[0445] In some embodiments, n is 0 or 1.

[0446] In some embodiments, n is 0, 1, or 2.

[0447] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

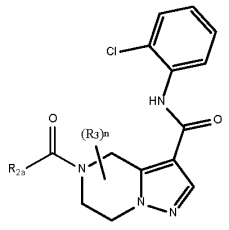
[0448] In some embodiments, the compound of Formula (III) is of Formula (III-a):



(III-a),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

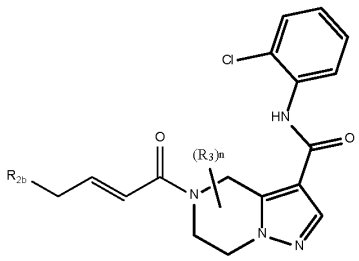
[0449] In some embodiments, the compound of Formula (III) is of Formula (III-b):



(III-b),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0450] In some embodiments, the compound of Formula (III) is of Formula (III-c):



(III-c),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0451] In some embodiments, the compound is selected from the compounds described in Tables 1, 2, and 3 and prodrugs and pharmaceutically acceptable salts thereof.

[0452] In some embodiments, the compound is selected from the compounds described in Tables 1, 2, and 3 and pharmaceutically acceptable salts thereof.

[0453] In some embodiments, the compound is selected from the compounds described in Tables 1, 2, and 3.

[0454] In some embodiments, the compound is selected from the compounds described in Table 1 and prodrugs and pharmaceutically acceptable salts thereof.

[0455] In some embodiments, the compound is selected from the compounds described in Table 1 and pharmaceutically acceptable salts thereof.

[0456] In some embodiments, the compound is selected from the compounds described in Table 1.

[0457] In some embodiments, the compound is selected from the compounds described in Table 2 and prodrugs and pharmaceutically acceptable salts thereof.

[0458] In some embodiments, the compound is selected from the compounds described in Table 2 and pharmaceutically acceptable salts thereof.

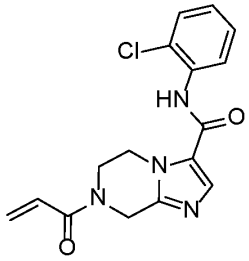
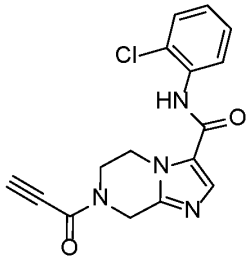
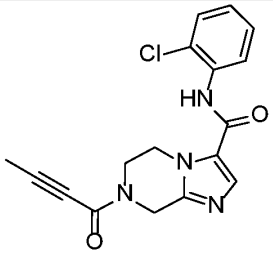
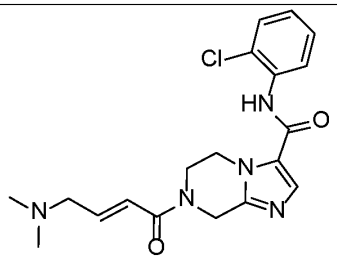
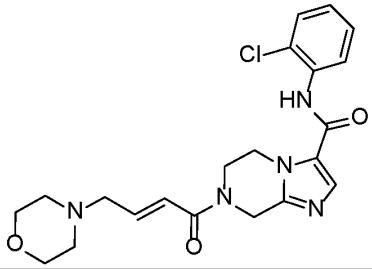
[0459] In some embodiments, the compound is selected from the compounds described in Table 2.

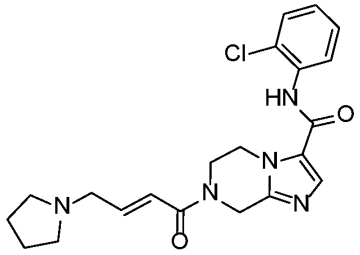
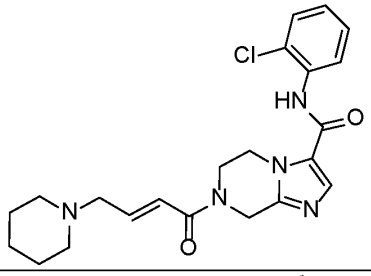
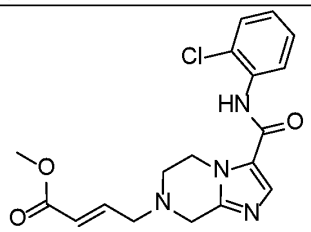
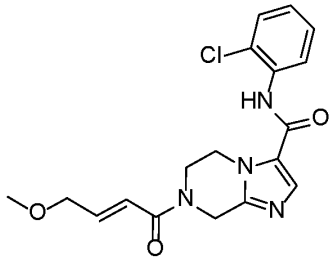
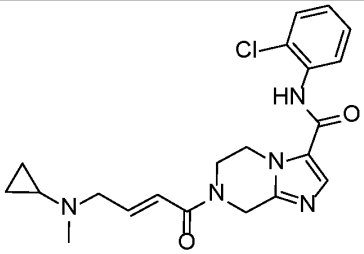
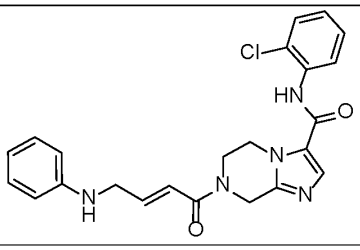
[0460] In some embodiments, the compound is selected from the compounds described in Table 3 and prodrugs and pharmaceutically acceptable salts thereof.

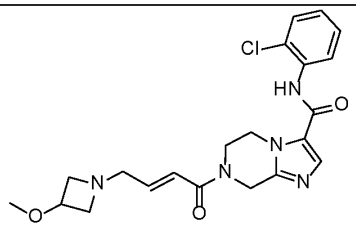
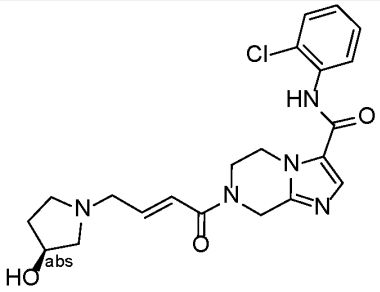
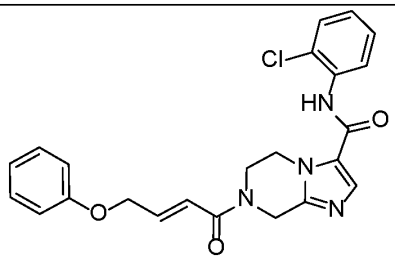
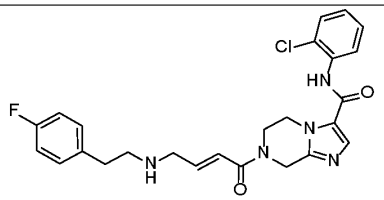
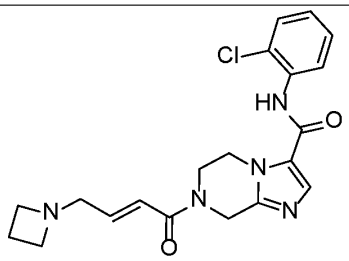
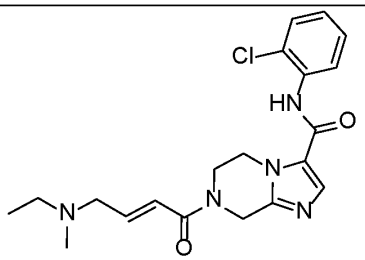
[0461] In some embodiments, the compound is selected from the compounds described in Table 3 and pharmaceutically acceptable salts thereof.

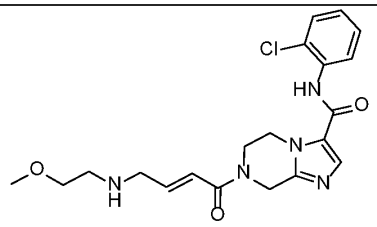
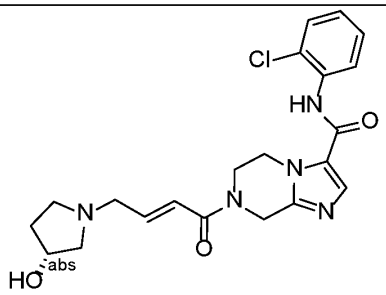
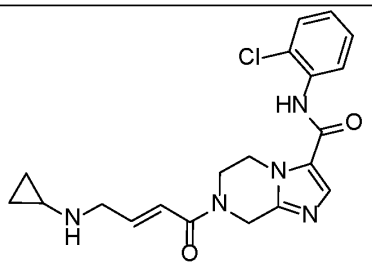
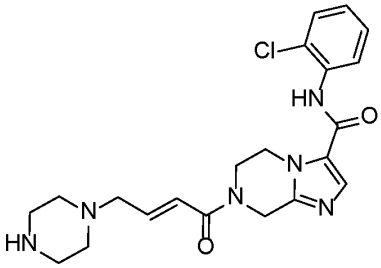
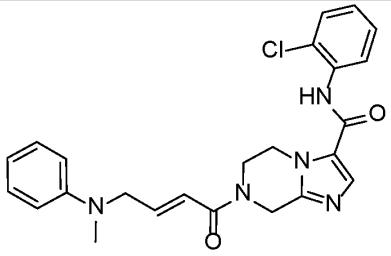
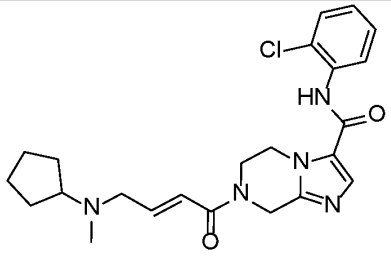
[0462] In some embodiments, the compound is selected from the compounds described in Table 3.

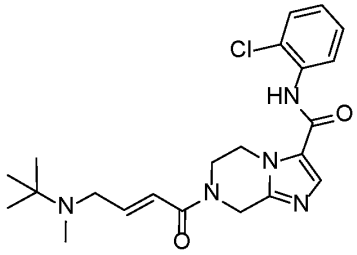
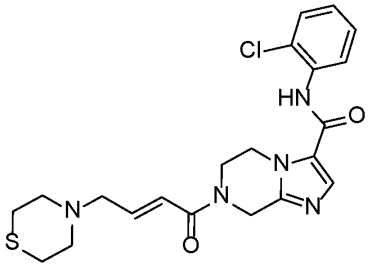
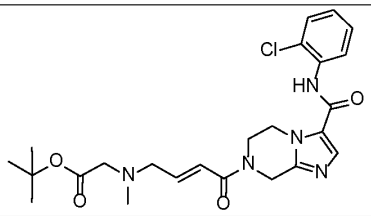
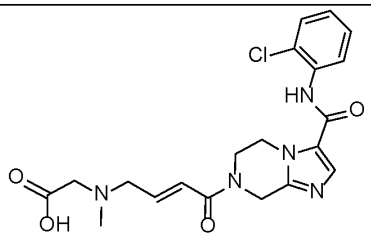
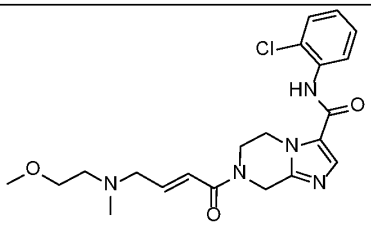
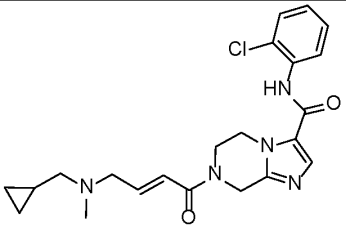
Table 1.

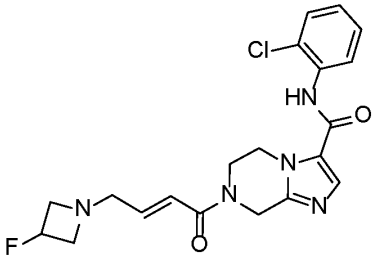
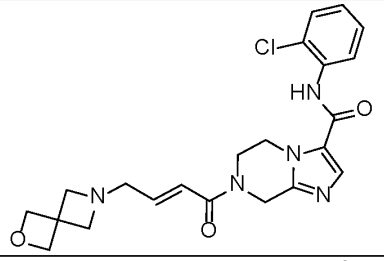
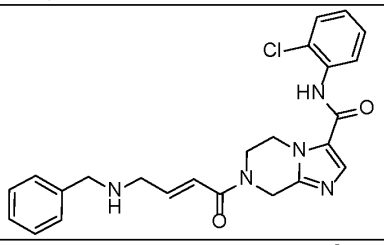
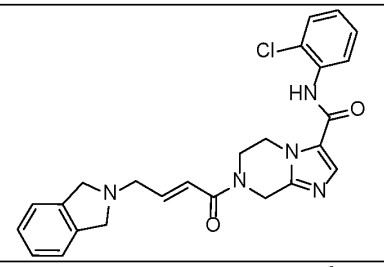
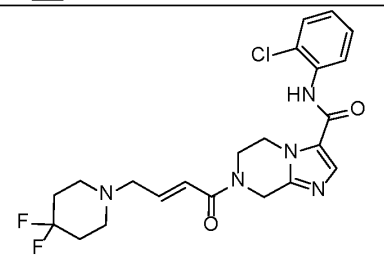
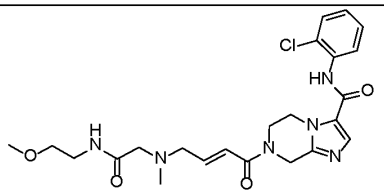
Compound No.	Structure	Compound Name
1		7-acryloyl-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
2		N-(2-chlorophenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
3		7-(but-2-ynoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
4		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
5		(E)-N-(2-chlorophenyl)-7-(4-morpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

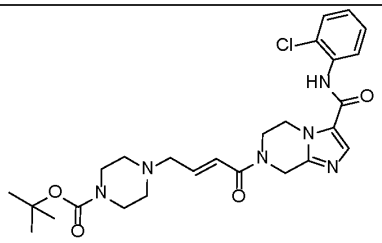
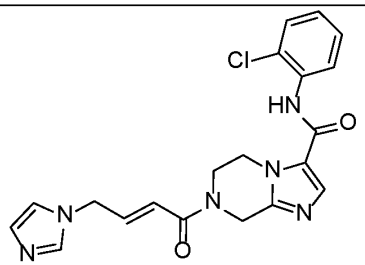
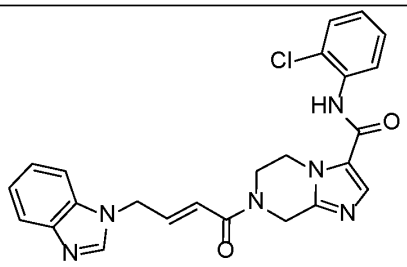
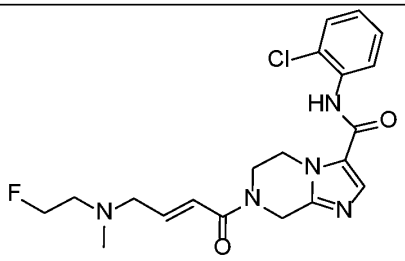
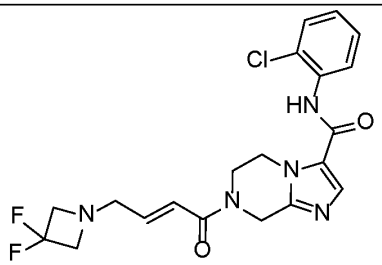
Compound No.	Structure	Compound Name
6		(E)-N-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
7		(E)-N-(2-chlorophenyl)-7-(4-(piperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
8		methyl (E)-4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)but-2-enoate
9		(E)-N-(2-chlorophenyl)-7-(4-methoxybut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
10		(E)-N-(2-chlorophenyl)-7-(4-(cyclopropyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
11		(E)-N-(2-chlorophenyl)-7-(4-(phenylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

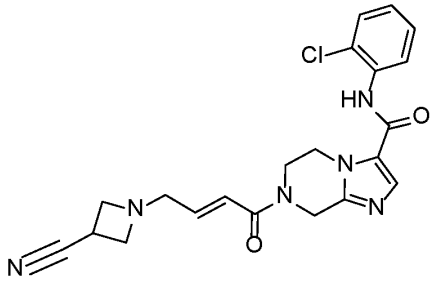
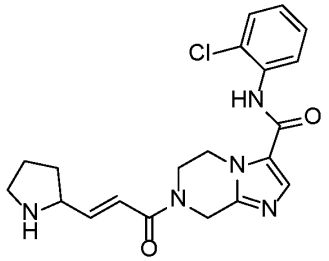
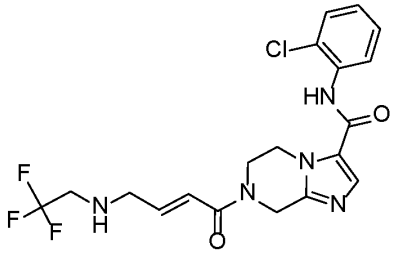
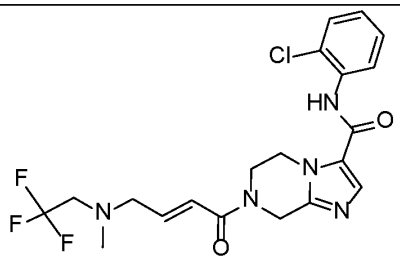
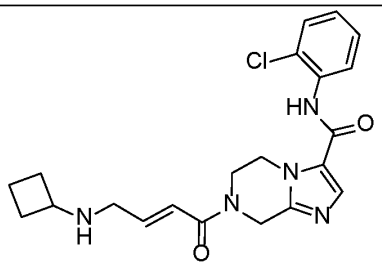
Compound No.	Structure	Compound Name
12		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
13		(S,E)-N-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
14		(E)-N-(2-chlorophenyl)-7-(4-phenoxybut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
15		(E)-N-(2-chlorophenyl)-7-(4-((4-fluorophenethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
16		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
17		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

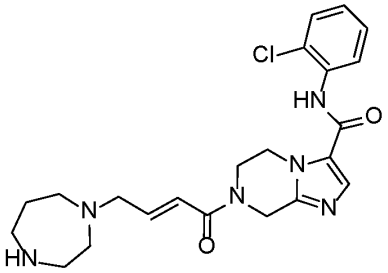
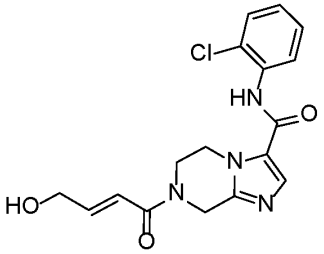
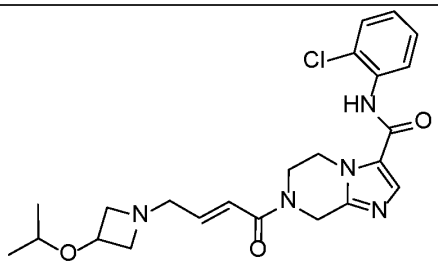
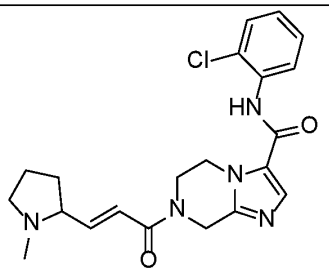
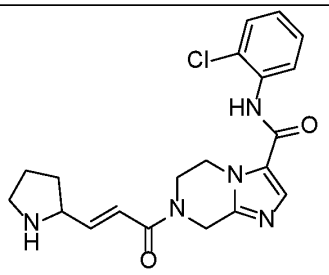
Compound No.	Structure	Compound Name
18		(E)-N-(2-chlorophenyl)-7-(4-((2-methoxyethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
19		(R,E)-N-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
20		(E)-N-(2-chlorophenyl)-7-(4-(cyclopropylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
21		(E)-N-(2-chlorophenyl)-7-(4-(piperazin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
22		(E)-N-(2-chlorophenyl)-7-(4-(methyl(phenyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
23		(E)-N-(2-chlorophenyl)-7-(4-(cyclopentyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

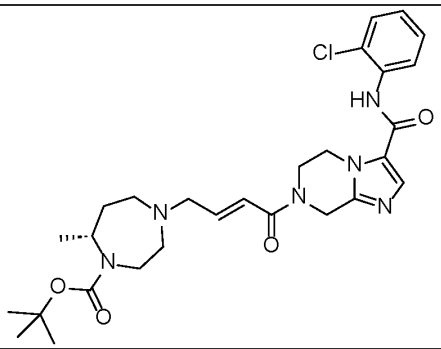
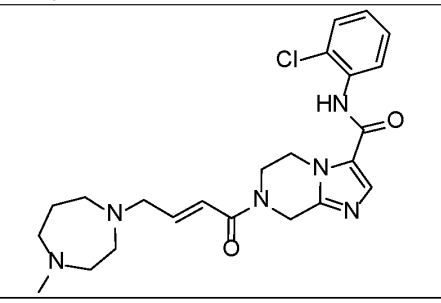
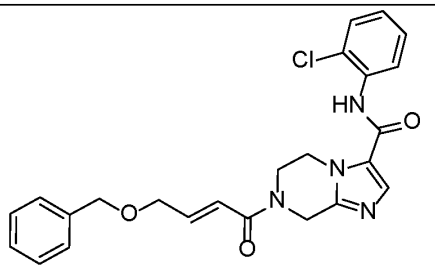
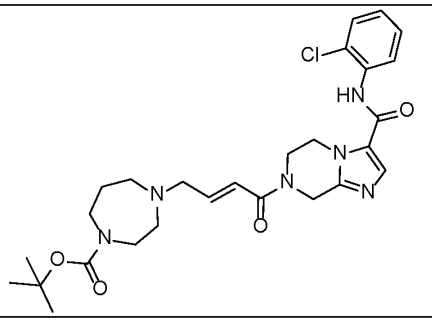
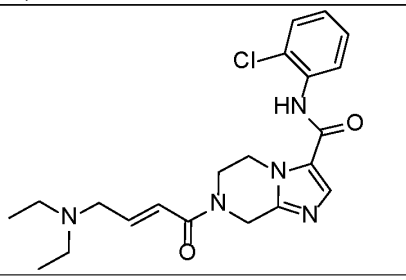
Compound No.	Structure	Compound Name
24		(E)-7-(4-(tert-butyl(methyl)amino)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
25		(E)-N-(2-chlorophenyl)-7-(4-thiomorpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
26		tert-butyl (E)-N-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-oxobut-2-en-1-yl)-N-methylglycinate
27		(E)-N-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-oxobut-2-en-1-yl)-N-methylglycine
28		(E)-N-(2-chlorophenyl)-7-(4-((2-methoxyethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
29		(E)-N-(2-chlorophenyl)-7-(4-((cyclopropylmethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

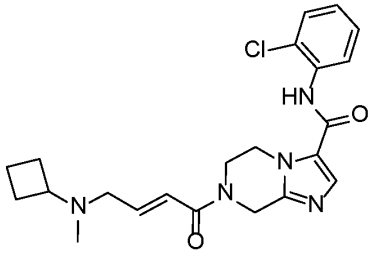
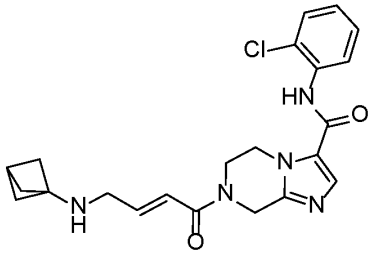
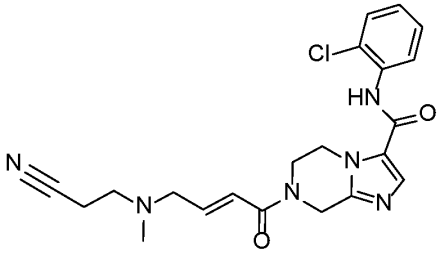
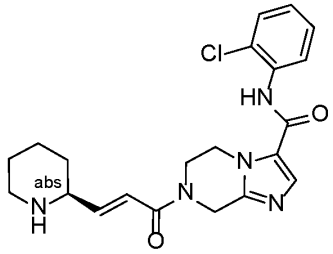
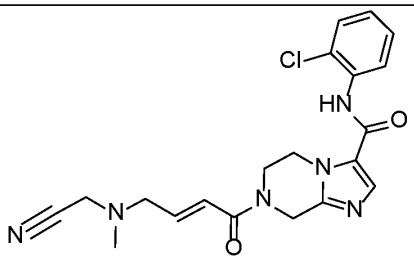
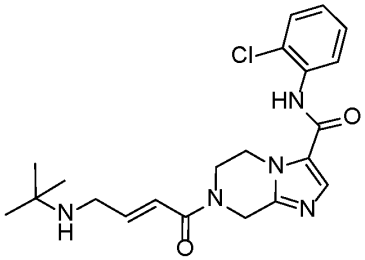
Compound No.	Structure	Compound Name
30		(E)-N-(2-chlorophenyl)-7-(4-(3-fluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
31		(E)-7-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
32		(E)-7-(4-(benzylamino)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
33		(E)-N-(2-chlorophenyl)-7-(4-(isoindolin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
34		(E)-N-(2-chlorophenyl)-7-(4-(4,4-difluoropiperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
35		(E)-N-(2-chlorophenyl)-7-(4-((2-((2-methoxyethyl)amino)-2-oxoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

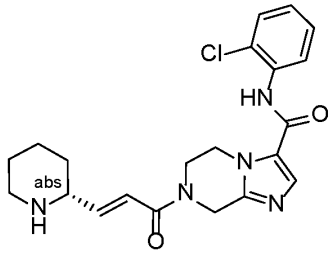
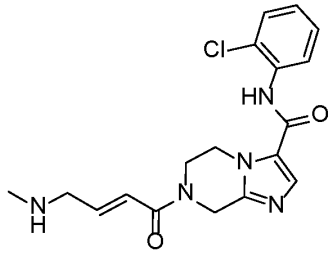
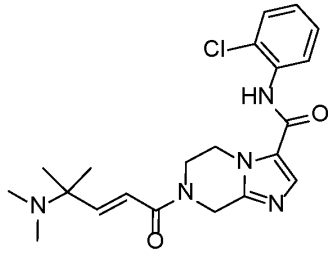
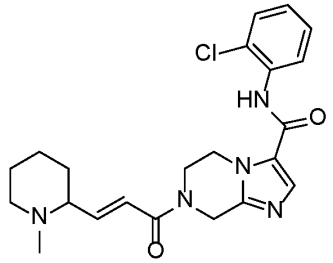
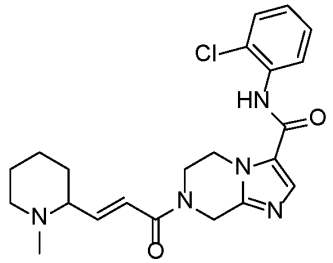
Compound No.	Structure	Compound Name
36		tert-butyl (E)-4-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-oxobut-2-en-1-yl)piperazine-1-carboxylate
37		(E)-7-(4-(1H-imidazol-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
38		(E)-7-(4-(1H-benzo[d]imidazol-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
39		(E)-N-(2-chlorophenyl)-7-(4-((2-fluoroethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
40		(E)-N-(2-chlorophenyl)-7-(4-(3,3-difluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

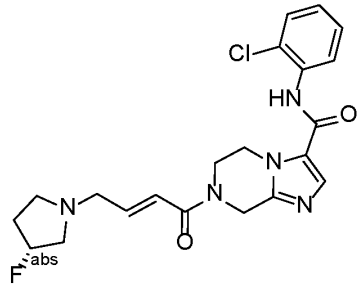
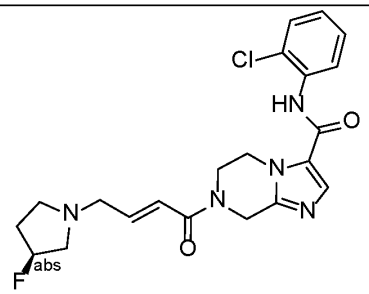
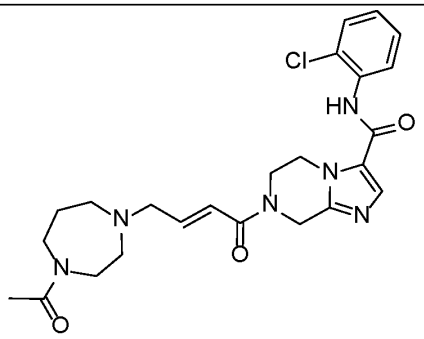
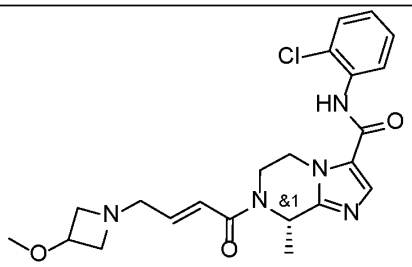
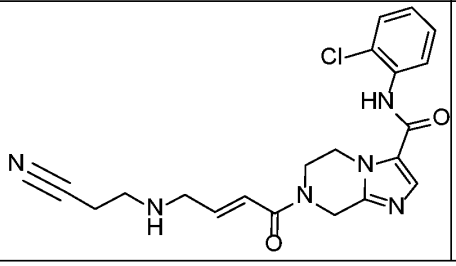
Compound No.	Structure	Compound Name
41		(E)-N-(2-chlorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
42		(E)-N-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
43		(E)-N-(2-chlorophenyl)-7-(4-((2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
44		(E)-N-(2-chlorophenyl)-7-(4-(methyl(2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
45		(E)-N-(2-chlorophenyl)-7-(4-(cyclobutylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

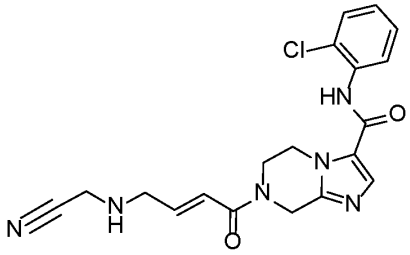
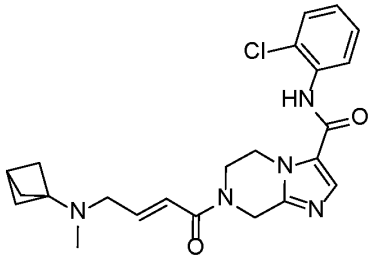
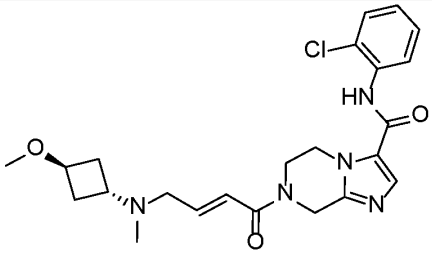
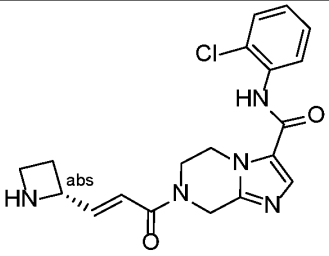
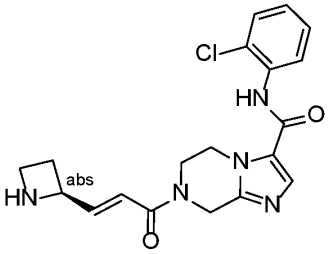
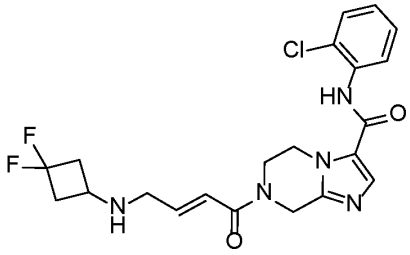
Compound No.	Structure	Compound Name
46		(E)-7-(4-(1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
47		(E)-N-(2-chlorophenyl)-7-(4-hydroxybut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
48		(E)-N-(2-chlorophenyl)-7-(4-(3-isopropoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
49		(E)-N-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
50		(E)-N-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

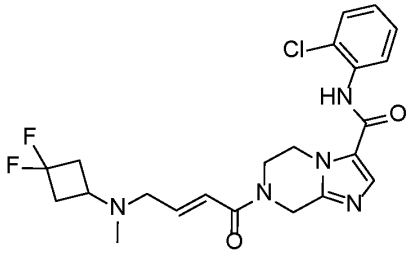
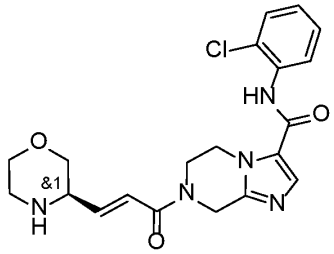
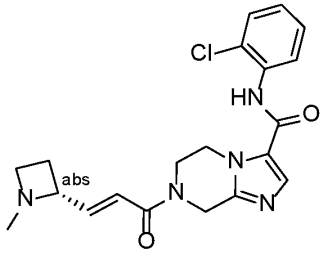
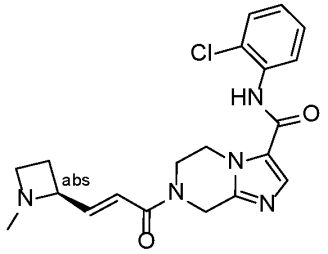
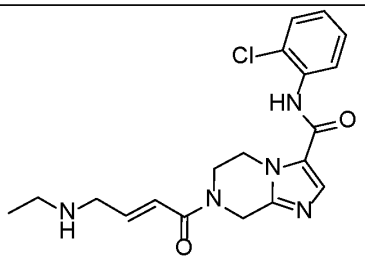
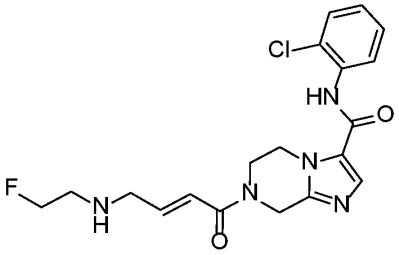
Compound No.	Structure	Compound Name
51		tert-butyl (7R)-4-[(E)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-7-methyl-1,4-diazepane-1-carboxylate
52		(E)-N-(2-chlorophenyl)-7-(4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
53		(E)-7-(4-(benzyloxy)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
54		tert-butyl (E)-4-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-oxobut-2-en-1-yl)-1,4-diazepane-1-carboxylate
55		(E)-N-(2-chlorophenyl)-7-(4-(diethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

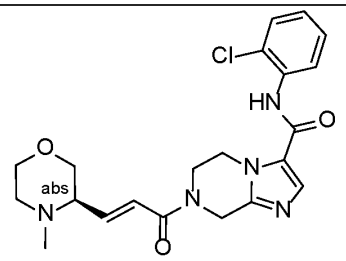
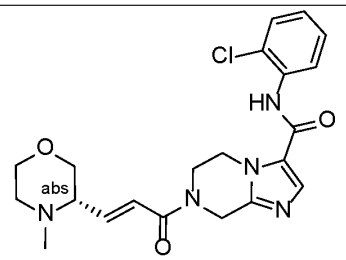
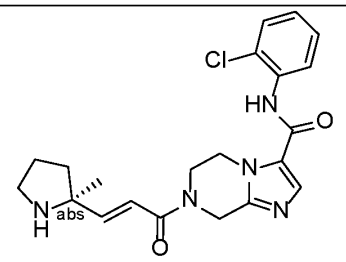
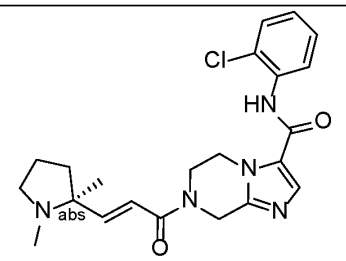
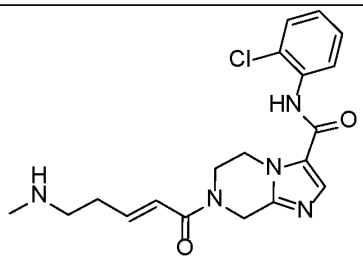
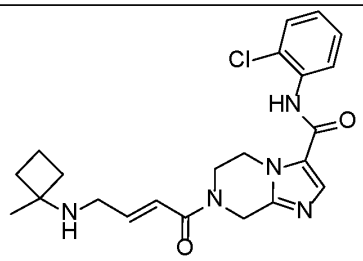
Compound No.	Structure	Compound Name
56		(E)-N-(2-chlorophenyl)-7-(4-(cyclobutyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
57		(E)-7-(4-(bicyclo[1.1.1]pentan-1-ylamino)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
58		(E)-N-(2-chlorophenyl)-7-(4-((2-cyanoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
59		(S,E)-N-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
60		(E)-N-(2-chlorophenyl)-7-(4-((cyanomethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
61		(E)-7-(4-(tert-butylamino)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

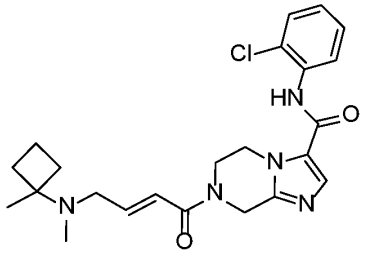
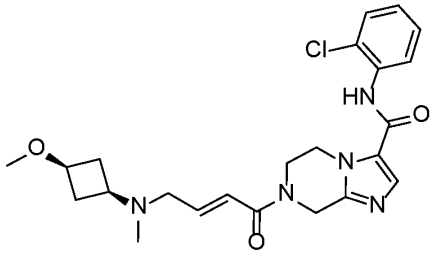
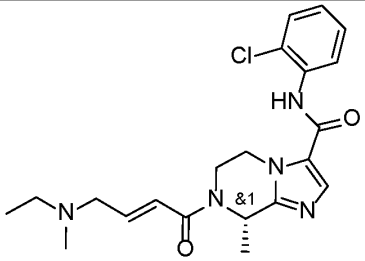
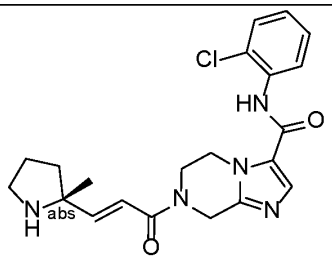
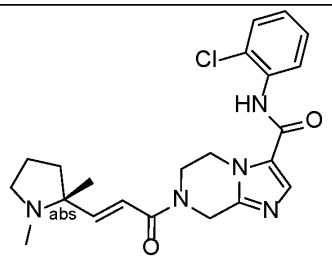
Compound No.	Structure	Compound Name
62		(R,E)-N-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
63		(E)-N-(2-chlorophenyl)-7-(4-(methylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
64		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)-4-methylpent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
65		(E)-N-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
66		(E)-N-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

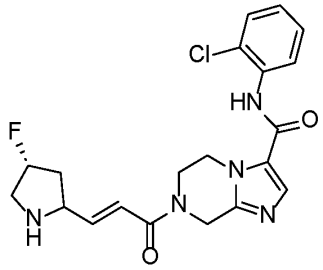
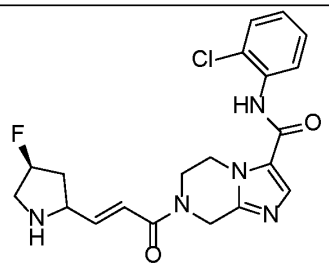
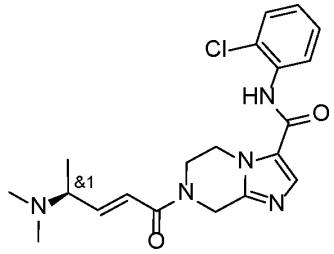
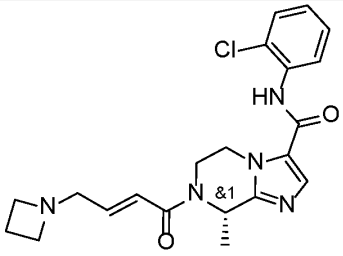
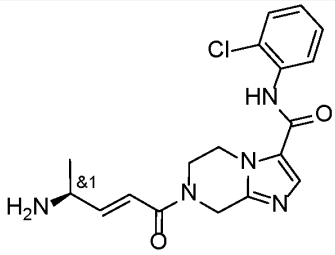
Compound No.	Structure	Compound Name
67		(R,E)-N-(2-chlorophenyl)-7-(4-(3-fluoropyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
68		(S,E)-N-(2-chlorophenyl)-7-(4-(3-fluoropyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
69		(E)-7-(4-(4-acetyl-1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
70		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
71		(E)-N-(2-chlorophenyl)-7-(4-((2-cyanoethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

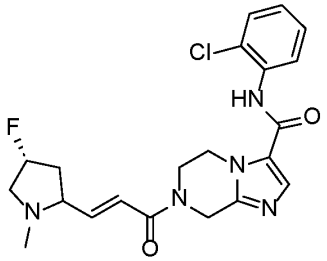
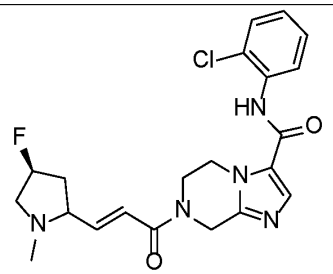
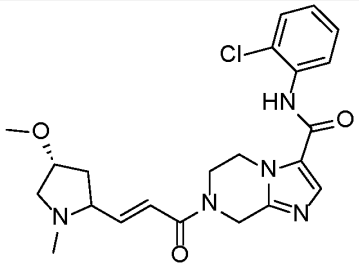
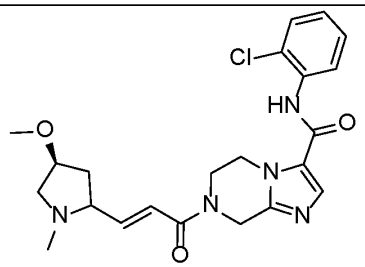
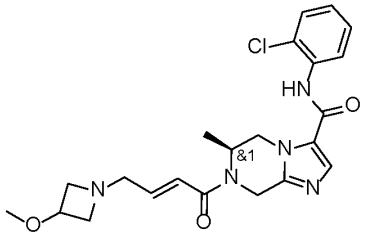
Compound No.	Structure	Compound Name
72		(E)-N-(2-chlorophenyl)-7-(4-((cyanomethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
73		(E)-7-(4-(bicyclo[1.1.1]pentan-1-yl(methyl)amino)but-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
74		N-(2-chlorophenyl)-7-((E)-4-(((1r,3r)-3-methoxycyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
75		(R,E)-7-(3-(azetidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
76		(S,E)-7-(3-(azetidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
77		(E)-N-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

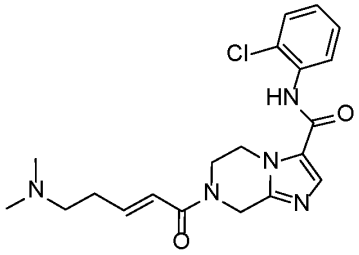
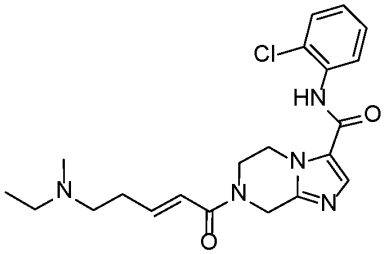
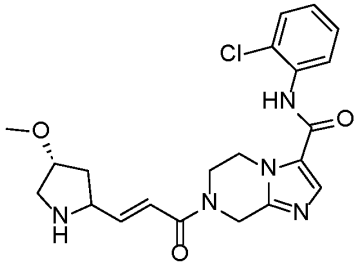
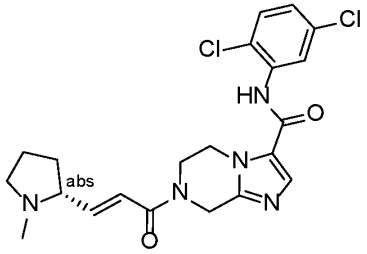
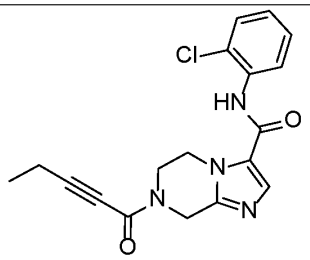
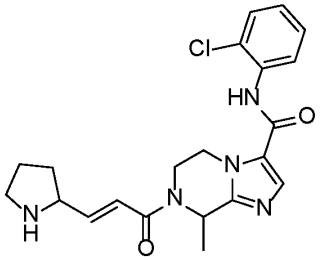
Compound No.	Structure	Compound Name
78		(E)-N-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
79		(E)-N-(2-chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
80		(R,E)-N-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
81		(S,E)-N-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
82		(E)-N-(2-chlorophenyl)-7-(4-(ethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
83		(E)-N-(2-chlorophenyl)-7-(4-((2-fluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

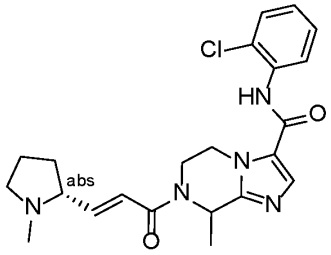
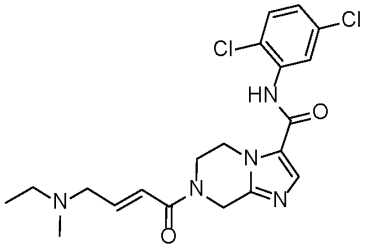
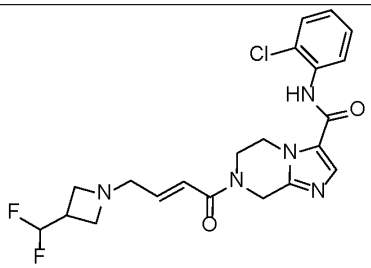
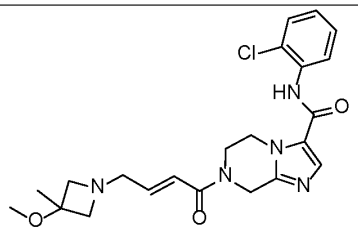
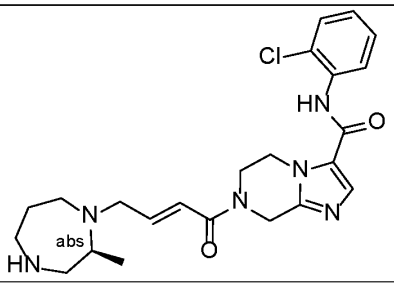
Compound No.	Structure	Compound Name
84		(R,E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
85		(S,E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
86		(S,E)-N-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
87		(S,E)-N-(2-chlorophenyl)-7-(3-(1,2-dimethylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
88		(E)-N-(2-chlorophenyl)-7-(5-(methylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
89		(E)-N-(2-chlorophenyl)-7-(4-((1-methylcyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

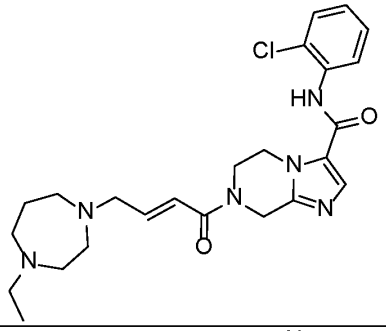
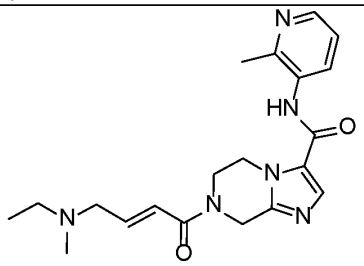
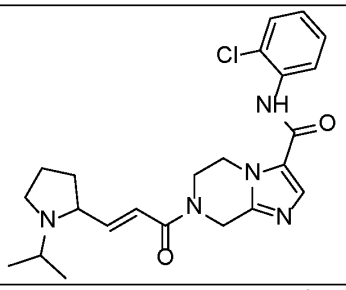
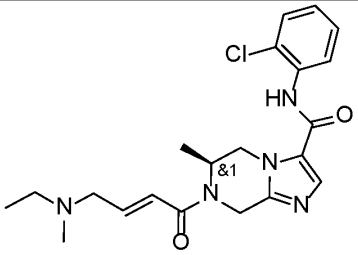
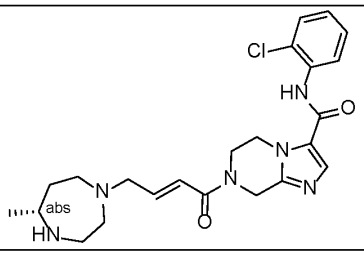
Compound No.	Structure	Compound Name
90		(E)-N-(2-chlorophenyl)-7-(4-(methyl(1-methylcyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
91		N-(2-chlorophenyl)-7-((E)-4-(((1s,3s)-3-methoxycyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
92		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
93		(R,E)-N-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
94		(R,E)-N-(2-chlorophenyl)-7-(3-(1,2-dimethylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

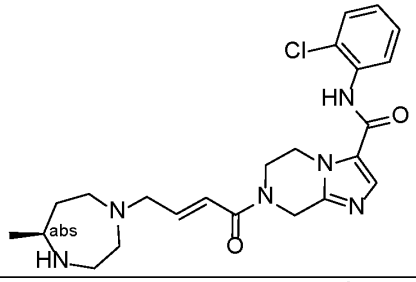
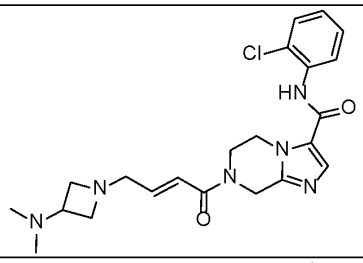
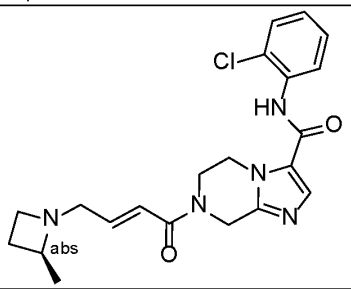
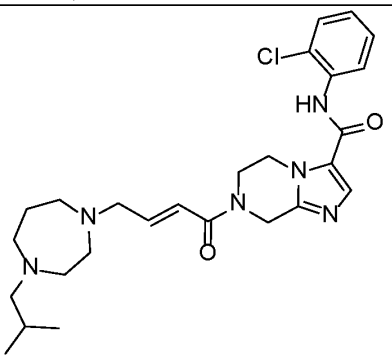
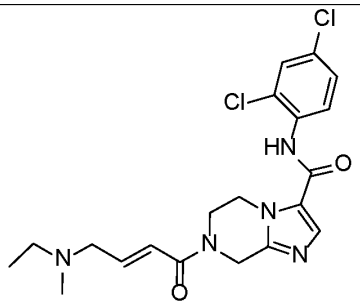
Compound No.	Structure	Compound Name
95		N-(2-chlorophenyl)-7-((E)-3-((4R)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
96		N-(2-chlorophenyl)-7-((E)-3-((4S)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
97		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
98		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
99		(E)-7-(4-aminopent-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

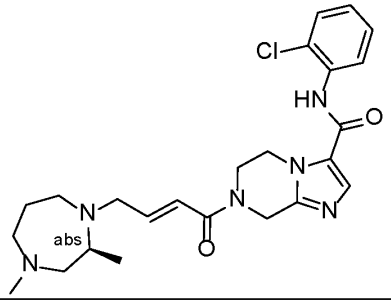
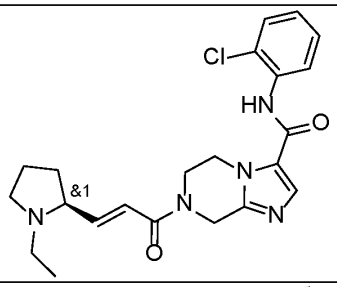
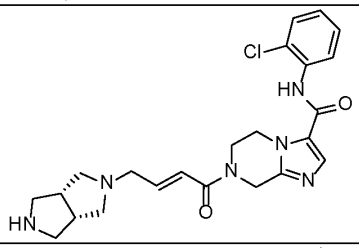
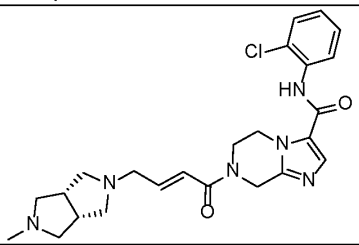
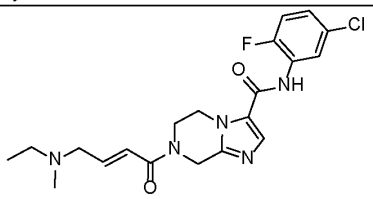
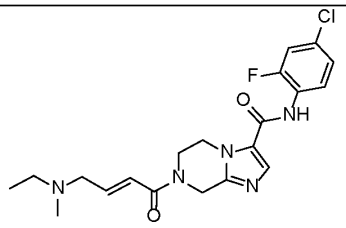
Compound No.	Structure	Compound Name
100		N-(2-chlorophenyl)-7-((E)-3-((4R)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
101		N-(2-chlorophenyl)-7-((E)-3-((4S)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
102a		N-(2-chlorophenyl)-7-((E)-3-((4R)-4-methoxy-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
102b		N-(2-chlorophenyl)-7-((E)-3-((4S)-4-methoxy-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
103		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

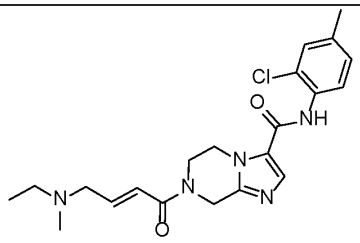
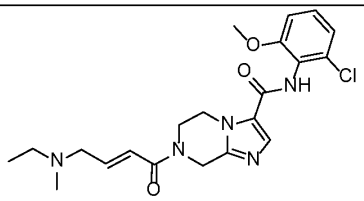
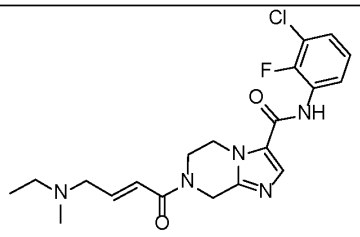
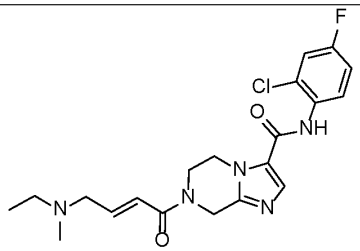
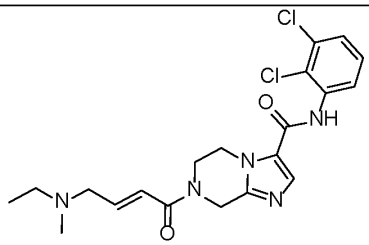
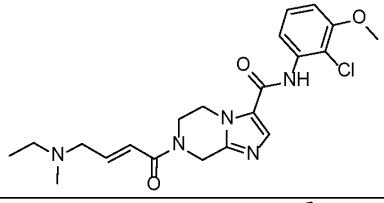
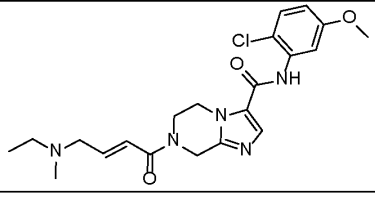
Compound No.	Structure	Compound Name
104		(E)-N-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
105		(E)-N-(2-chlorophenyl)-7-(5-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
106		N-(2-chlorophenyl)-7-((E)-3-((4R)-4-methoxypyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
107		(R,E)-N-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
108		N-(2-chlorophenyl)-7-(pent-2-ynoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
109		N-(2-chlorophenyl)-8-methyl-7-((E)-3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

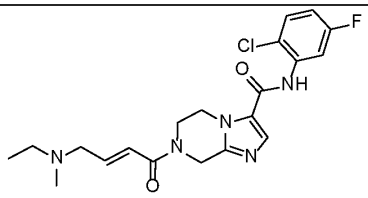
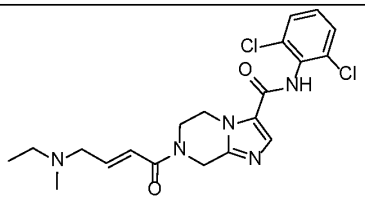
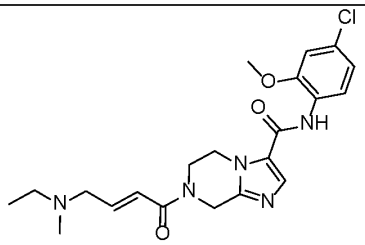
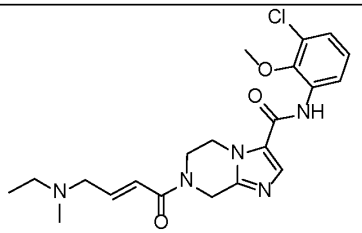
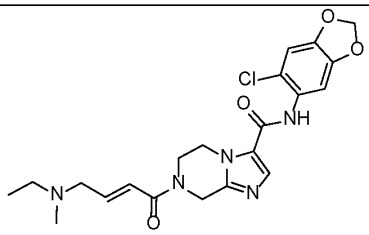
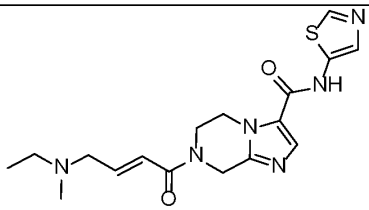
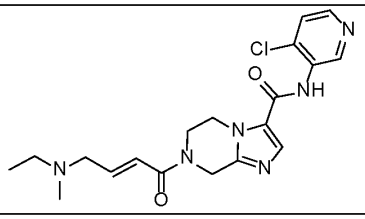
Compound No.	Structure	Compound Name
110		N-(2-chlorophenyl)-8-methyl-7-((E)-3-((R)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
111		(E)-N-(2,5-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
112		(E)-N-(2-chlorophenyl)-7-(4-(3-(difluoromethyl)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
113		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxy-3-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
114		(S,E)-N-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

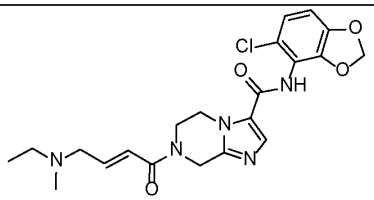
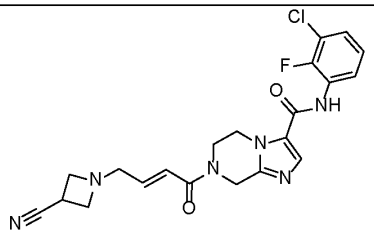
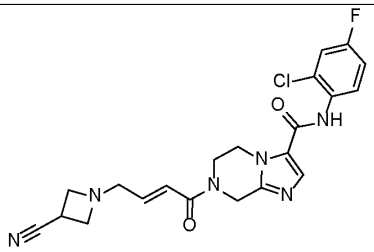
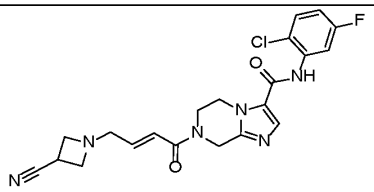
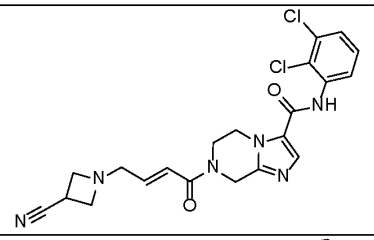
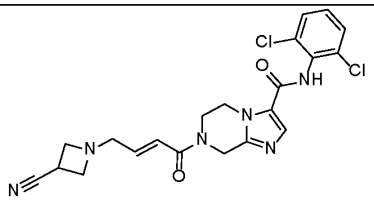
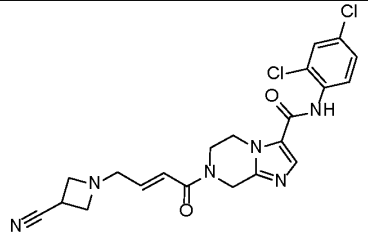
Compound No.	Structure	Compound Name
115		(E)-N-(2-chlorophenyl)-7-(4-(4-ethyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
116		(E)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-N-(2-methylpyridin-3-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
117		(E)-N-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
118		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
119a		(R,E)-N-(2-chlorophenyl)-7-(4-(5-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

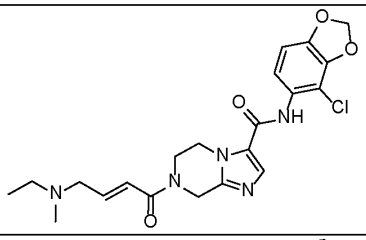
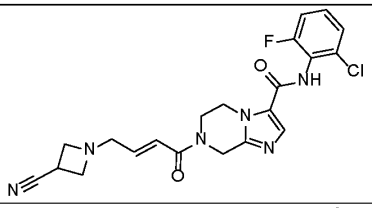
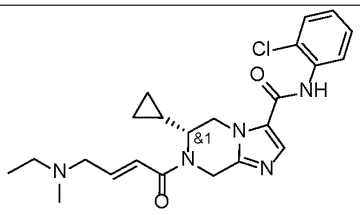
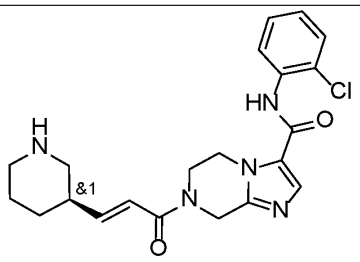
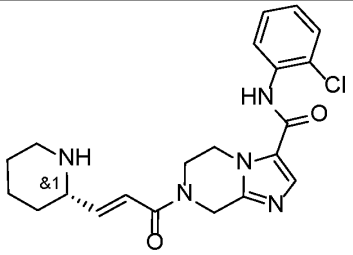
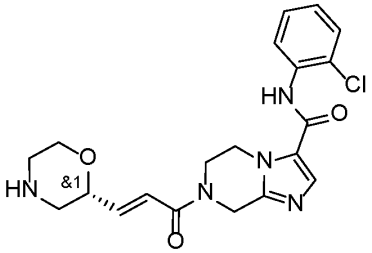
Compound No.	Structure	Compound Name
119b		(S,E)-N-(2-chlorophenyl)-7-(4-(5-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
120		(E)-N-(2-chlorophenyl)-7-(4-(3-(dimethylamino)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
121		(S,E)-N-(2-chlorophenyl)-7-(4-(2-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
122		(E)-N-(2-chlorophenyl)-7-(4-(4-isobutyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
124		(E)-N-(2,4-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

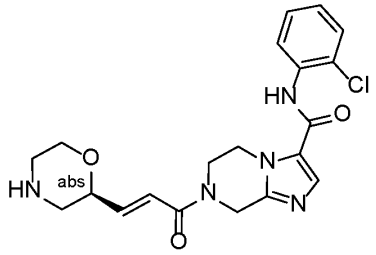
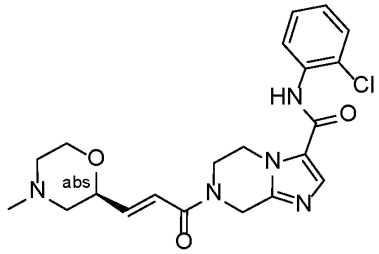
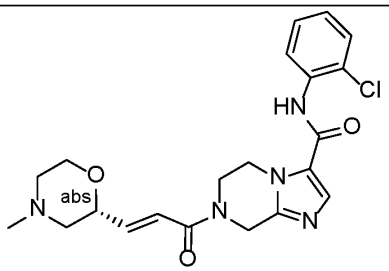
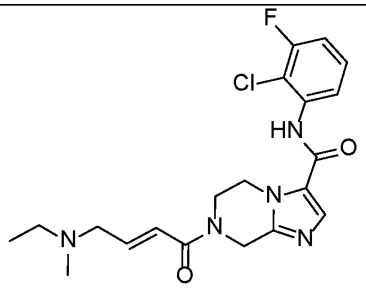
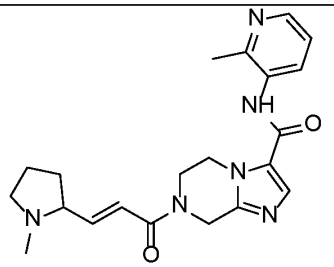
Compound No.	Structure	Compound Name
125		(S,E)-N-(2-chlorophenyl)-7-(4-(2,4-dimethyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
126		(E)-N-(2-chlorophenyl)-7-(3-(1-ethylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
127		N-(2-chlorophenyl)-7-((E)-4-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
128		N-(2-chlorophenyl)-7-((E)-4-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
129		(E)-N-(5-chloro-2-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
130		(E)-N-(4-chloro-2-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

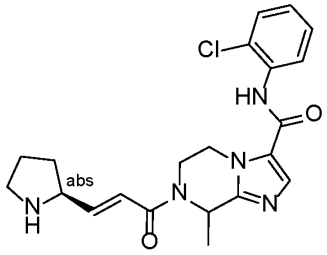
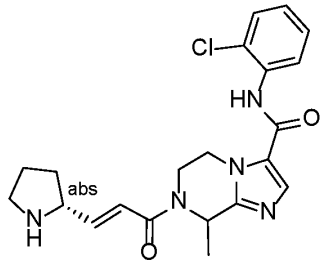
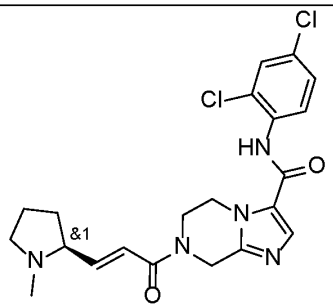
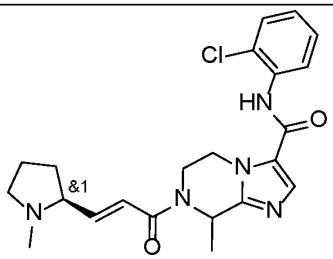
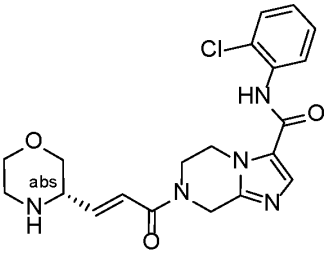
Compound No.	Structure	Compound Name
131		(E)-N-(2-chloro-4-methylphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
132		(E)-N-(2-chloro-6-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
133		(E)-N-(3-chloro-2-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
134		(E)-N-(2-chloro-4-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
135		(E)-N-(2,3-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
136		(E)-N-(2-chloro-3-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
137		(E)-N-(2-chloro-5-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

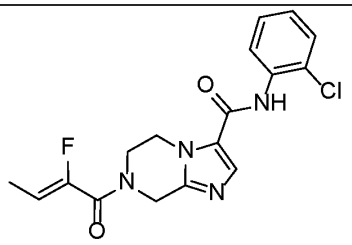
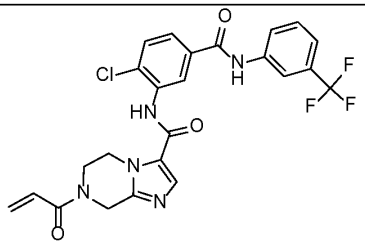
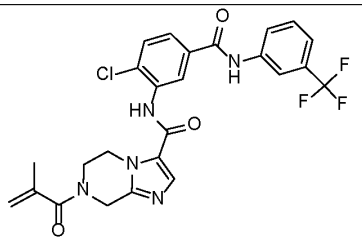
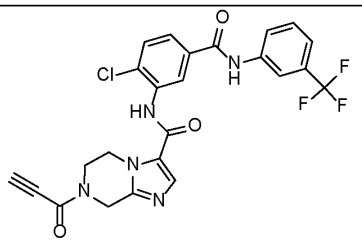
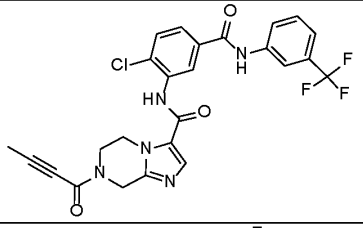
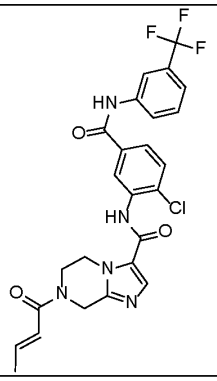
Compound No.	Structure	Compound Name
138		(E)-N-(2-chloro-5-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
139		(E)-N-(2,6-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
140		(E)-N-(4-chloro-2-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
141		(E)-N-(3-chloro-2-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
142		(E)-N-(6-chlorobenzo[d][1,3]dioxol-5-yl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
143		(E)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-N-(thiazol-5-yl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
144		(E)-N-(4-chloropyridin-3-yl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

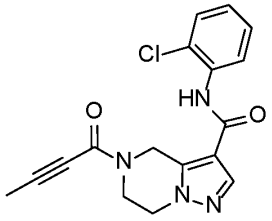
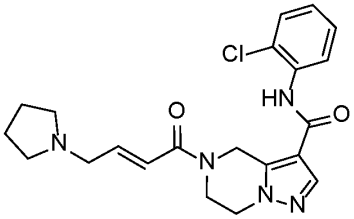
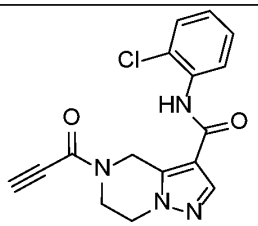
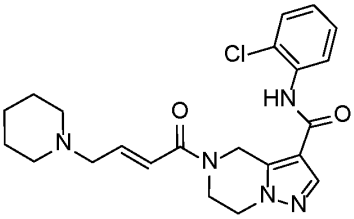
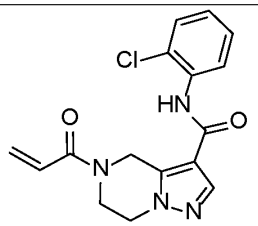
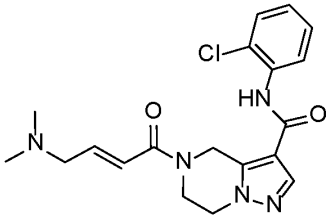
Compound No.	Structure	Compound Name
145		(E)-N-(5-chlorobenzo[d][1,3]dioxol-4-yl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
146		(E)-N-(3-chloro-2-fluorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
147		(E)-N-(2-chloro-4-fluorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
148		(E)-N-(2-chloro-5-fluorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
149		(E)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-N-(2,3-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
150		(E)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-N-(2,6-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
151		(E)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

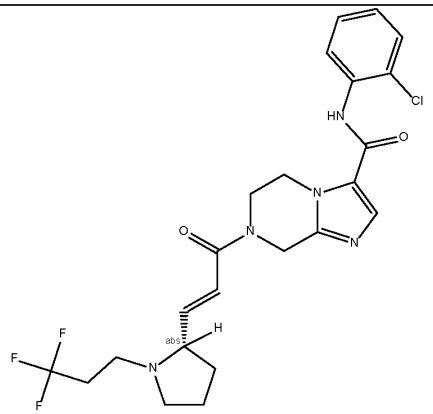
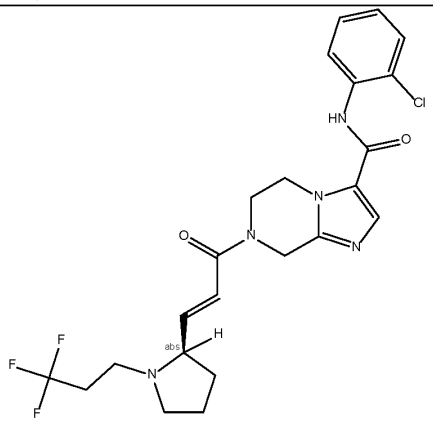
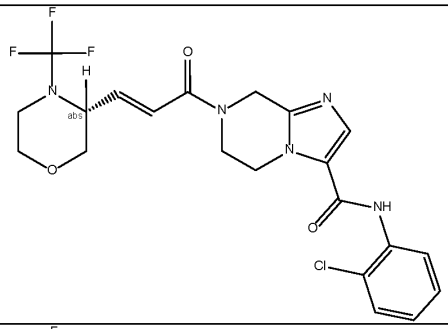
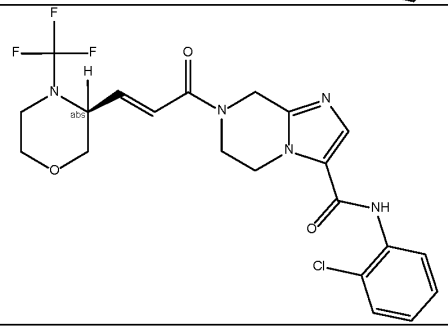
Compound No.	Structure	Compound Name
152		(E)-N-(4-chlorobenzo[d][1,3]dioxol-5-yl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
153		(E)-N-(2-chloro-6-fluorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
154		(E)-N-(2-chlorophenyl)-6-cyclopropyl-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
155		(E)-N-(2-chlorophenyl)-7-(3-(piperidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
156		(E)-N-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
157		(E)-N-(2-chlorophenyl)-7-(3-(morpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

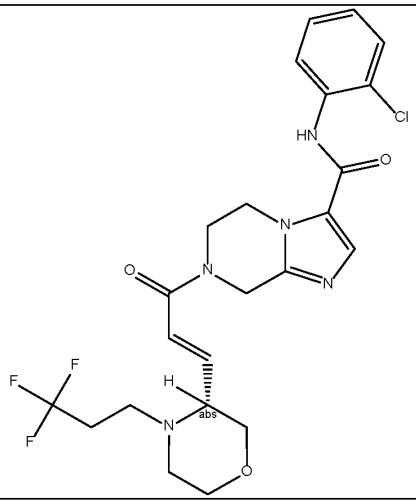
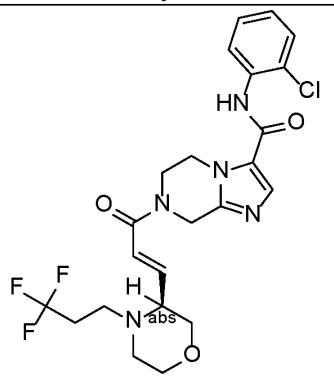
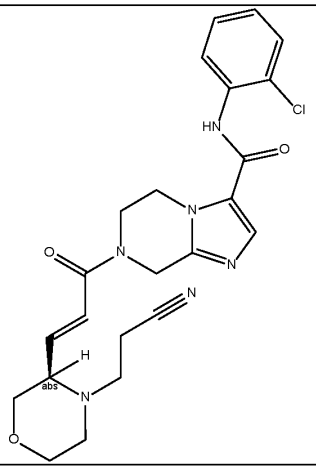
Compound No.	Structure	Compound Name
158		(S,E)-N-(2-chlorophenyl)-7-(3-(morpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
159a		(S,E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
159b		(R,E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
160		(E)-N-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
161		(E)-N-(2-methylpyridin-3-yl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

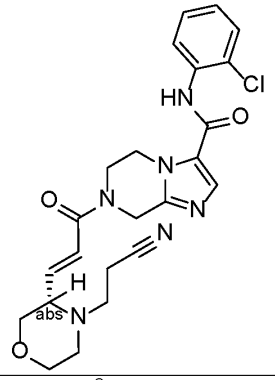
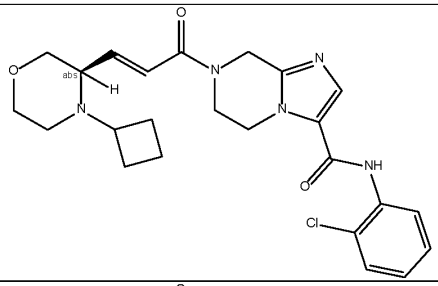
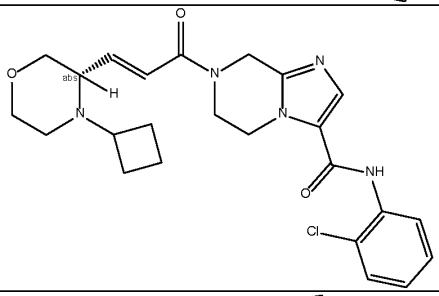
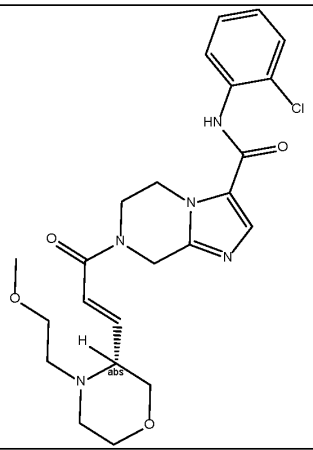
Compound No.	Structure	Compound Name
162a		N-(2-chlorophenyl)-8-methyl-7-((E)-3-((S)-pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
162b		N-(2-chlorophenyl)-8-methyl-7-((E)-3-((R)-pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
163		(E)-N-(2,4-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
164		N-(2-chlorophenyl)-8-methyl-7-((E)-3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
165		(S,E)-N-(2-chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

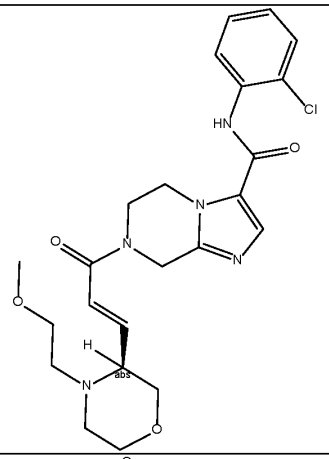
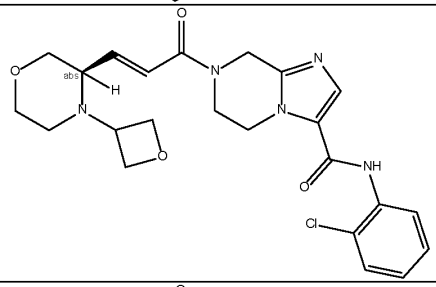
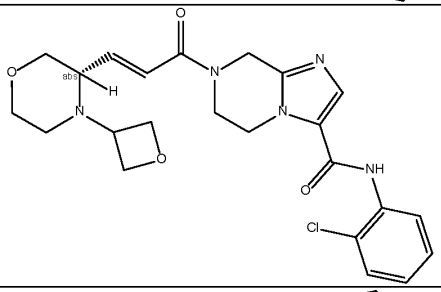
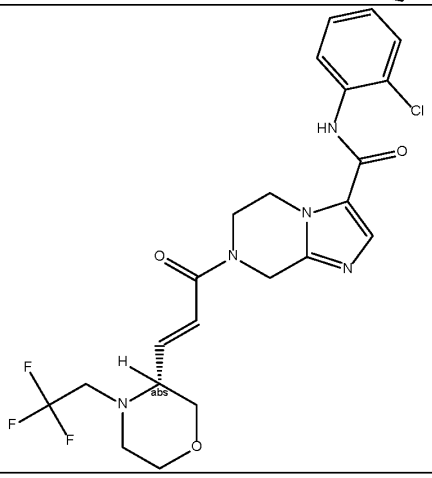
Compound No.	Structure	Compound Name
166		(Z)-N-(2-chlorophenyl)-7-(2-fluorobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
167		7-acryloyl-N-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
168		N-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-methacryloyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
169		N-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
170		7-(but-2-ynoyl)-N-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
171		(E)-7-(but-2-enoyl)-N-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

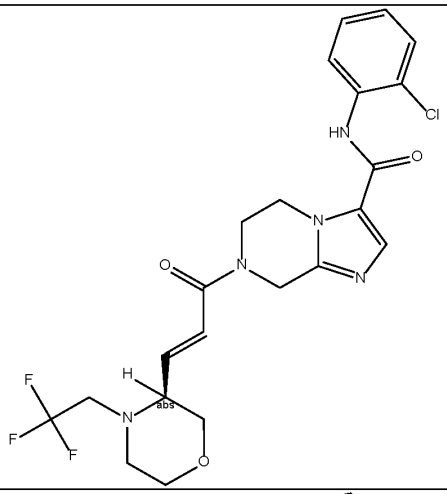
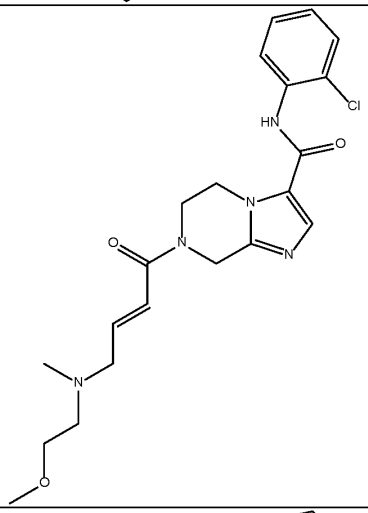
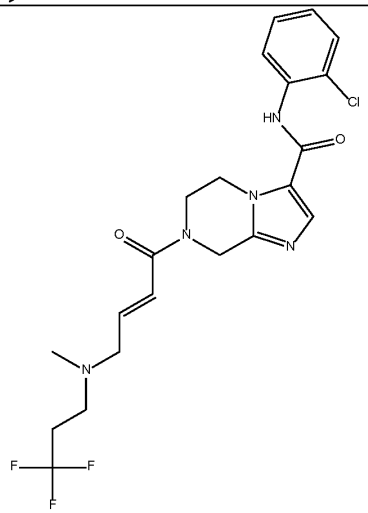
Compound No.	Structure	Compound Name
172		5-(but-2-ynoyl)-N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
173		(E)-N-(2-chlorophenyl)-5-(4-(pyrrolidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
174		N-(2-chlorophenyl)-5-propioloyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
175		(E)-N-(2-chlorophenyl)-5-(4-(piperidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
176		5-acryloyl-N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
177		(E)-N-(2-chlorophenyl)-5-(4-(dimethylamino)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide

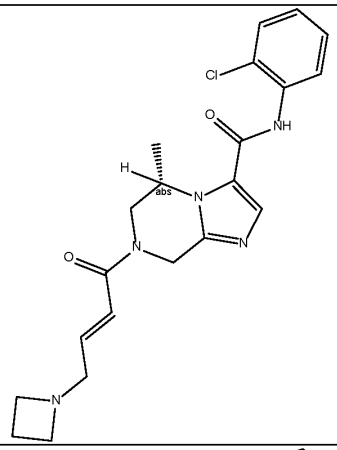
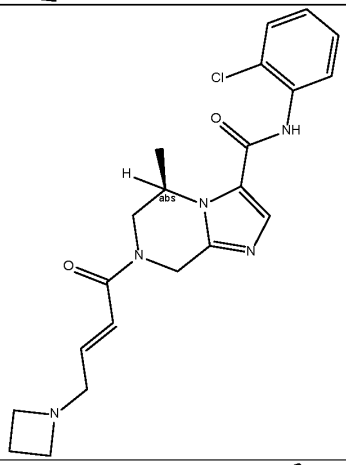
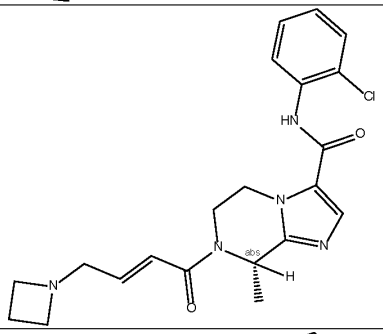
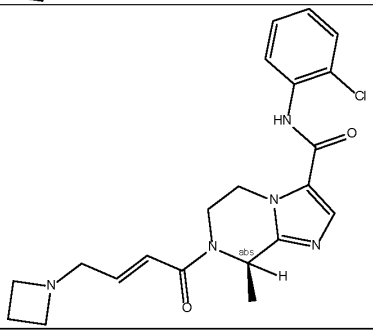
Compound No.	Structure	Compound Name
178		(S,E)-N-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
179		(R,E)-N-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
180a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(trifluoromethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
180b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(trifluoromethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

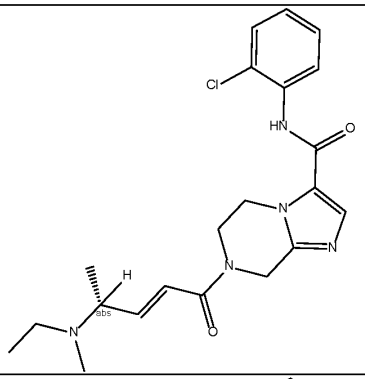
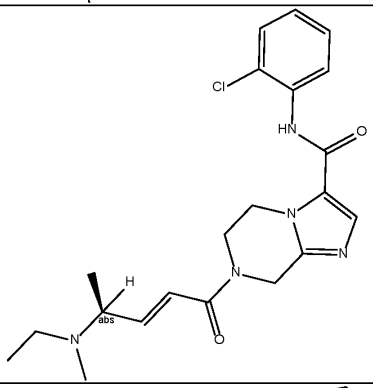
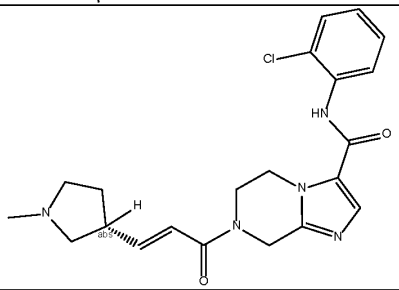
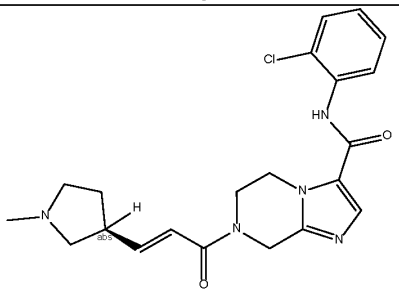
Compound No.	Structure	Compound Name
181a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(3,3,3-trifluoropropyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
181b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(3,3,3-trifluoropropyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
182a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(2-cyanoethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

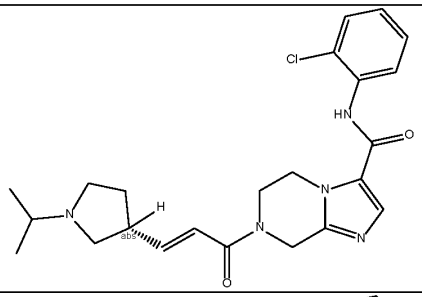
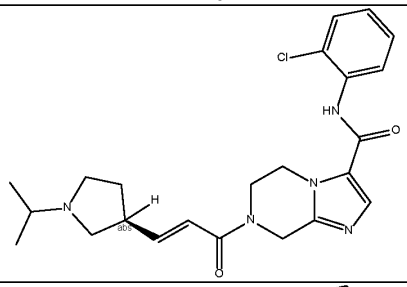
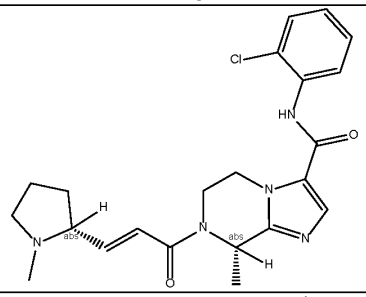
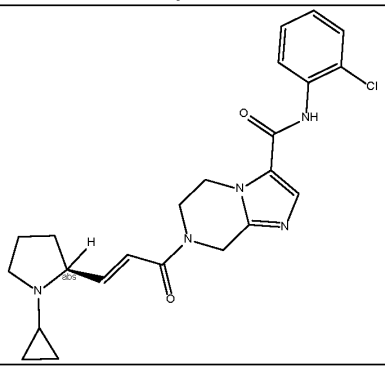
Compound No.	Structure	Compound Name
182b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(2-cyanoethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
183a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-cyclobutylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
183b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-cyclobutylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
184a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(2-methoxyethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

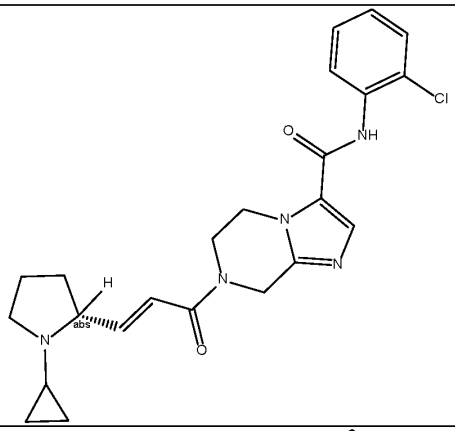
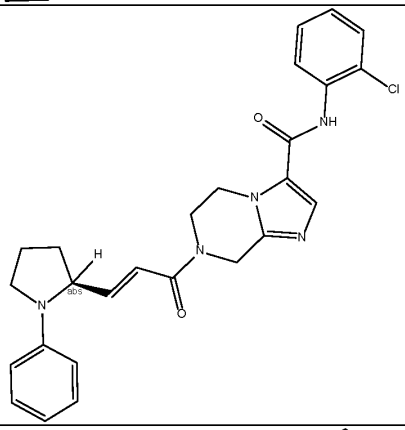
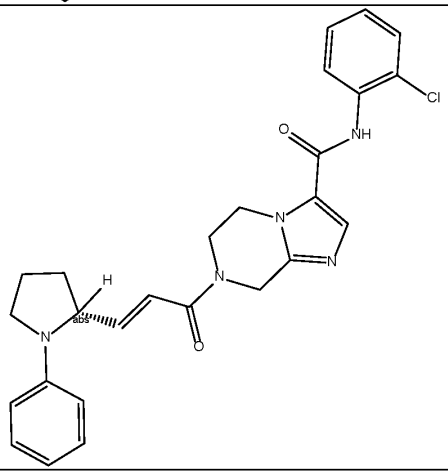
Compound No.	Structure	Compound Name
184b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(2-methoxyethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
185a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(oxetan-3-yl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
185b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(oxetan-3-yl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
186a		(R,E)-N-(2-chlorophenyl)-7-(3-(4-(2,2,2-trifluoroethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

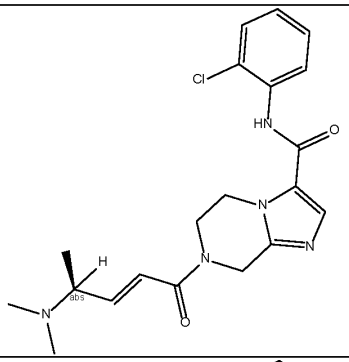
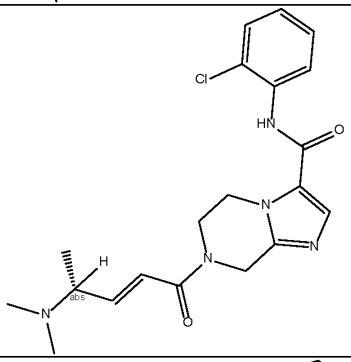
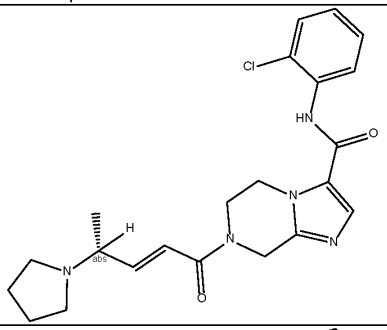
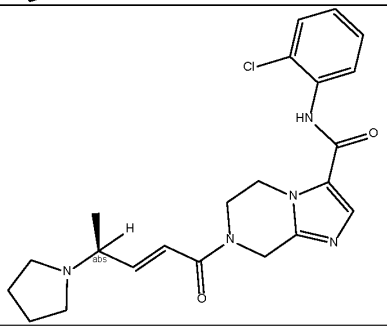
Compound No.	Structure	Compound Name
186b		(S,E)-N-(2-chlorophenyl)-7-(3-(4-(2,2,2-trifluoroethyl)morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
187		(E)-N-(2-chlorophenyl)-7-(4-((2-methoxyethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
188		(E)-N-(2-chlorophenyl)-7-(4-(methyl(3,3,3-trifluoropropyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
189		(S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
190		(R,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
191		(S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
192		(R,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
193		(R,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
194		(S,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
195		(R,E)-N-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
196		(S,E)-N-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
197		(R,E)-N-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
198		(S,E)-N-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
199		(S)-N-(2-chlorophenyl)-8-methyl-7-((E)-3-((R)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
200		(S,E)-N-(2-chlorophenyl)-7-(3-(1-cyclopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
201		(R,E)-N-(2-chlorophenyl)-7-(3-(1-cyclopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
202a		(S,E)-N-(2-chlorophenyl)-7-(3-(1-phenylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
202b		(R,E)-N-(2-chlorophenyl)-7-(3-(1-phenylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
203		(S,E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
204		(R,E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
205		(R,E)-N-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
206		(S,E)-N-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

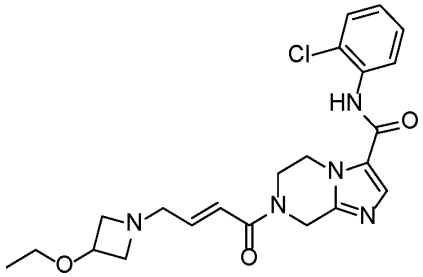
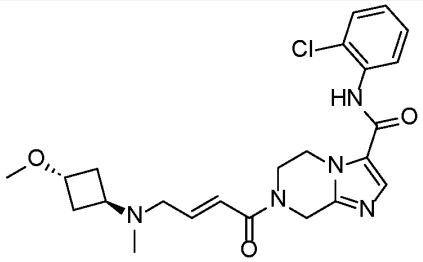
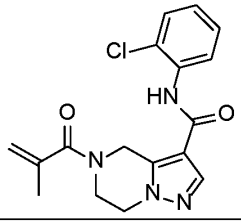
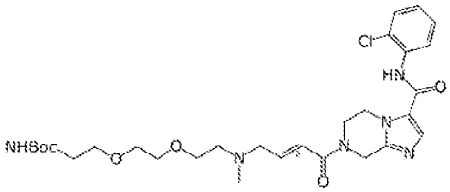
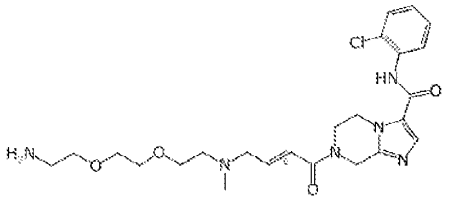
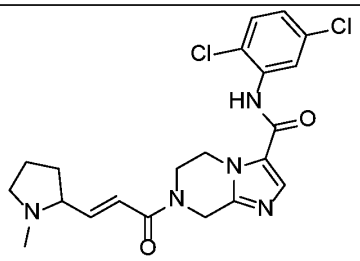
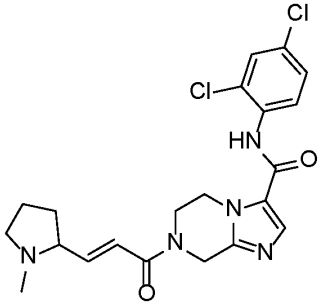
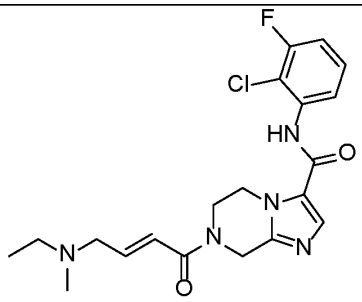
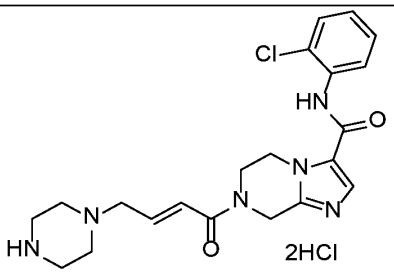
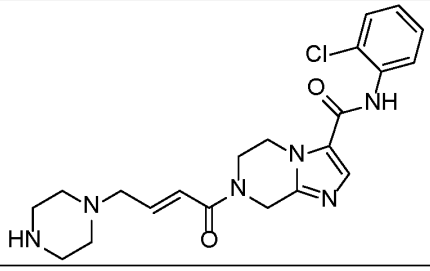
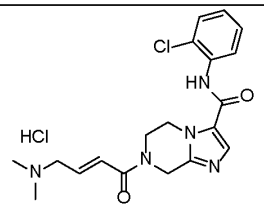
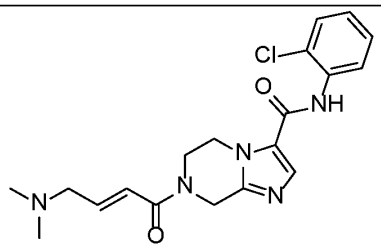
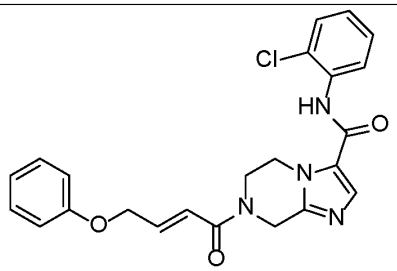
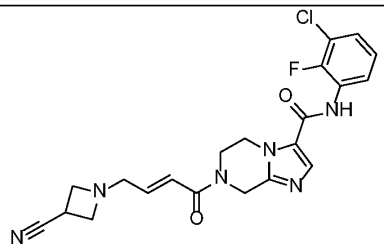
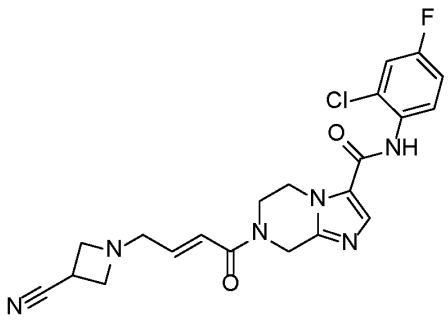
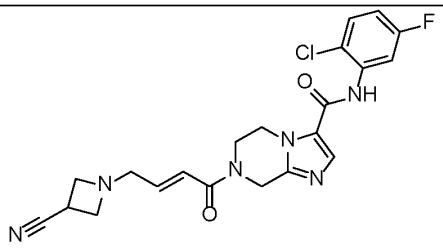
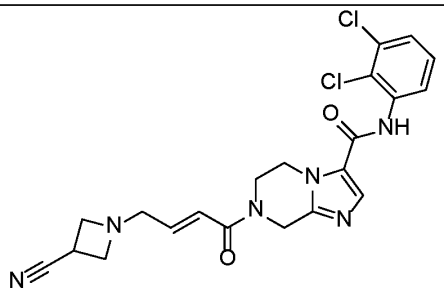
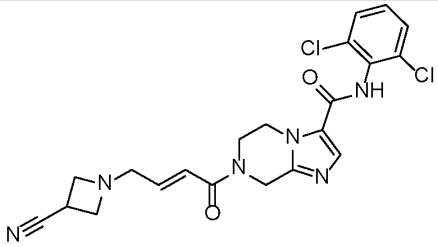
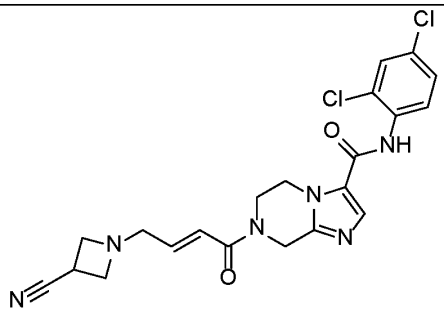
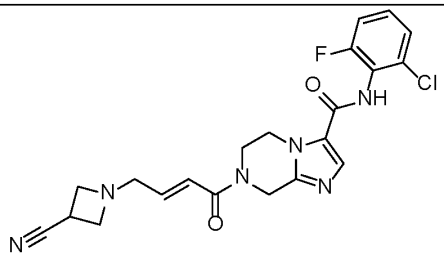
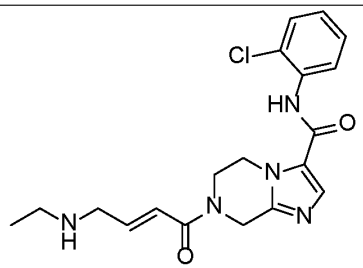
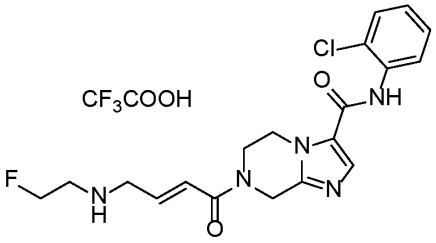
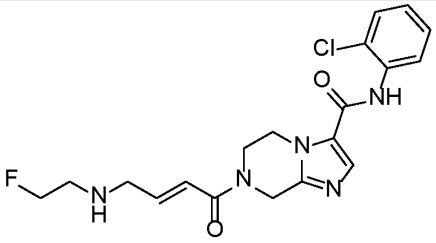
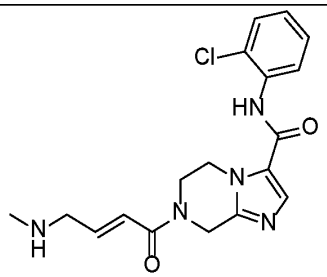
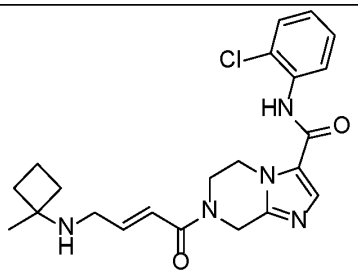
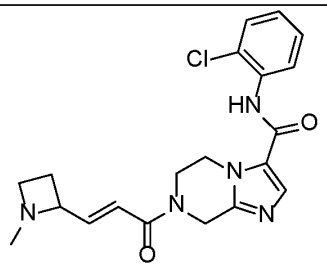
Compound No.	Structure	Compound Name
207		(E)-N-(2-chlorophenyl)-7-(4-(3-ethoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
208		*N*-(2-chlorophenyl)-7-((*E*)-4-(((1*r*,3*r*)-3-methoxycyclobutyl)(methyl) amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide
209		*N*-(2-chlorophenyl)-5-methacryloyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide
210		tert-butyl N-[2-[2-[2-[[(E)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-methyl-amino]ethoxy]ethoxy]ethyl]carbamate
211		7-[(E)-4-[2-[2-(2-aminoethoxy)ethoxy]ethyl-methyl-amino]but-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

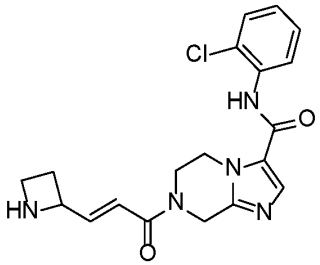
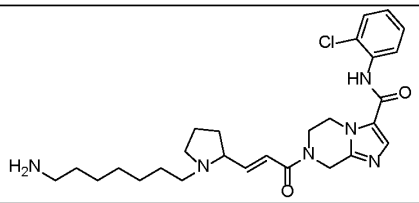
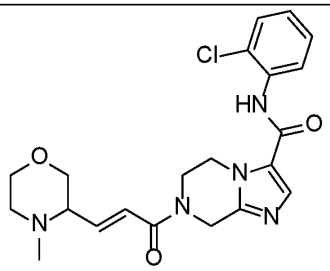
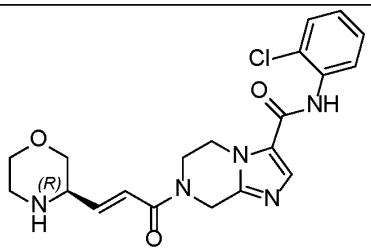
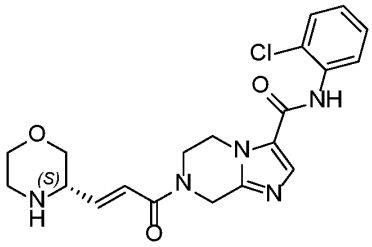
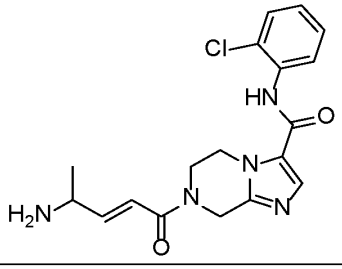
Table 2.

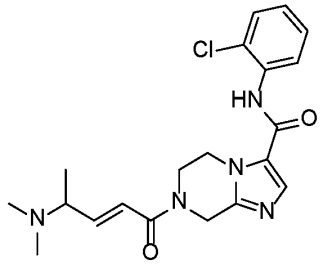
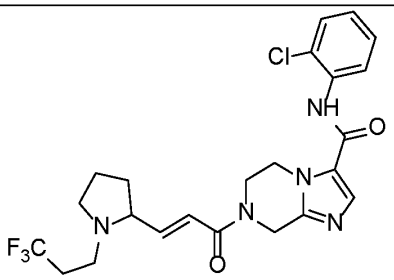
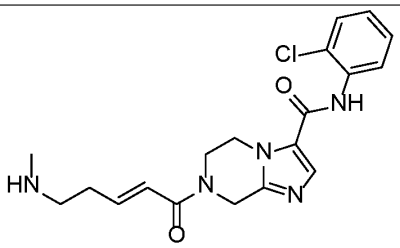
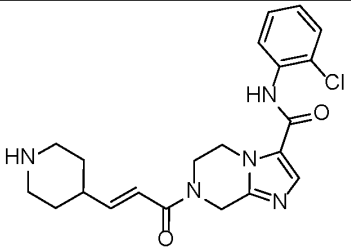
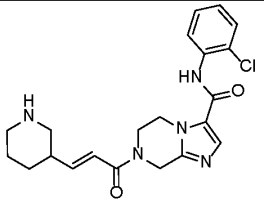
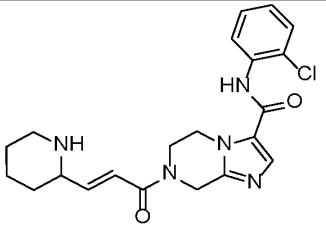
Compound No.	Structure	Compound Name
212		(E)-N-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
213		(E)-N-(2,4-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.
214		(E)-N-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
215		N-(2-chlorophenyl)-7-[(E)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide dihydrochloride
215a		N-(2-chlorophenyl)-7-[(E)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

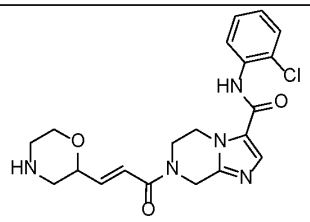
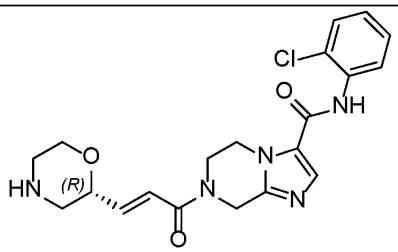
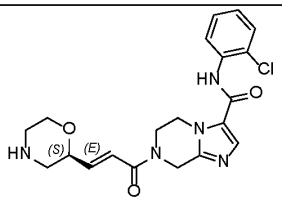
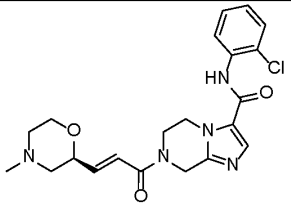
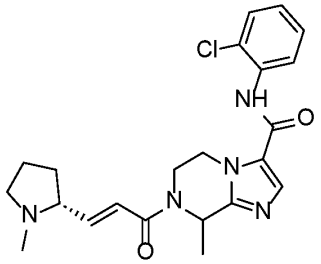
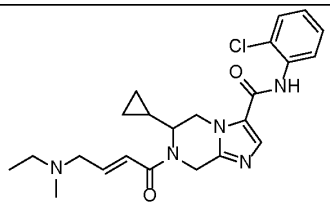
Compound No.	Structure	Compound Name
216		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride
216a		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
217		N-(2-chlorophenyl)-7-[(E)-4-phenoxybut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
218		N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-(3- cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
219		N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- (3-cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
220		N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

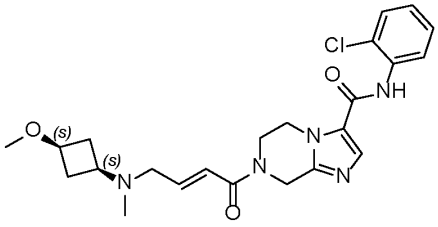
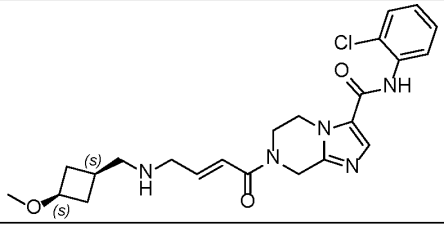
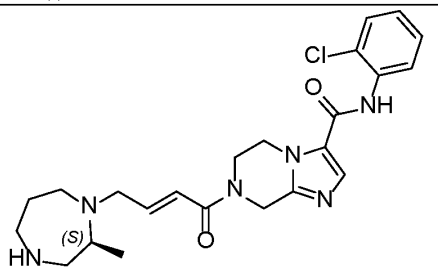
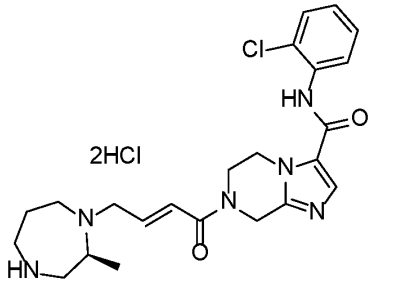
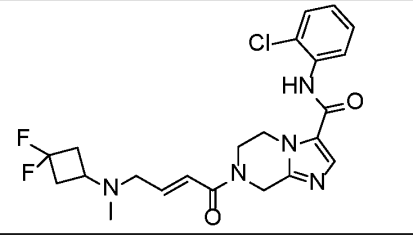
Compound No.	Structure	Compound Name
221		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,3-dichlorophenyl)-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
222		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,6-dichlorophenyl) -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
223		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -N-(2,4-dichlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
224		N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
225		N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

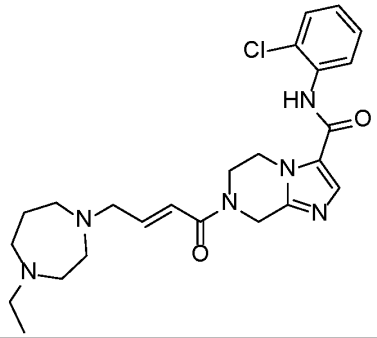
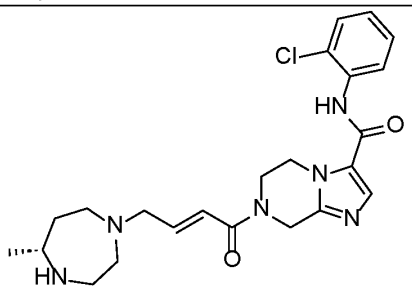
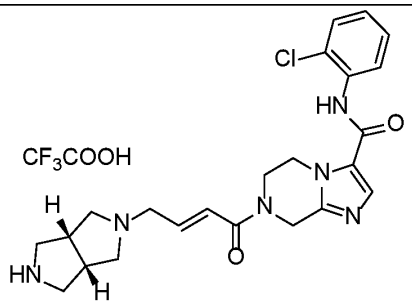
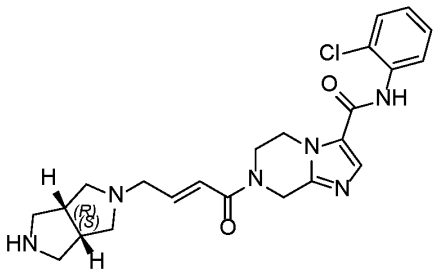
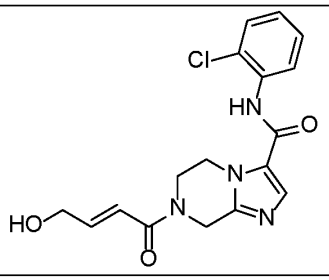
Compound No.	Structure	Compound Name
226		N-(2-chlorophenyl)-7-[(E)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide trifluoroacetic acid
226a		N-(2-chlorophenyl)-7-[(E)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
227		N-(2-chlorophenyl)-7-[(E)-4-(methylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
228		N-(2-chlorophenyl)-7-[(E)-4-[(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
229		(E)-N-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

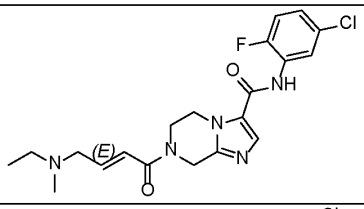
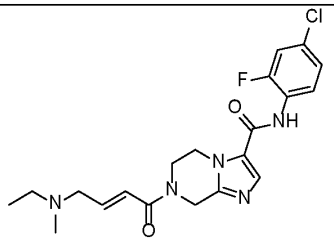
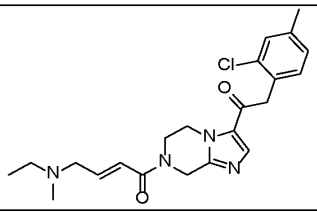
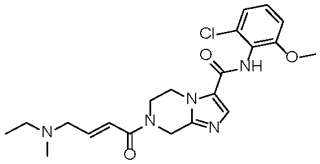
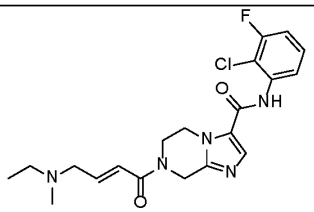
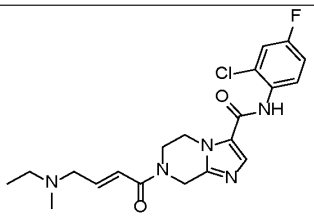
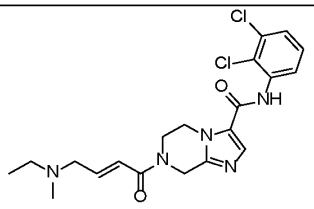
Compound No.	Structure	Compound Name
230		(E)-7-(3-(azetidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
231		(E)-7-(3-(1-(7-aminoheptyl)pyrrolidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
232		N-(2-chlorophenyl)-7-[(E)-3-(4-methylmorpholin-3-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
233		(R,E)-N-(2-chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
234		(S,E)-N-(2-chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
235		7-[(E)-4-aminopent-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

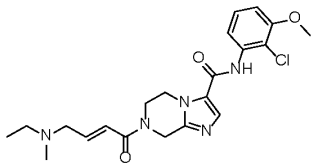
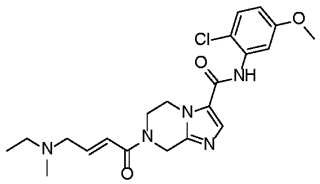
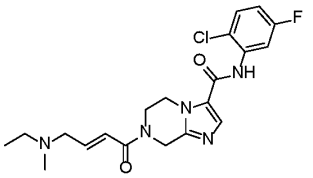
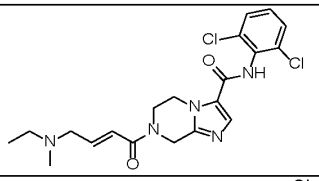
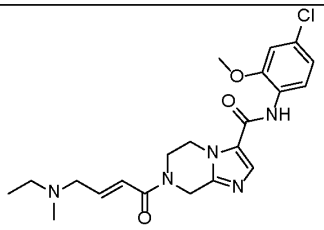
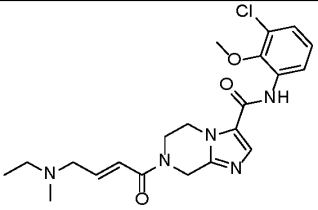
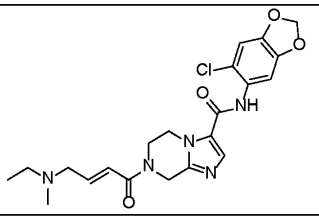
Compound No.	Structure	Compound Name
236		N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
237		(E)-N-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
238		(E)-N-(2-chlorophenyl)-7-(5-(methylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
239		N-(2-chlorophenyl)-7-[(E)-3-(4-piperidyl)prop-2-enoyl]-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-3-carboxamide
240		N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide
241		N-(2-chlorophenyl)-7-[(E)-3-(2-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide

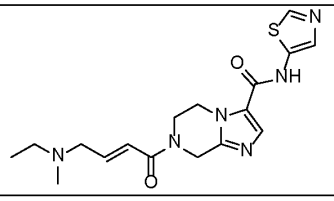
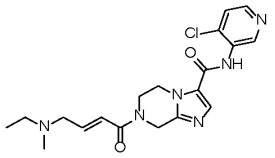
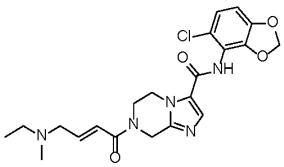
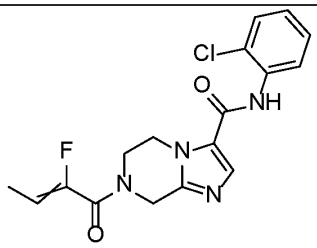
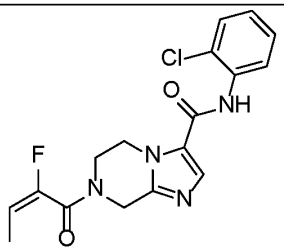
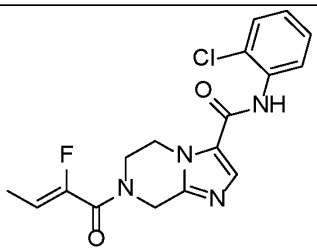
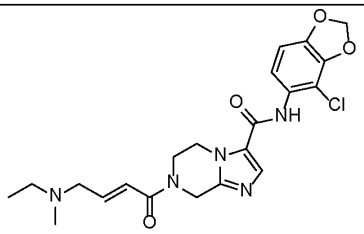
Compound No.	Structure	Compound Name
242		(E)-N-(2-chlorophenyl)-7-(3-(morpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
243		N-(2-chlorophenyl)-7-[(E)-3-[(2R)-morpholin-2-yl]prop-2 -enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
244		N-(2-chlorophenyl)-7-[(E)-3-[(2S)-morpholin-2-yl]prop-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
245		N-(2-chlorophenyl)-7-[(E)-3-[(2S)-4-methylmorpholin-2-yl]prop -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
246		N-(2-chlorophenyl)-8-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
247		N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

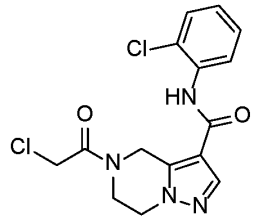
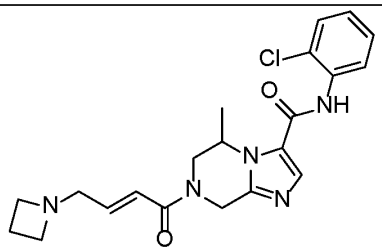
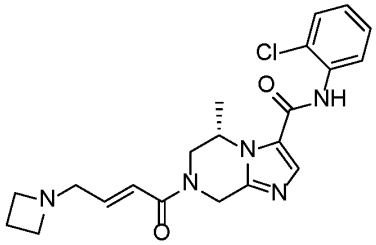
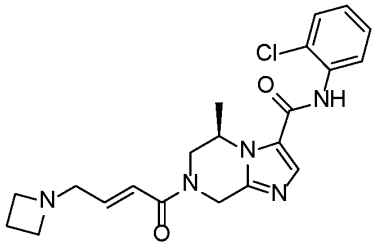
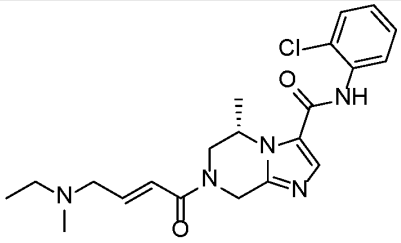
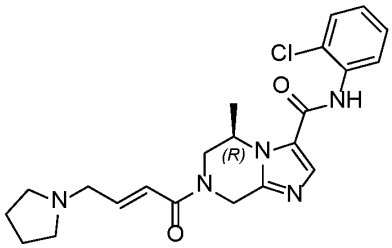
Compound No.	Structure	Compound Name
248		N-(2-chlorophenyl)-7-((E)-4-(((1s,3s)-3-methoxycyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
249		N-(2-chlorophenyl)-7-((E)-4-(((1s,3s)-3-methoxycyclobutyl)(methyl) amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
250		(S,E)-N-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
251		(S,E)-N-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide dihydrochloride
252		(E)-N-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

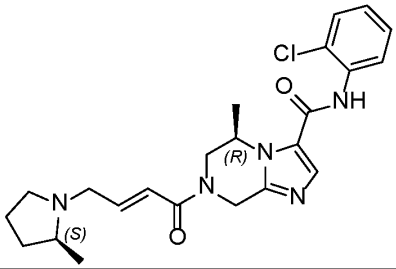
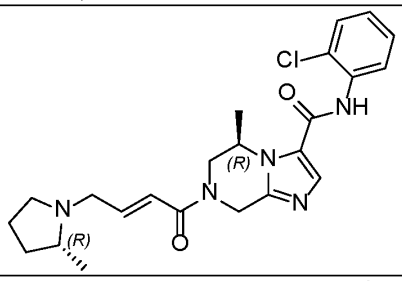
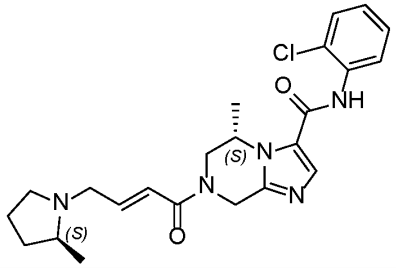
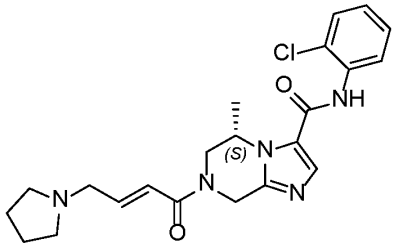
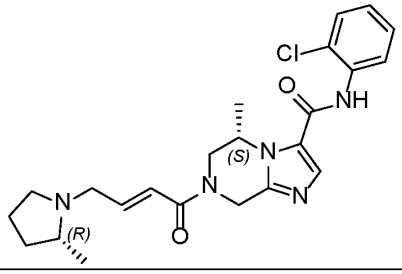
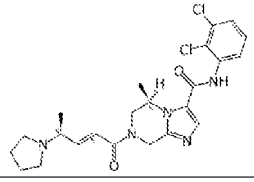
Compound No.	Structure	Compound Name
253		N-(2-chlorophenyl)-7-[(E)-4-(4-ethyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
254		N-(2-chlorophenyl)-7-[(E)-4-[(5R)-5-methyl-1,4-diazepan-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
255		N-(2-chlorophenyl)-7-((E)-4-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide 2,2,2-trifluoroacetate
255a		N-(2-chlorophenyl)-7-((E)-4-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
256		N-(2-chlorophenyl)-7-[(E)-4-hydroxybut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

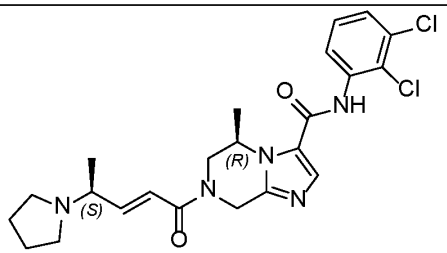
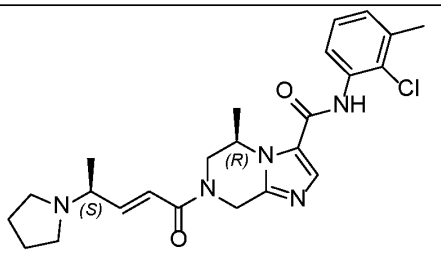
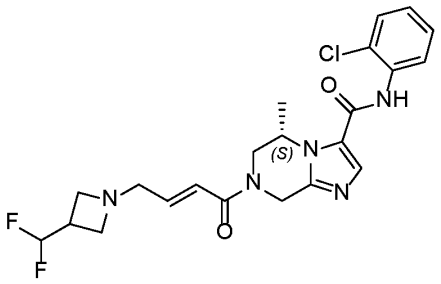
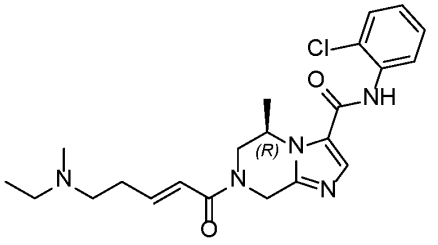
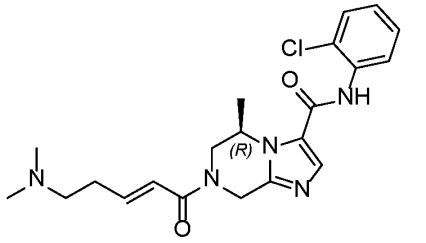
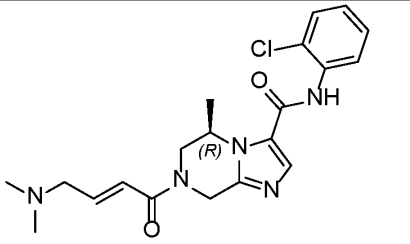
Compound No.	Structure	Compound Name
257		N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
258		N-(4-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
259		N-(2-chloro-4-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
260		N-(2-chloro-6-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
261		N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
262		N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- [ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
263		N-(2,3-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

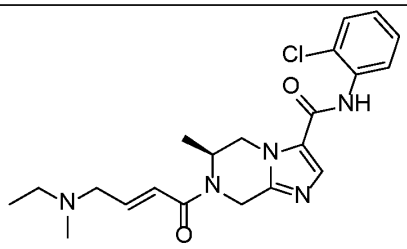
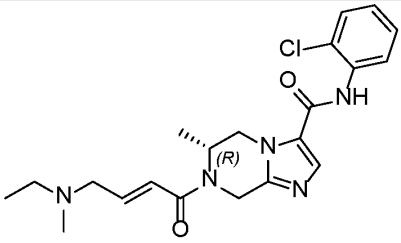
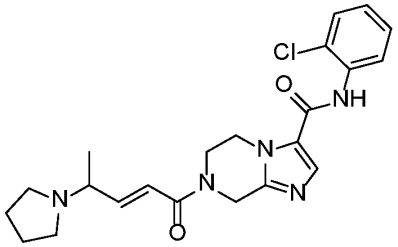
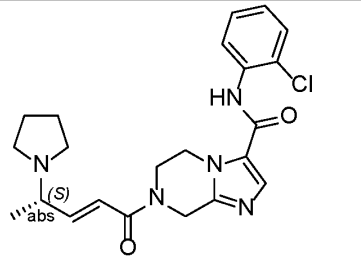
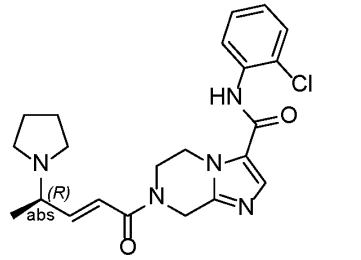
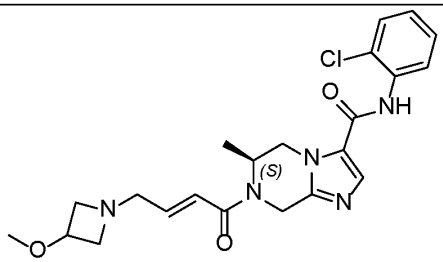
Compound No.	Structure	Compound Name
264		N-(2-chloro-3-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
265		N-(2-chloro-5-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
266		N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
267		(E)-N-(2,6-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
268		N-(4-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
269		N-(3-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
270		N-(6-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

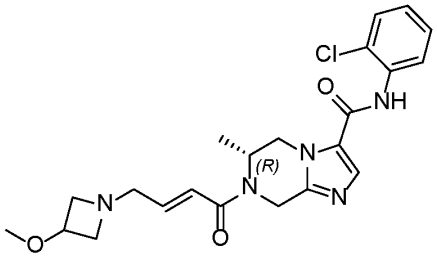
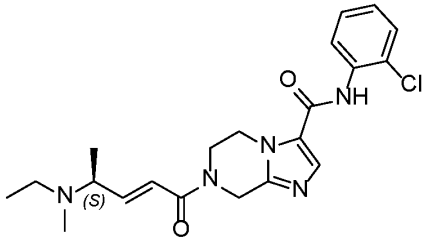
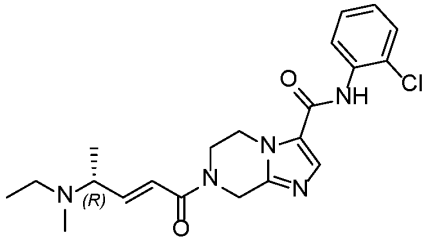
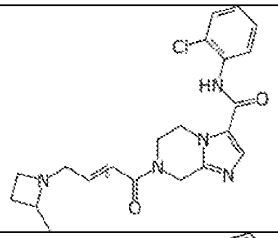
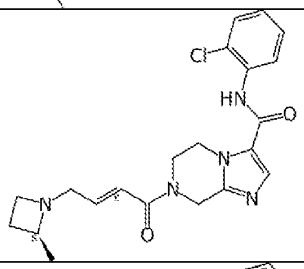
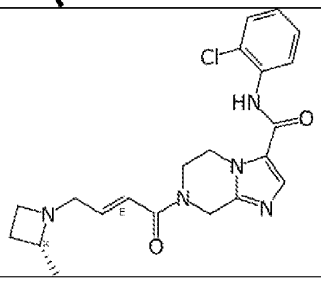
Compound No.	Structure	Compound Name
271		7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxamide
272		N-(4-chloro-3-pyridyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
273		N-(5-chloro-1,3-benzodioxol-4-yl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
274		N-(2-chlorophenyl)-7-[2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide
275		N-(2-chlorophenyl)-7-[(E)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
276		N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
277		N-(4-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl (methyl)amino]but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

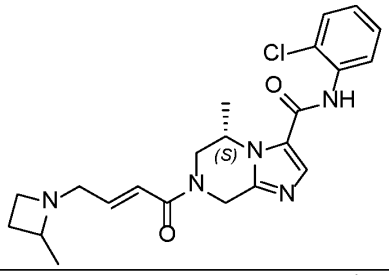
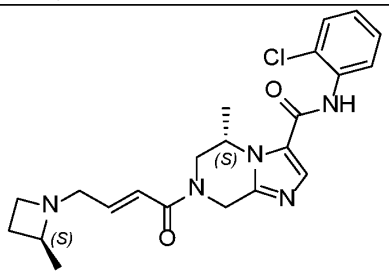
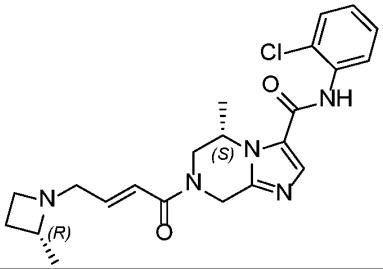
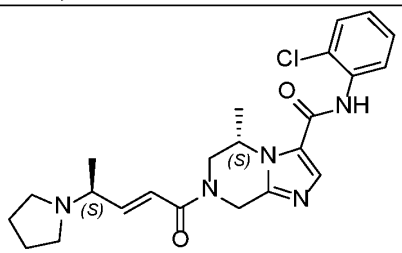
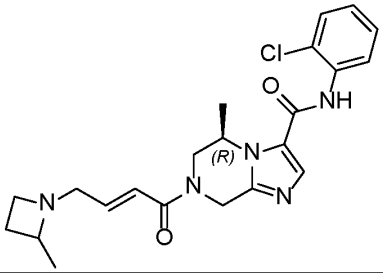
Compound No.	Structure	Compound Name
278		5-(2-chloroacetyl)-N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
279		N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
280		(5S)-N-(2-chlorophenyl) -5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
281		(5R)-N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
282		(5S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
283		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

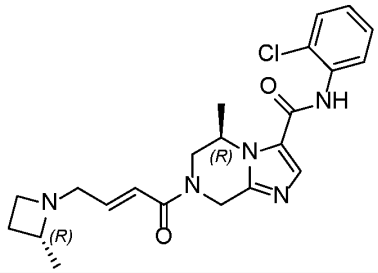
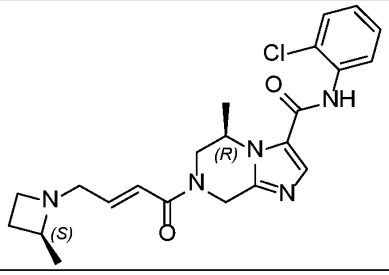
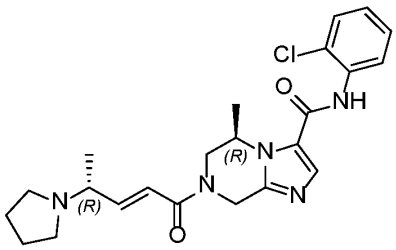
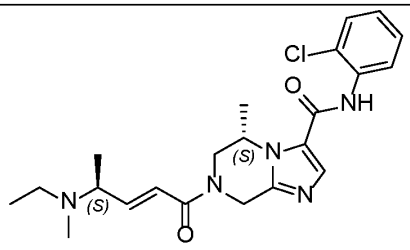
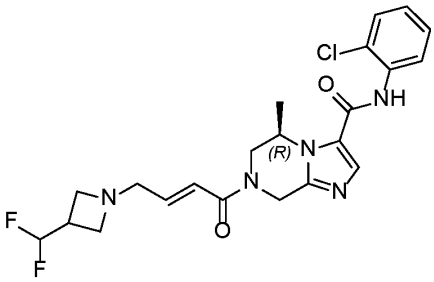
Compound No.	Structure	Compound Name
284		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
285		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylpyrrolidin -1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
286		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
287		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
288		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
289		(5R)-N-(2,3-dichlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

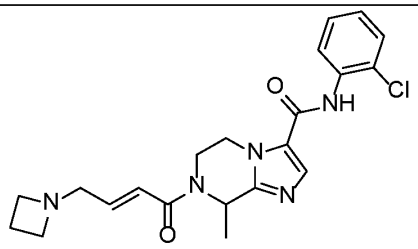
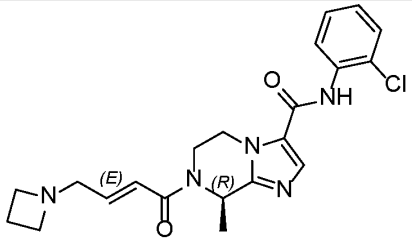
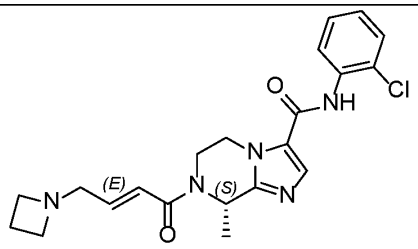
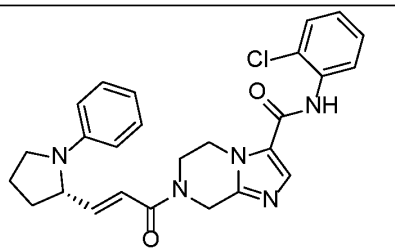
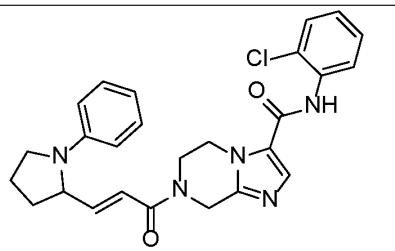
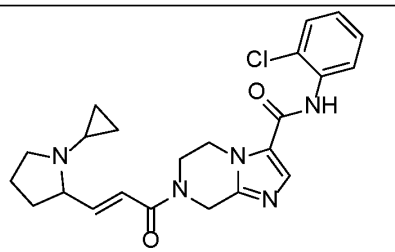
Compound No.	Structure	Compound Name
290		(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
291		(5R)-N-(2-chloro-3-methyl-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
292		(5S)-N-(2-chlorophenyl)-7-[(E)-4-[3-(difluoromethyl)azetidin-1-yl]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
293		(5R)-N-(2-chlorophenyl)-7-[(E)-5-[ethyl (methyl)amino] pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
294		(5R)-N-(2-chlorophenyl)-7-[(E)-5-(dimethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
295		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

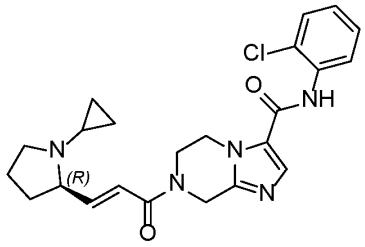
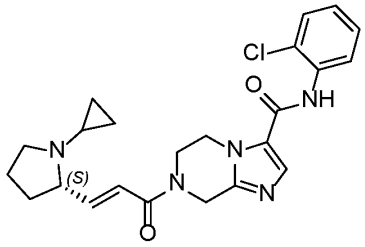
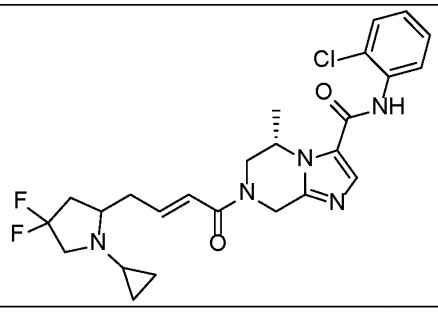
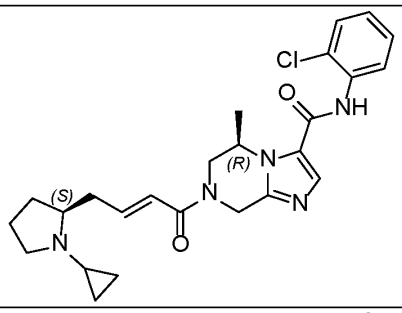
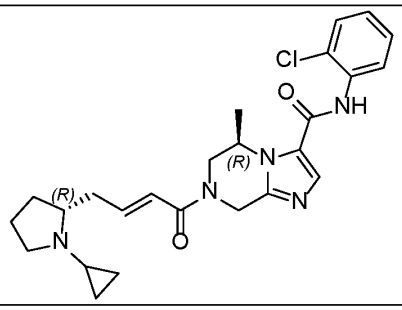
Compound No.	Structure	Compound Name
296		(6S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
297		(6R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
298		(E)-N-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
299		N-(2-chlorophenyl)-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide
300		N-(2-chlorophenyl)-7-[(E,4R)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
301		(6S)-N-(2-chlorophenyl)-6-methyl-7-[rac-(E)-4-(3-methoxyazetidin- 1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

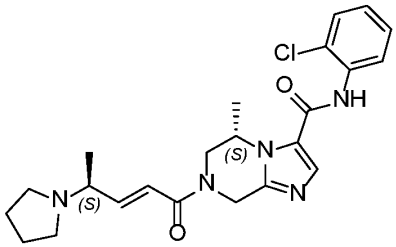
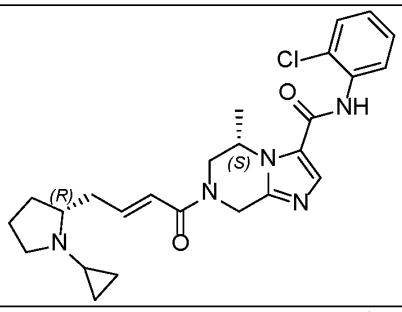
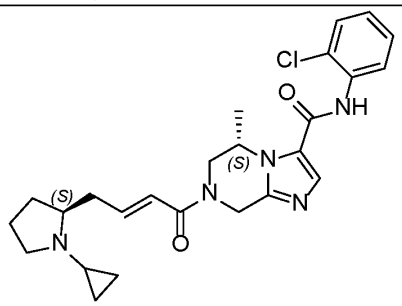
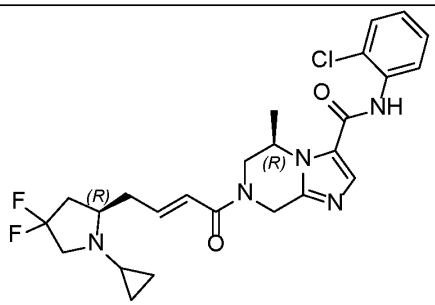
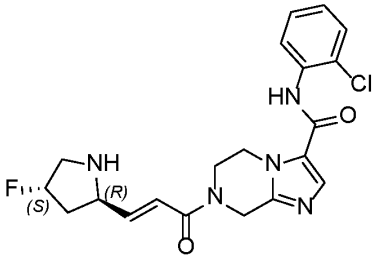
Compound No.	Structure	Compound Name
302		(6R)-N-(2-chlorophenyl)-6-methyl-7-[rac-(E)-4-(3-methoxyazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
303		(S,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
304		(R,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
305		N-(2-chlorophenyl)-7-[(E)-4-(2-methylazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
306		N-(2-chlorophenyl)-7-[(E)-4-[(2R)-2-methylazetidin-1-yl]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
307		N-(2-chlorophenyl)-7-[(E)-4-[(2S)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

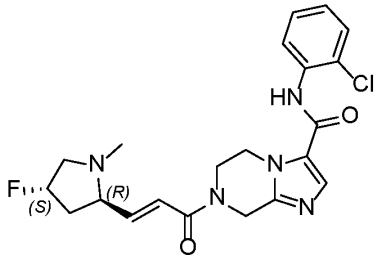
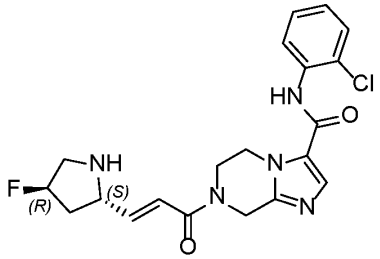
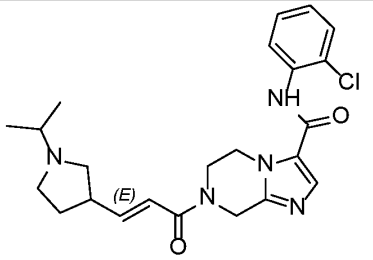
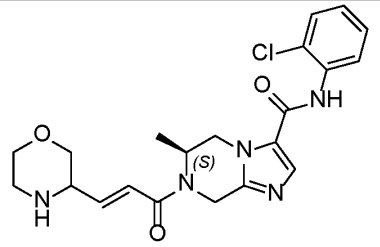
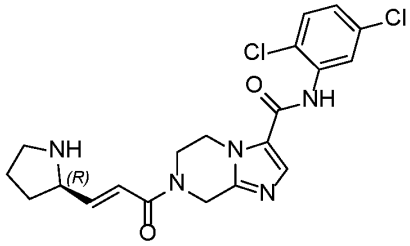
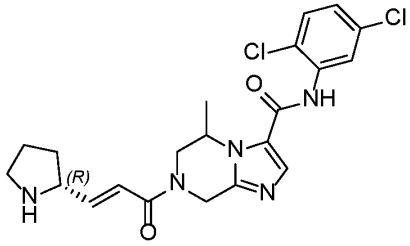
Compound No.	Structure	Compound Name
308		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-methylazetidin-1-yl)but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
309		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylazetidin-1-yl] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
310		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
311		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
312		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-methylazetidin-1-yl)but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

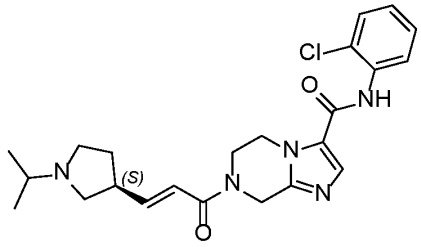
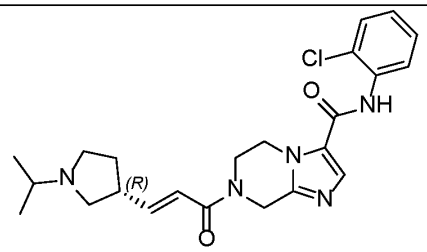
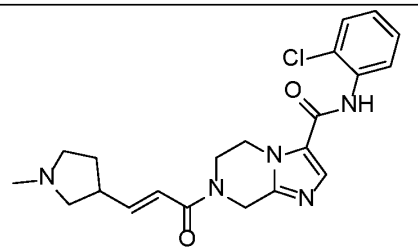
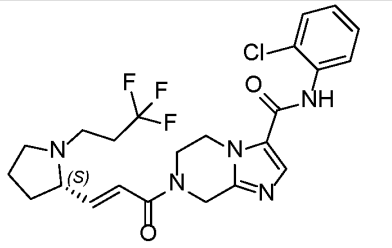
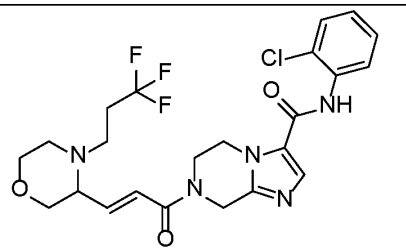
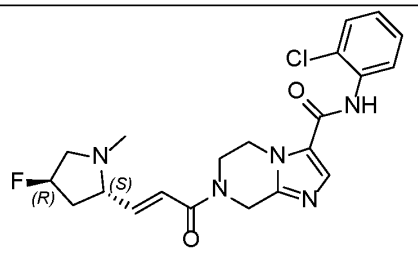
Compound No.	Structure	Compound Name
313		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylazetidin-1-yl] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
314		(5R)-N-(2- chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
315		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
316		(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-[ethyl(methyl)amino]pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
317		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[3-(difluoromethyl)azetidin-1-yl]-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (5R)-N-(2-chlorophenyl)-7-[(E)-4-[3-(difluoromethyl)azetidin-1-yl] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

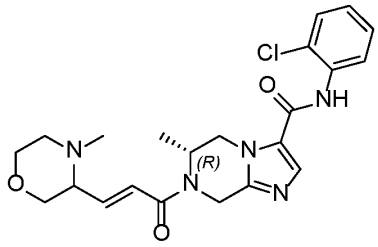
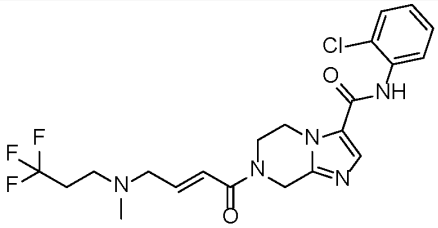
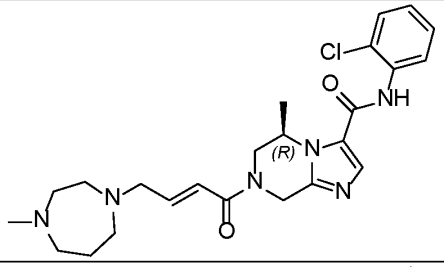
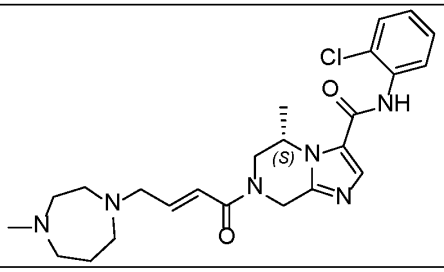
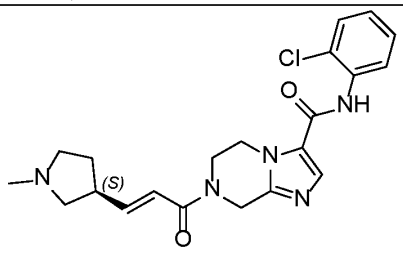
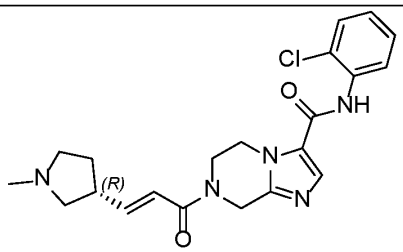
Compound No.	Structure	Compound Name
318		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
319		(R,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
320		(S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
321		N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-phenylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
322		(E)-N-(2-chlorophenyl)-7-(3-(1-phenylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
323		(E)-N-(2-chlorophenyl)-7-(3-(1-cyclopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

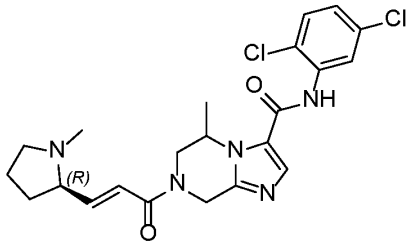
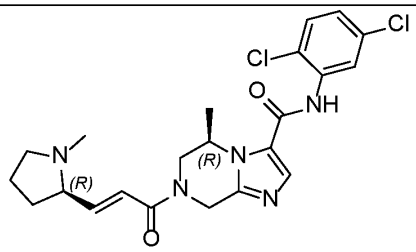
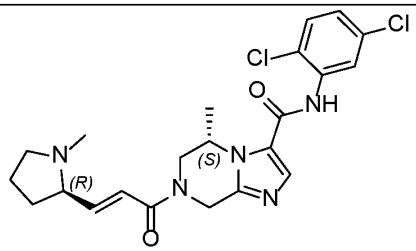
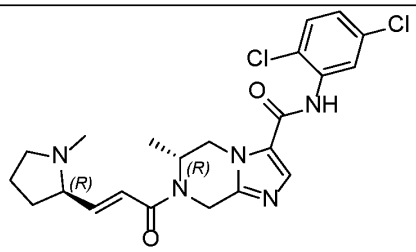
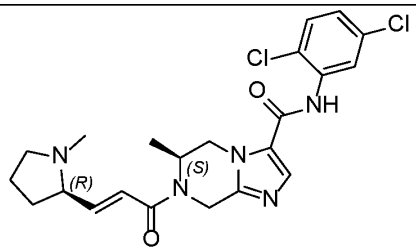
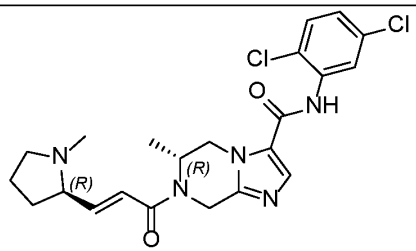
Compound No.	Structure	Compound Name
324		N-(2-chlorophenyl)-7-[(E)-3-[(2R)-1-cyclopropylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
325		N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-cyclopropylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
326		(5S)-N-(2-chlorophenyl)-7-[(E)-4-(1-cyclopropyl-4,4-difluoro-pyrrolidin -2-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
327		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
328		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

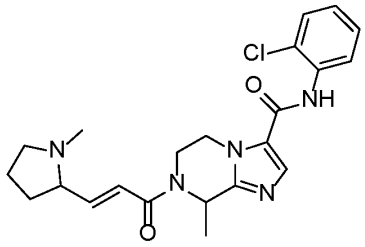
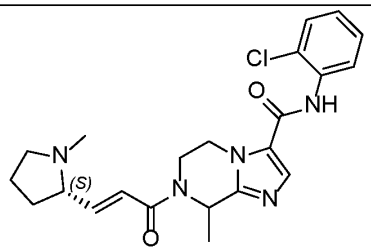
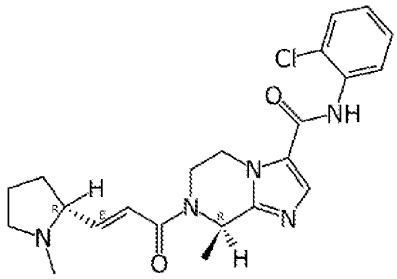
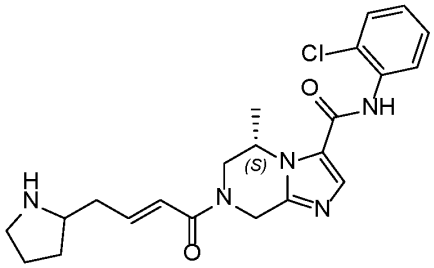
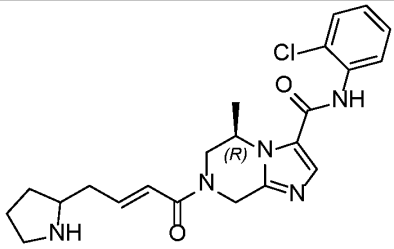
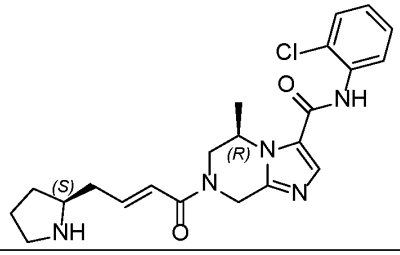
Compound No.	Structure	Compound Name
329		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
330		(S)-N-(2-chlorophenyl)-7-((E)-4-((R)-1-cyclopropylpyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
331		(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
332		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-1-cyclopropyl-4,4-difluoro-pyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
333		N-(2-chlorophenyl)-7-((E)-3-((2R,4S)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

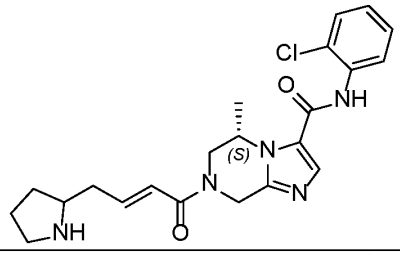
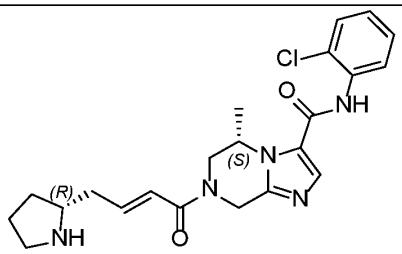
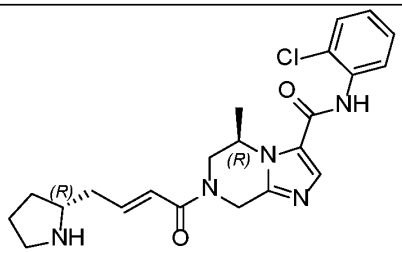
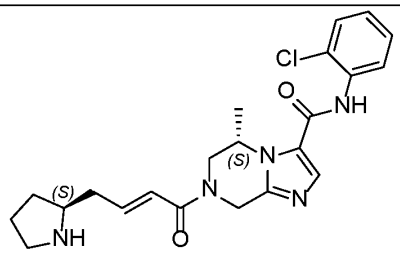
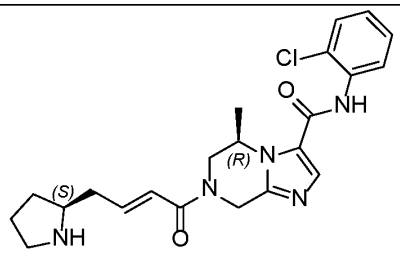
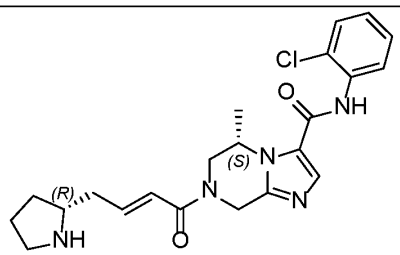
Compound No.	Structure	Compound Name
334		N-(2-chlorophenyl)-7-((E)-3-((2R,4S)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
335		N-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoropyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
336		N-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
337		(6S)-N-(2-chlorophenyl)-6-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
338		N-(2,5-dichlorophenyl)-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
339		N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

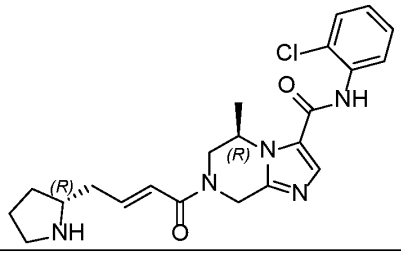
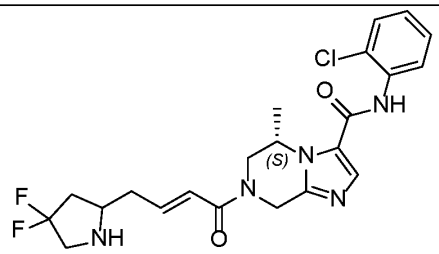
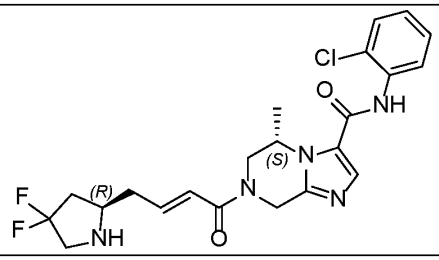
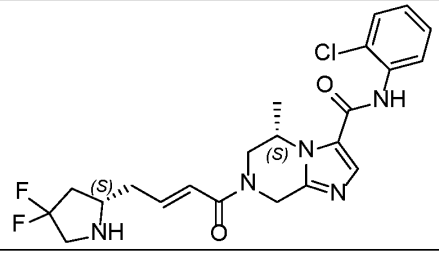
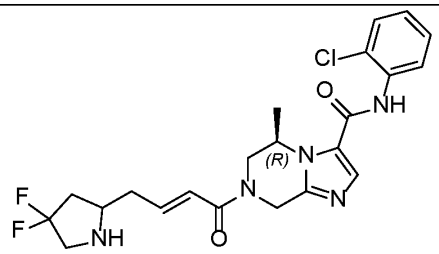
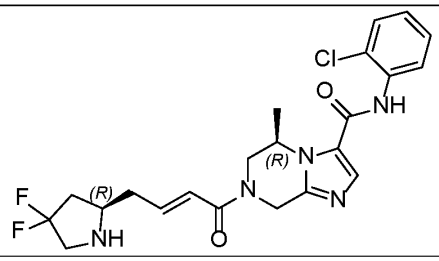
Compound No.	Structure	Compound Name
340		N-(2-chlorophenyl)-7-[(E)-3-[(3S)-1-isopropylpyrrolidin-3-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
341		N-(2-chlorophenyl)-7- [(E)-3-[(3R)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
342		N-(2-chlorophenyl)-7-[(E)-3-(1-methylpyrrolidin-3-yl)prop-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
343		N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
344		N-(2-chlorophenyl)-7-[(E)-3-[4-(3,3,3-trifluoropropyl)morpholin-3-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
345		N-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

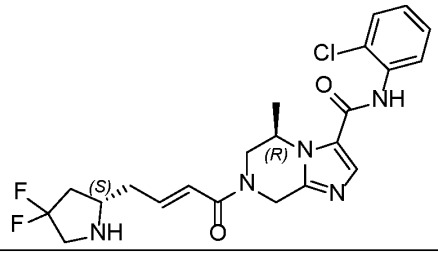
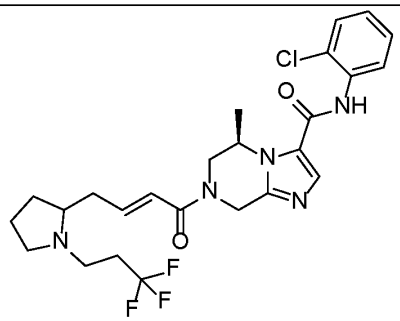
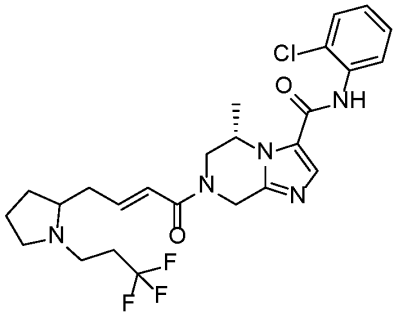
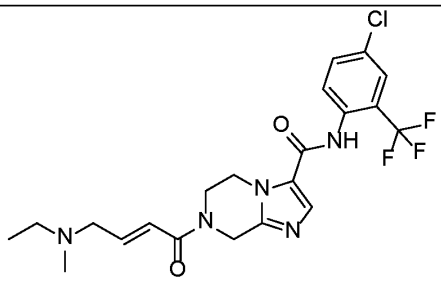
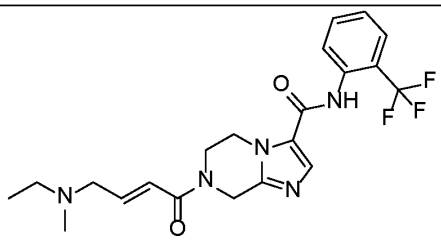
Compound No.	Structure	Compound Name
346		(6R)-N-(2-chlorophenyl)-6-methyl-7-[(E)-3-(4-methylmorpholin-3-yl) prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
347		N-(2-chlorophenyl)-7-[(E)-4-[methyl(3,3,3-trifluoropropyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
348		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(4-methyl-1,4-diazepan-1-yl)-but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
349		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(4-methyl-1,4-diazepan-1-yl)-but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
350		N-(2-chlorophenyl) -7-[(E)-3-[(3S)-1-methylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
351		N-(2-chlorophenyl) -7-[(E)-3-[(3R)-1-methylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

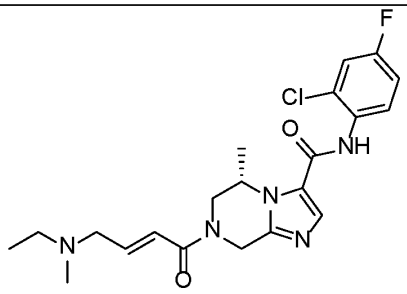
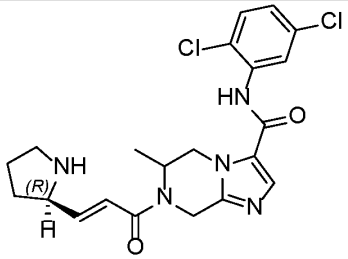
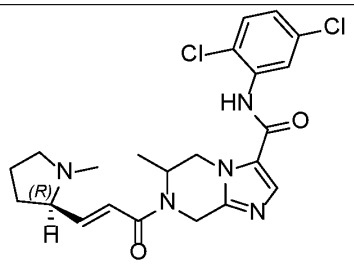
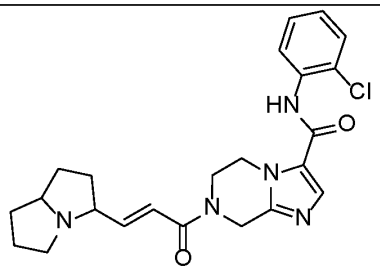
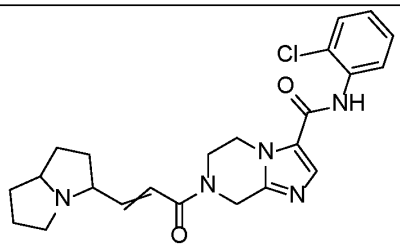
Compound No.	Structure	Compound Name
352		N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
353		(5R)-N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin -2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
354		(5S)-N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
355		(6R)-N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin -2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
356		(6S)-N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
357		(6R)-N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

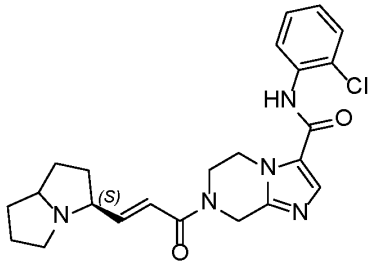
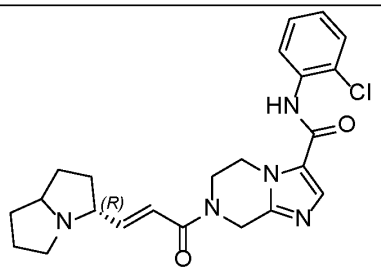
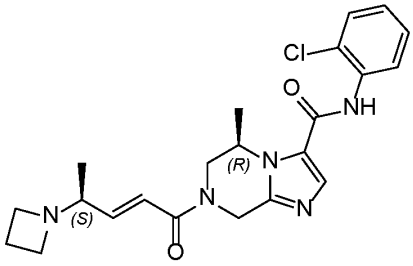
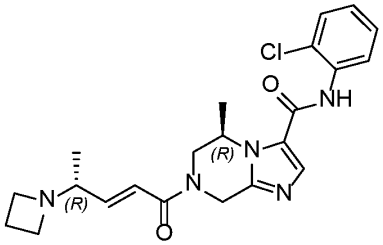
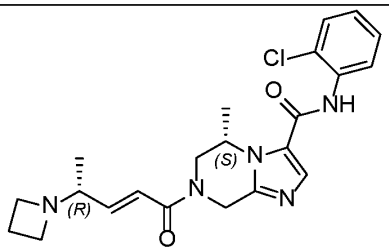
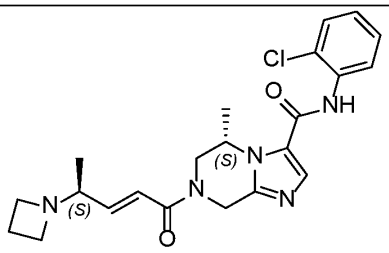
Compound No.	Structure	Compound Name
358		N-(2-chlorophenyl)-8-methyl-7-[(E)-3-(1-methylpyrrolidin -2-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
359		N-(2-chlorophenyl)-8-methyl-7-((E)-3-((S)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
360		(R)-N-(2-chlorophenyl)-8-methyl-7-((E)-3-((S)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
361		(5S)-N-(2-chlorophenyl)-5-methyl-7-((E)-4-(pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
362		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
363		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-pyrrolidin-2-yl]but- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

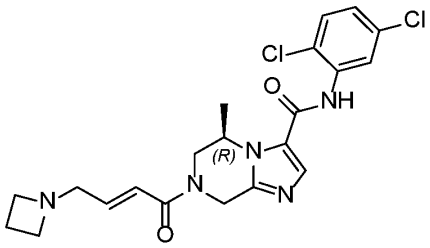
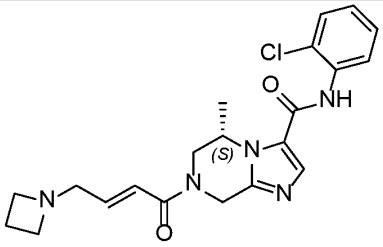
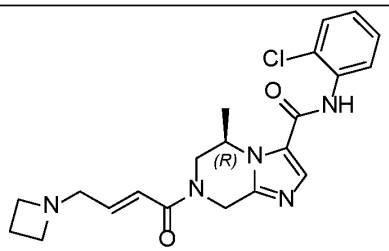
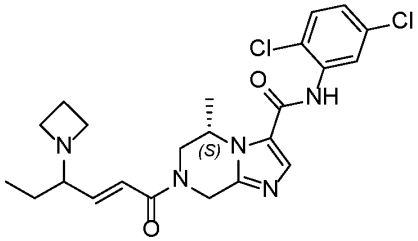
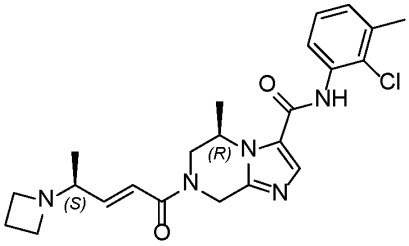
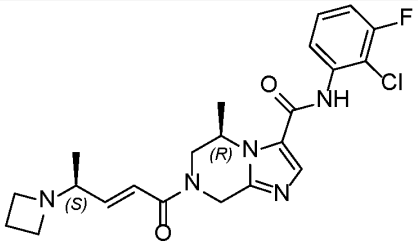
Compound No.	Structure	Compound Name
364		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
365		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
366		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
367		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
368		(R)-N-(2-chlorophenyl)-5-methyl-7-((E)-4-((S)-pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
369		(S)-N-(2-chlorophenyl)-5-methyl-7-((E)-4-((R)-pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

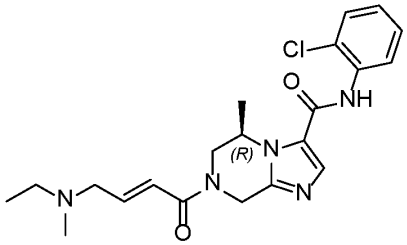
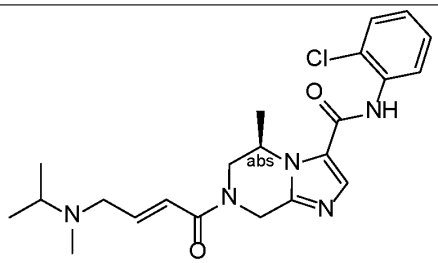
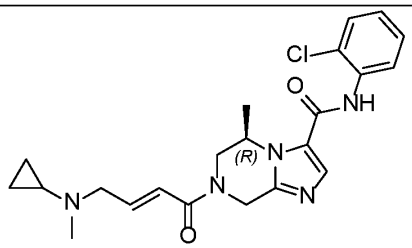
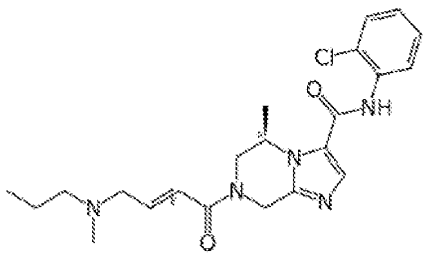
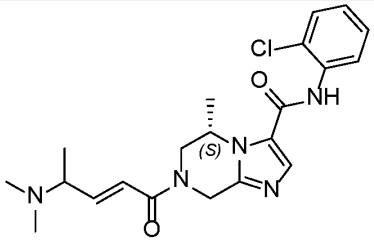
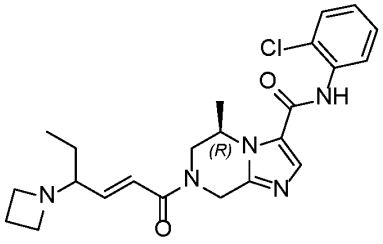
Compound No.	Structure	Compound Name
370		(R)-N-(2-chlorophenyl)-5-methyl-7-((E)-4-((R)-pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
371		(5S)-N-(2-chlorophenyl)-7-((E)-4-(4,4-difluoropyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
372		(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
373		(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
374		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(4,4-difluoropyrrolidin-2-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
375		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

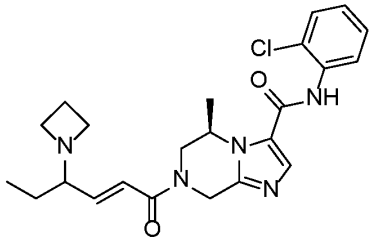
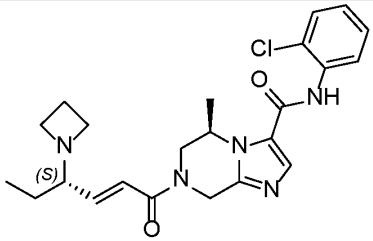
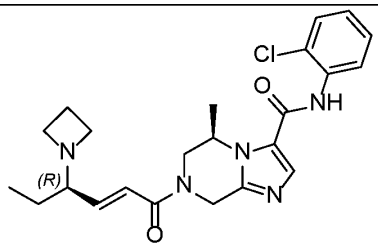
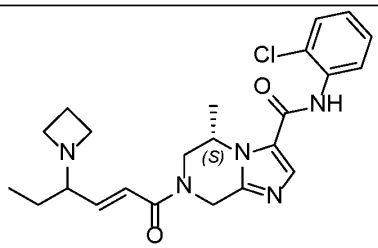
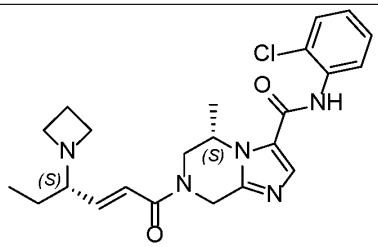
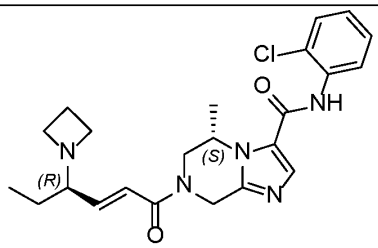
Compound No.	Structure	Compound Name
376		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
377		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
378		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl) pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
379		N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
380		7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-[2-(trifluoromethyl)phenyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

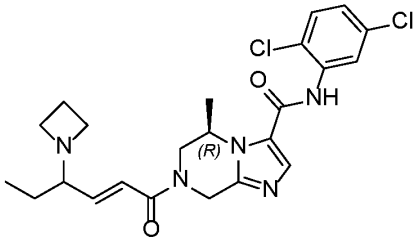
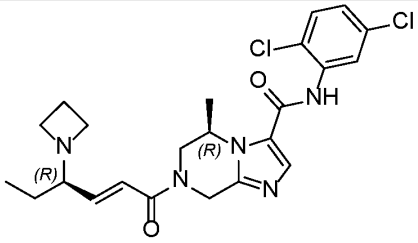
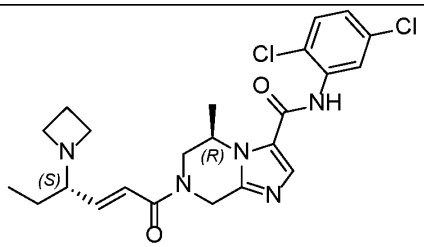
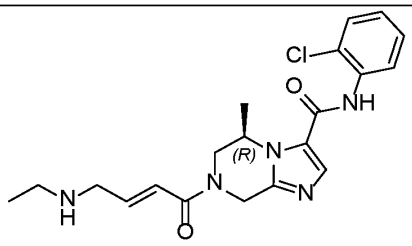
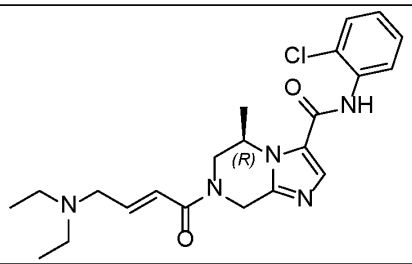
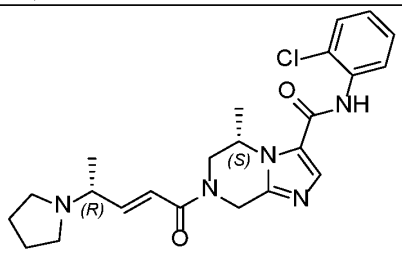
Compound No.	Structure	Compound Name
381		(5S)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
382		N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
383		N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
384		(E)-N-(2-chlorophenyl)-7-(3-(hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
385		N-(2-chlorophenyl)-7-(3-(hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

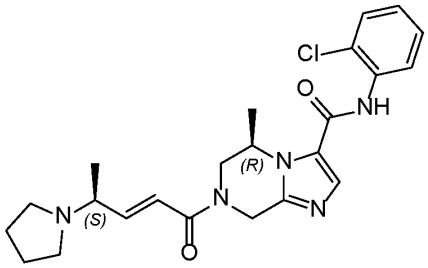
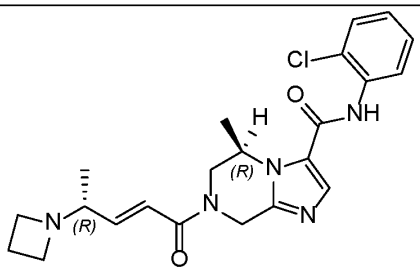
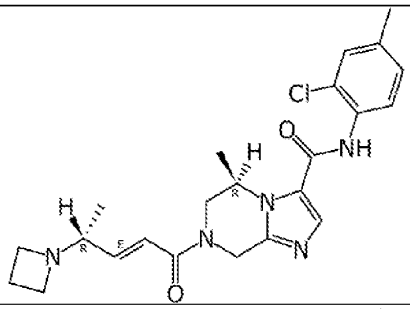
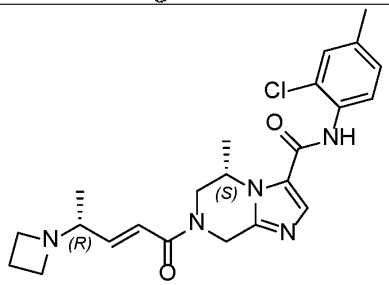
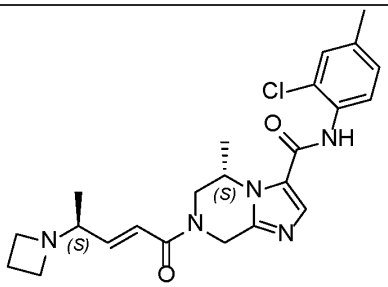
Compound No.	Structure	Compound Name
386		N-(2-chlorophenyl)-7-((E)-3-((3S)-hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
387		N-(2-chlorophenyl)-7-((E)-3-((3R)-hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
388		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
389		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
390		(S)-7-((R,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
391		(5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

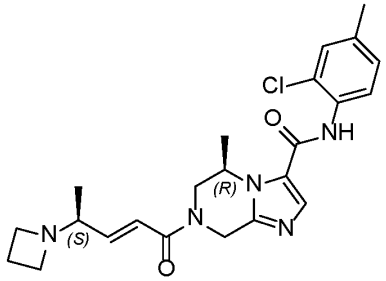
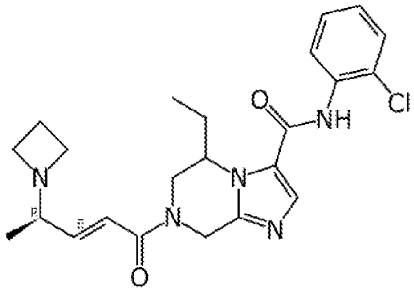
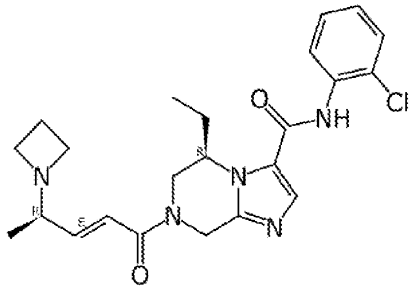
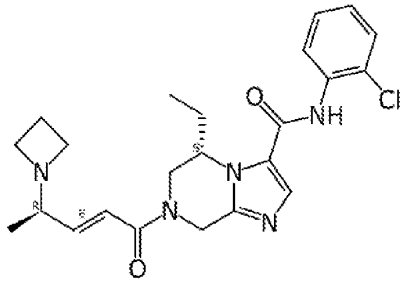
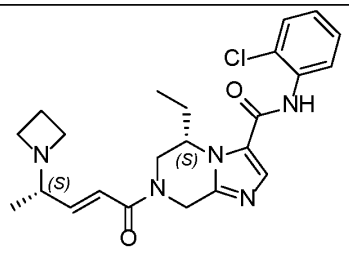
Compound No.	Structure	Compound Name
392		(5R)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2,5dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
393		(S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
394		(R,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
395		(5S)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
396		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
397		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-fluoro- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

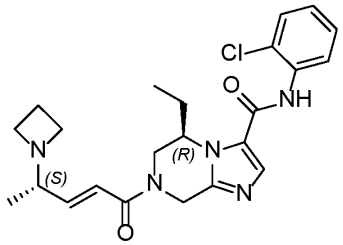
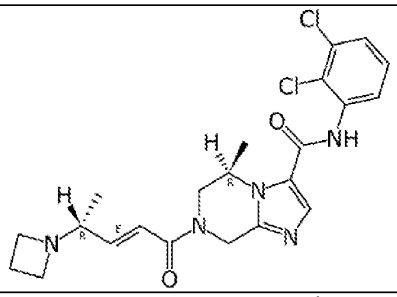
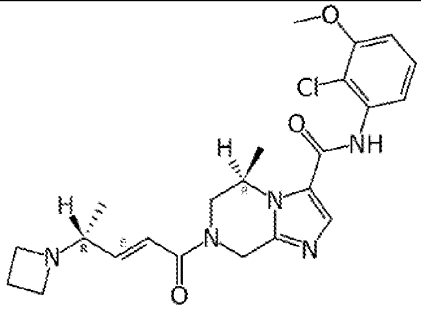
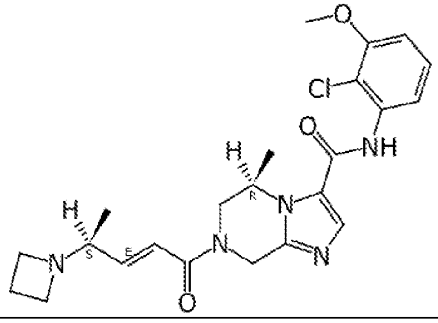
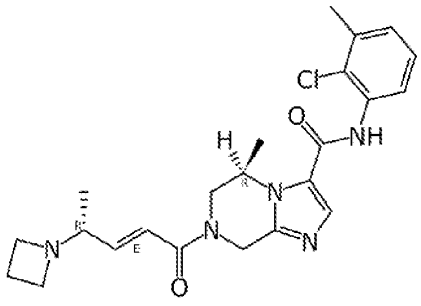
Compound No.	Structure	Compound Name
398		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
399		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[isopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
400		(5R)-N-(2-chlorophenyl)-7-[(E)-4-[cyclopropyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
401		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[methyl(propyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
402		(5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
403		(5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

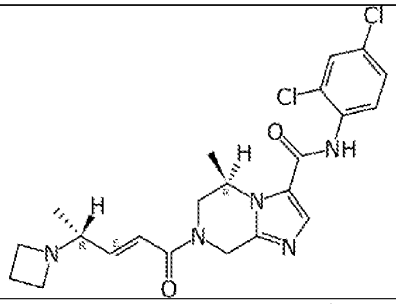
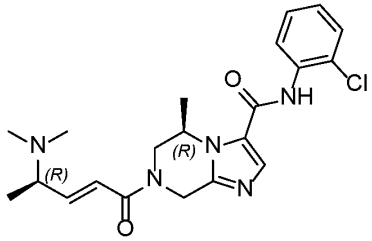
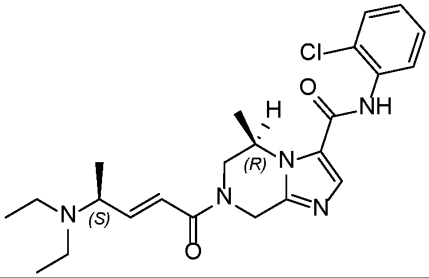
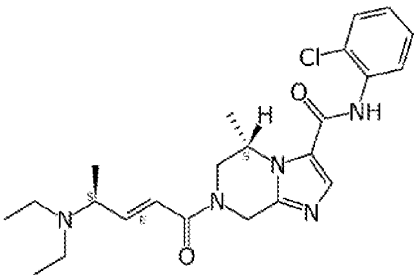
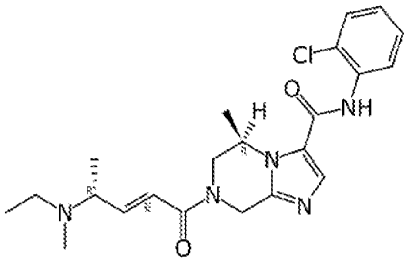
Compound No.	Structure	Compound Name
404		(5R)-7-((E)-4-(azetidin-1-yl)hex-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
405		(5R)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
406		(5R)-7-[(E,4R)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
407		(5S)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
408		(5S)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
409		(5S)-7-[(E,4R)-4- (azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

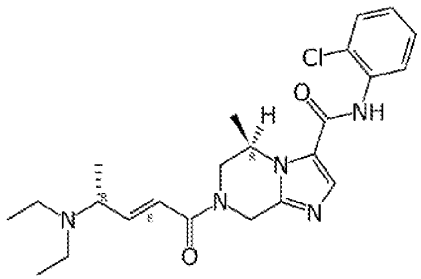
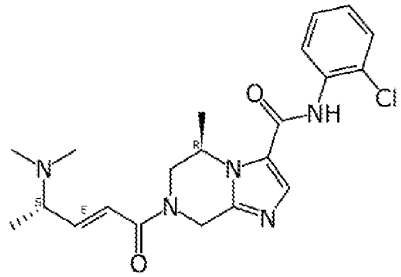
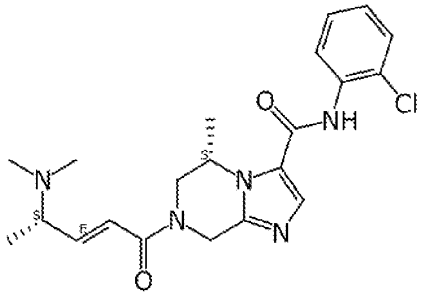
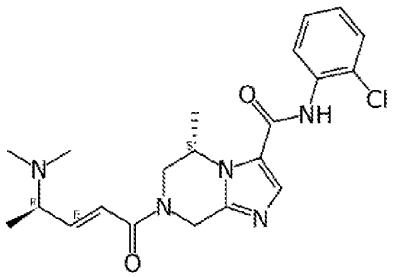
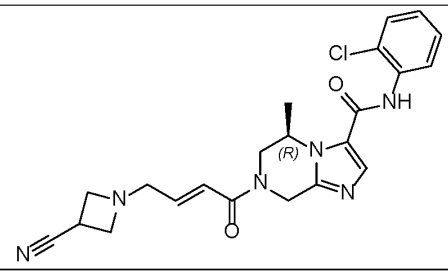
Compound No.	Structure	Compound Name
410		(5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
411		(5R)-7-[(E,4R)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
412		(5R)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
413		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
414		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(diethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
415		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

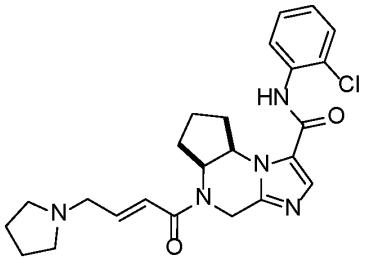
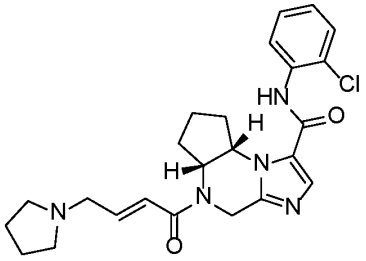
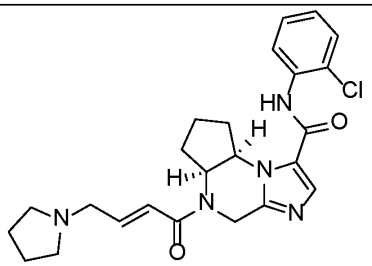
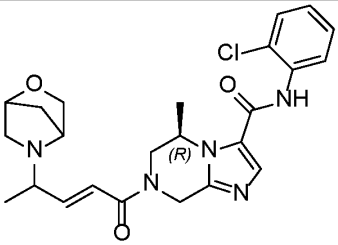
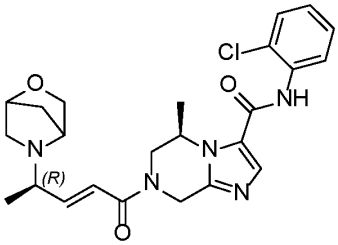
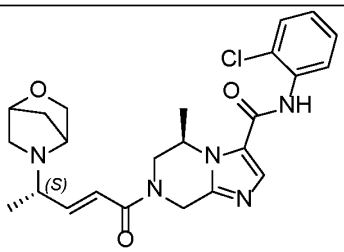
Compound No.	Structure	Compound Name
416		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
417		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
418		(R)-7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
419		(S)-7-((R,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
420		(S)-7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

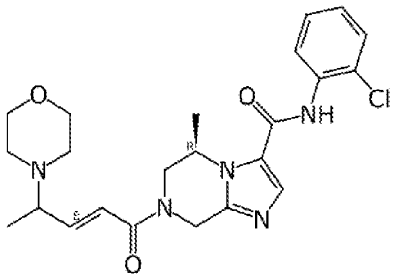
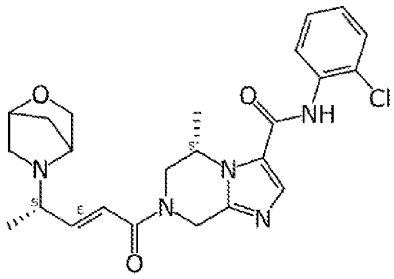
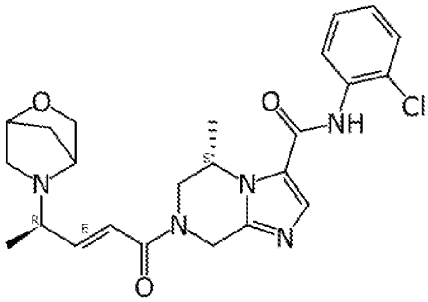
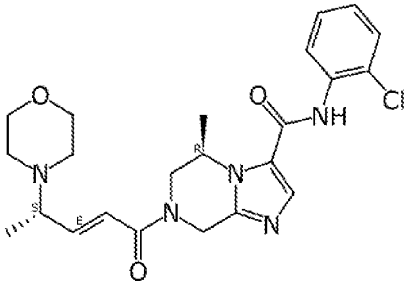
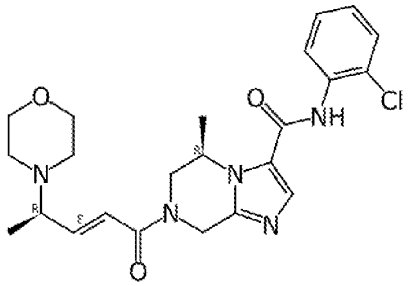
Compound No.	Structure	Compound Name
421		(R)-7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
422		7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
423		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
424		(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
425		(S)-7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

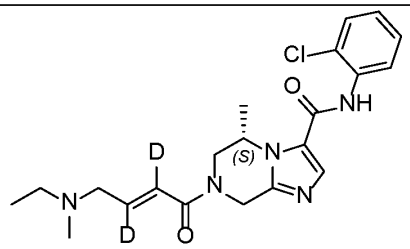
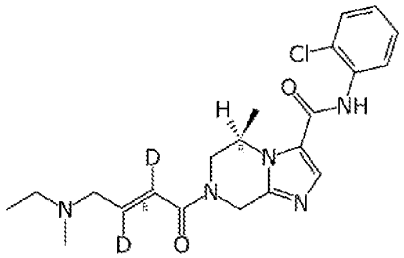
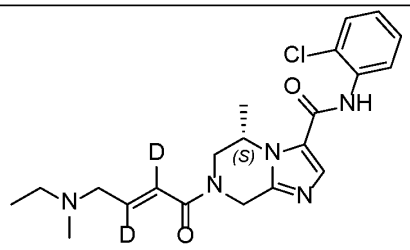
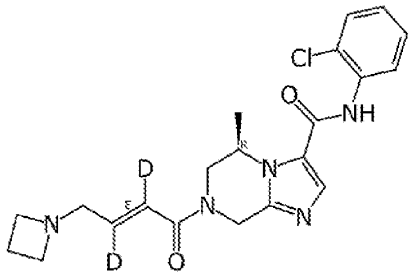
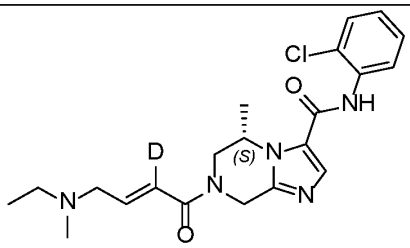
Compound No.	Structure	Compound Name
426		(R)-7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
427		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,3-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
428		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chloro-3-methoxy-phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
429		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chloro-3-methoxy-phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
430		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

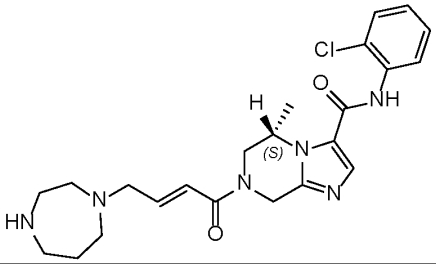
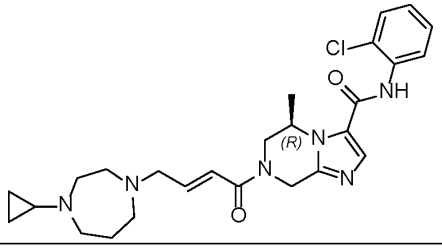
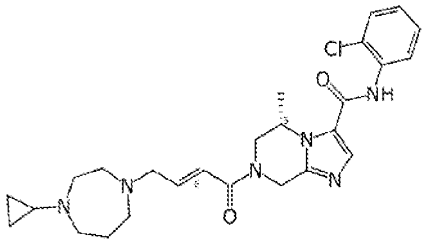
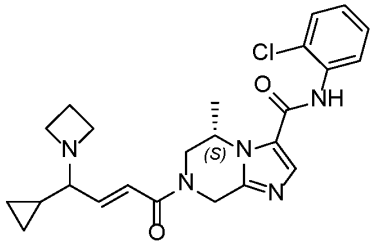
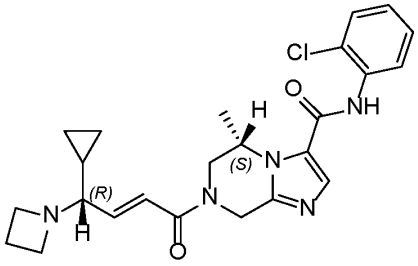
Compound No.	Structure	Compound Name
431		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,4-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
432		(5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
433		(5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
434		(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
435		(5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

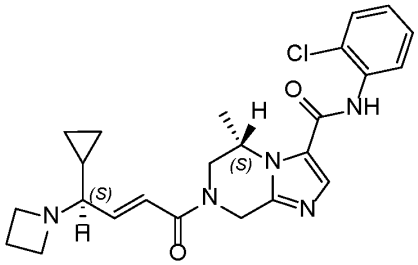
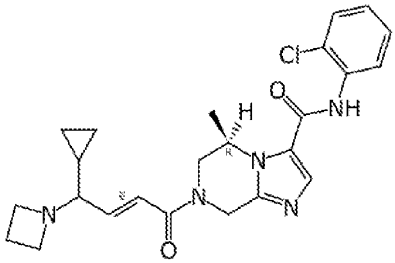
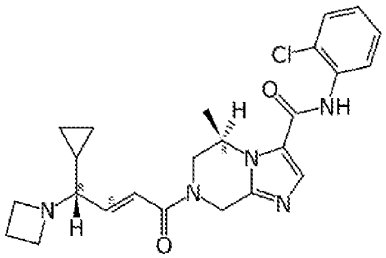
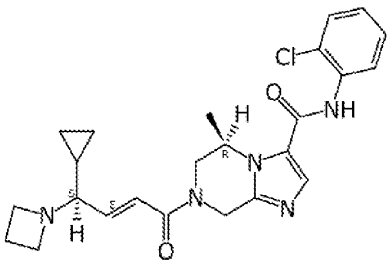
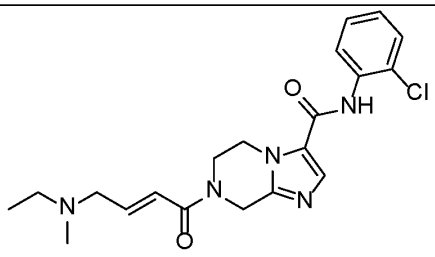
Compound No.	Structure	Compound Name
436		(5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
437		(5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(dimethylamino)pent-2-enoyl]-5 -methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
438		(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
439		(5S)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
440		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

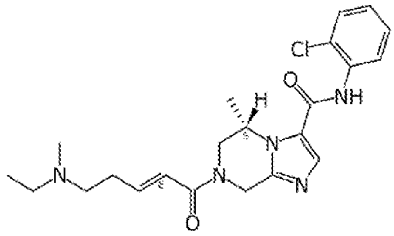
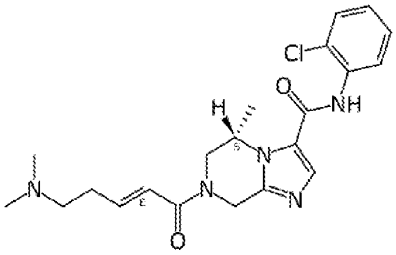
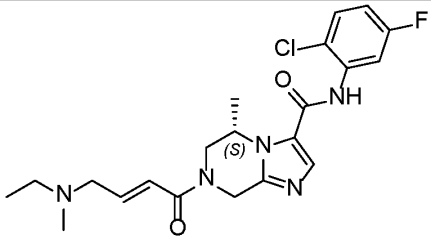
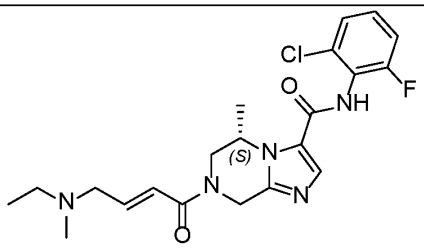
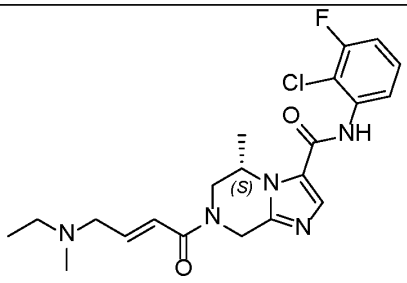
Compound No.	Structure	Compound Name
441		*cis*-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.02,6]dodeca-9,11-diene-12-carboxamide
442		(2S,6R)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.02,6]dodeca-9,11-diene-12-carboxamide
443		(2R,6S)-N-(2 -chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.02,6]dodeca-9,11-diene-12-carboxamide
444		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo [2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
445		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
446		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

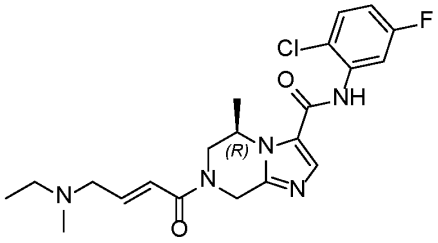
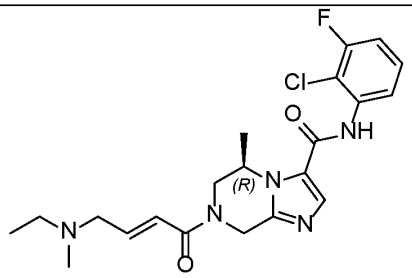
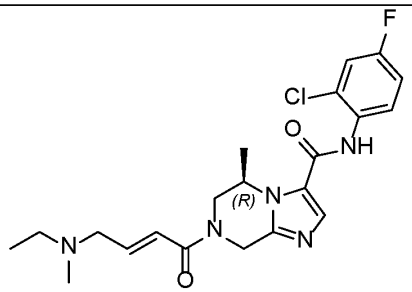
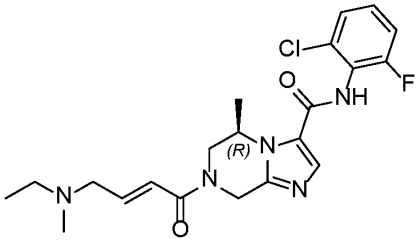
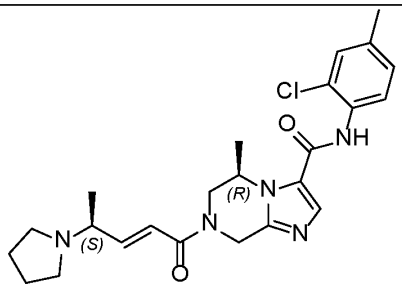
Compound No.	Structure	Compound Name
447		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-morpholinopent-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
448		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
449		(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
450		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-morpholinopent-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
451		(5R)-N-(2-chlorophenyl) -5-methyl-7-[(E,4S)-4-morpholinopent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

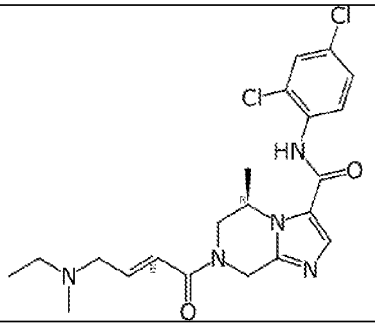
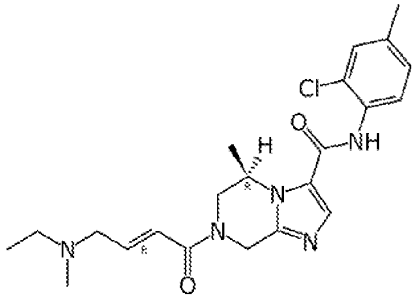
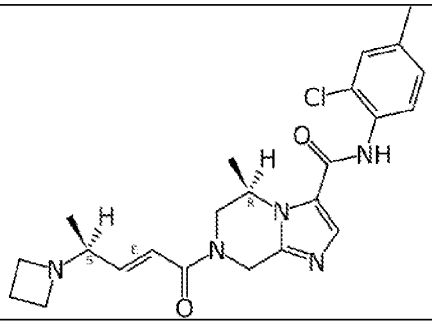
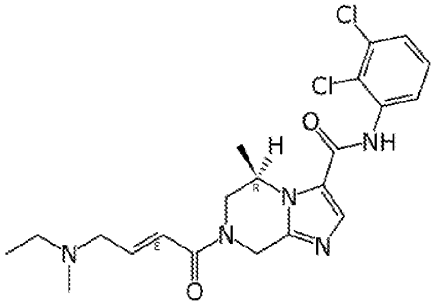
Compound No.	Structure	Compound Name
452		(5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
453		(5R)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
454		(5S)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
455		(5R)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
456		(5S)-N-(2-chlorophenyl)-7-[(E)-2-deuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

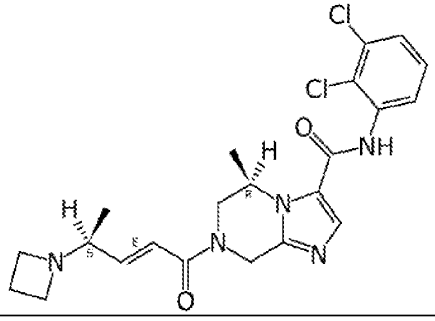
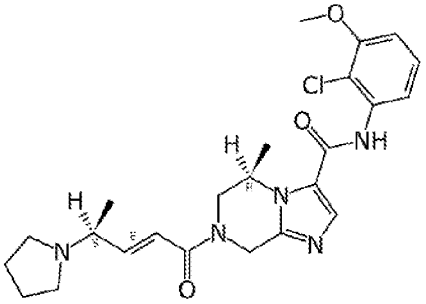
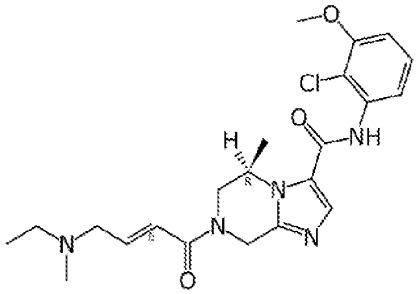
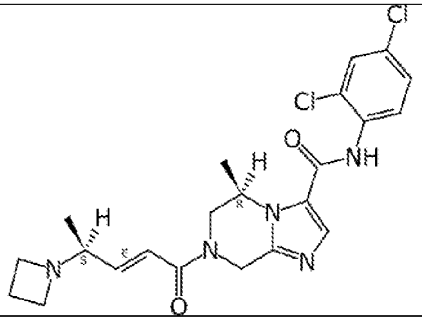
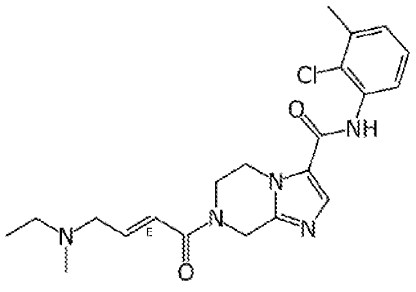
Compound No.	Structure	Compound Name
457		(S,E)-7-(4-(1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
458		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
459		(5S)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
460		(5S)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
461		(5S)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

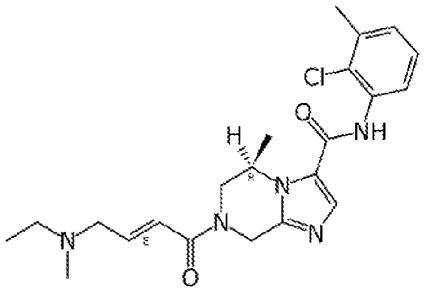
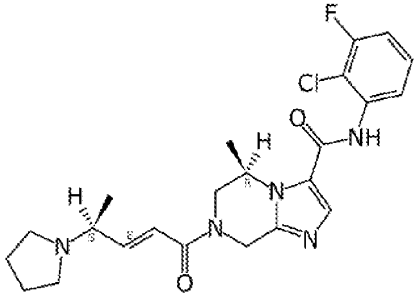
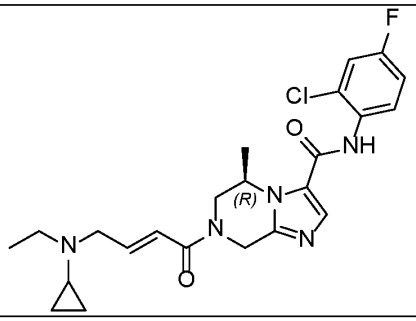
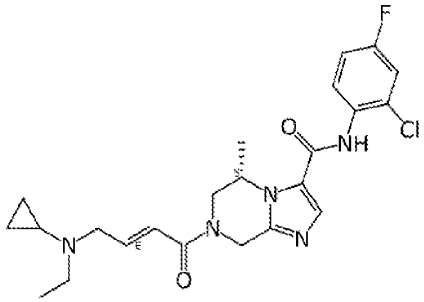
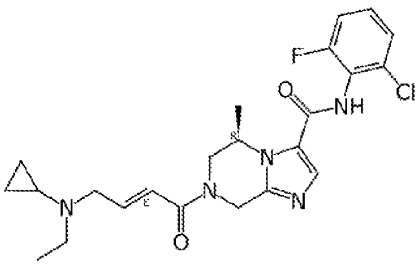
Compound No.	Structure	Compound Name
462		(5S)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
463		(5R)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
464		(5R)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
465		(5R)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
466		N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

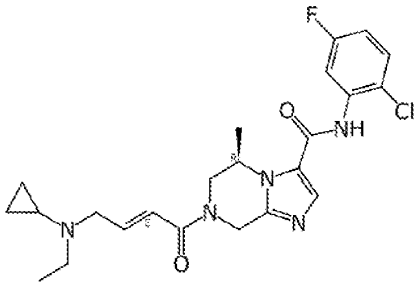
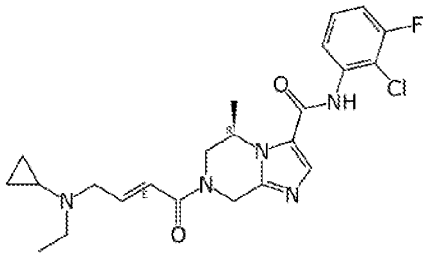
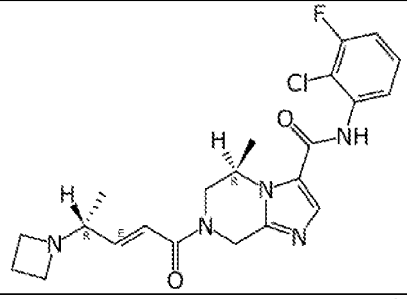
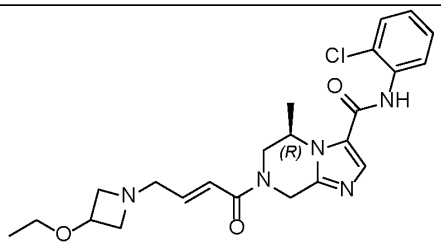
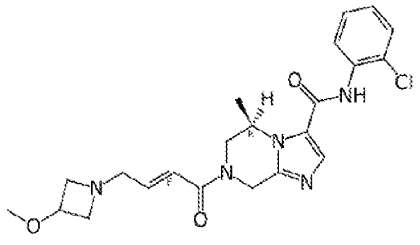
Compound No.	Structure	Compound Name
467		(5S)-N-(2-chlorophenyl)-7-[(E)-5-[ethyl(methyl)amino]pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
468		(5S)-N-(2-chlorophenyl)-7-[(E)-5-(dimethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
469		(5S)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
470		(5S)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
471		(5S)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

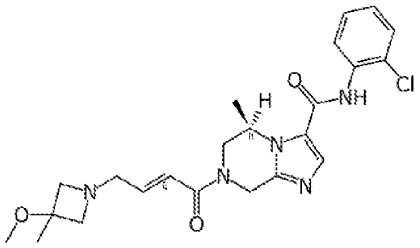
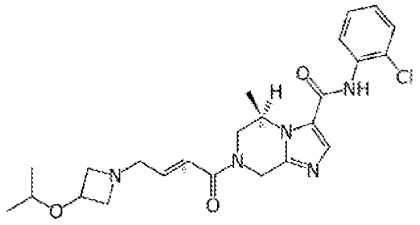
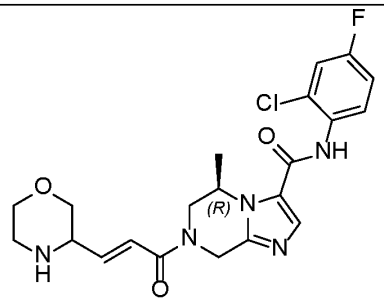
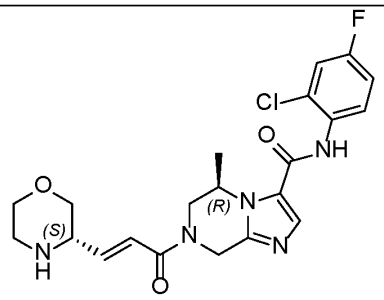
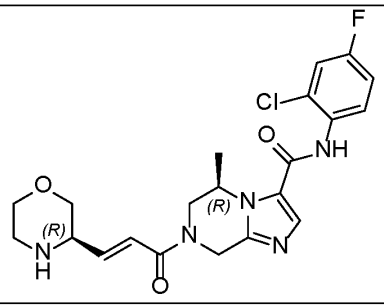
Compound No.	Structure	Compound Name
472		(5R)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
473		(5R)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
474		(5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
475		(5R)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
476		(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

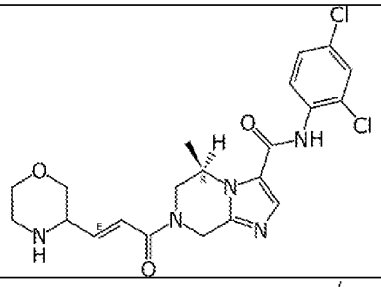
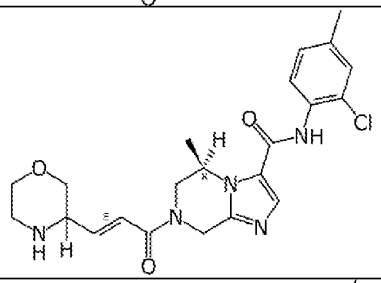
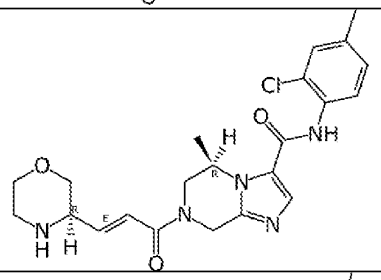
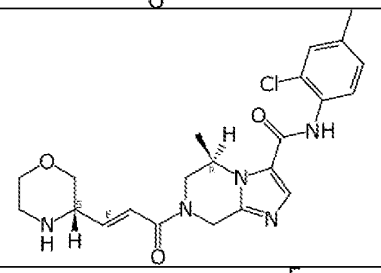
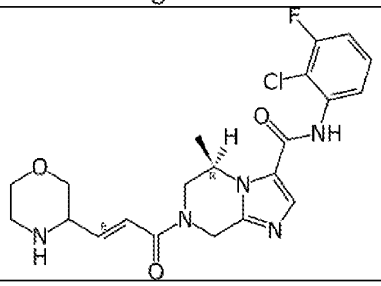
Compound No.	Structure	Compound Name
477		(5R)-N-(2,4-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
478		(5R)-N-(2-chloro-4-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
479		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-4-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
480		(5R)-N-(2,3-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

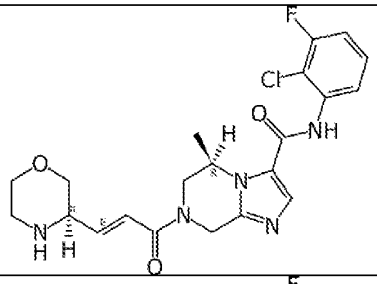
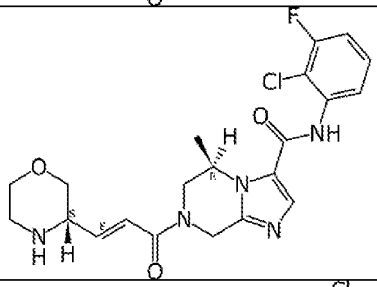
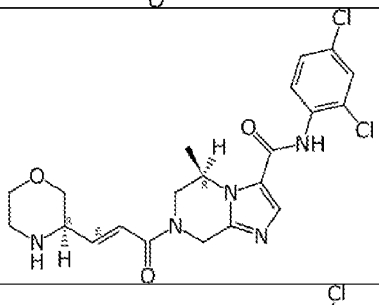
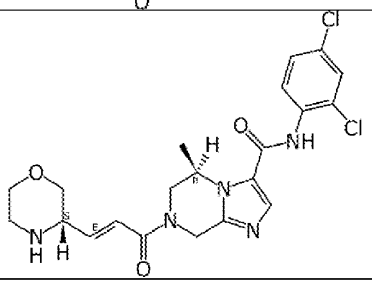
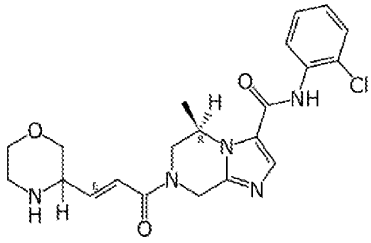
Compound No.	Structure	Compound Name
481		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,3-dichlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
482		(5R)-N-(2-chloro-3-methoxy-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
483		(5R)-N-(2-chloro-3-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
484		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,4-dichlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
485		N-(2-chloro-3-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

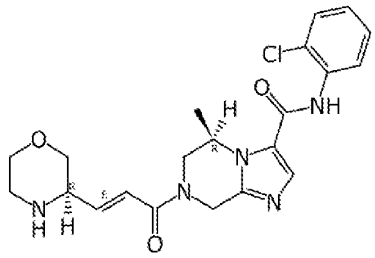
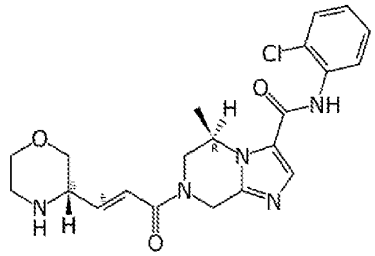
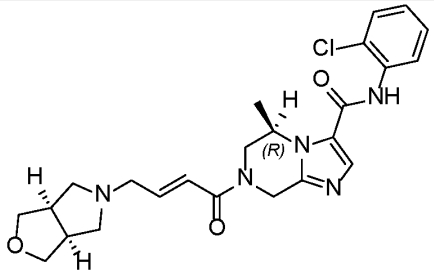
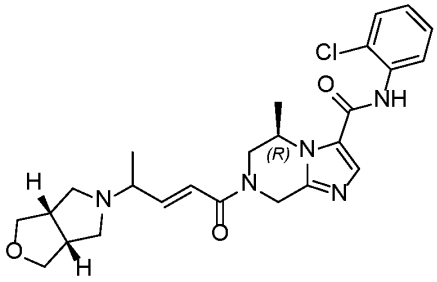
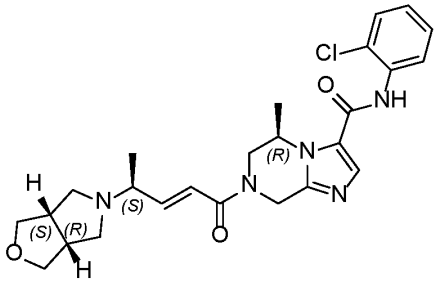
Compound No.	Structure	Compound Name
486		(5R)-N-(2-chloro-3-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
487		(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
488		(5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
489		(5S)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
490		(5R)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

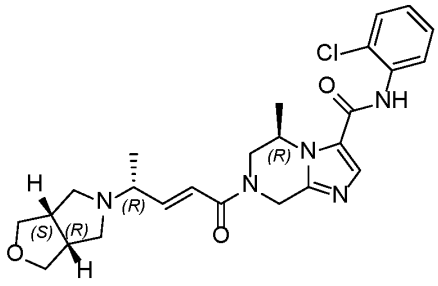
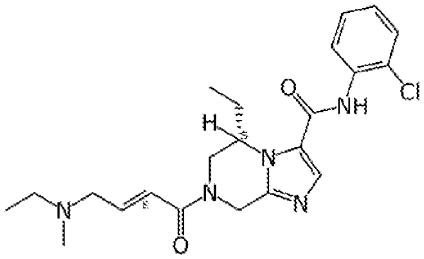
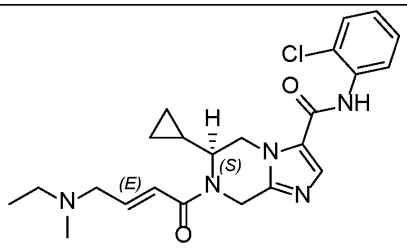
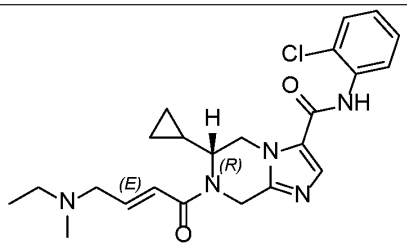
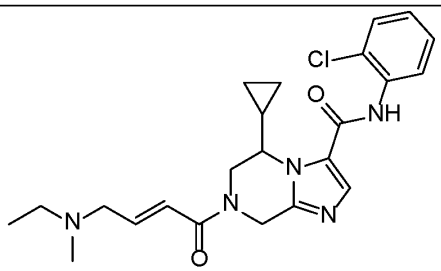
Compound No.	Structure	Compound Name
491		(5R)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
492		(5R)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
493		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-fluoro- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
494		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-ethoxyazetidin-1-yl)but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide b
495		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-methoxyazetidin-1-yl)but-2-enoyl]- 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

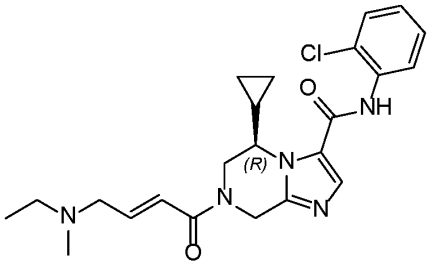
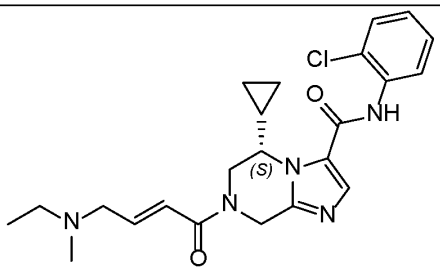
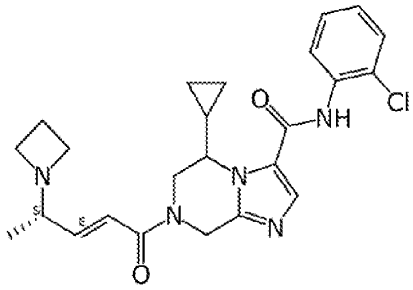
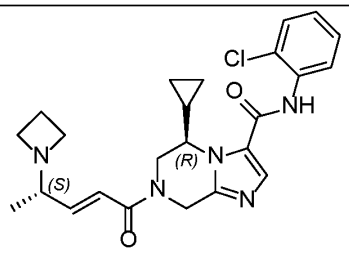
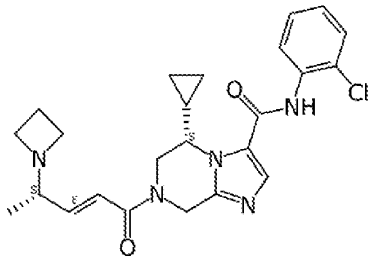
Compound No.	Structure	Compound Name
496		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-methoxy-3-methyl-azetidin-1-yl) but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
497		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-isopropoxyazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
498		(5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3- ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
499		(5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3- yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
500		(5R)-N- (2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

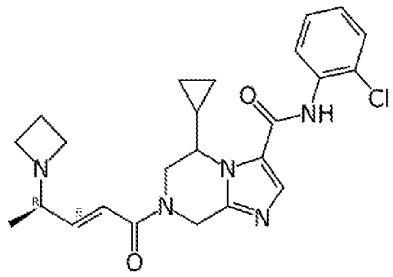
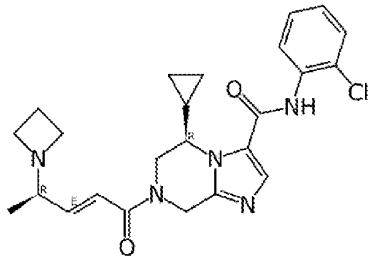
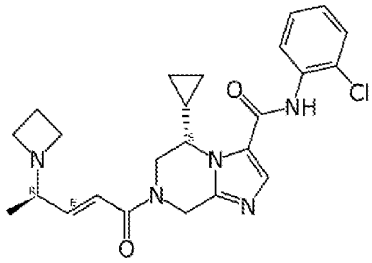
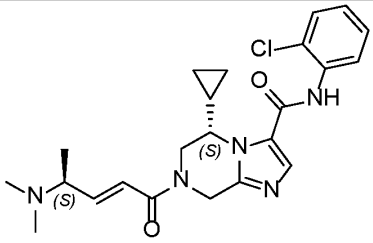
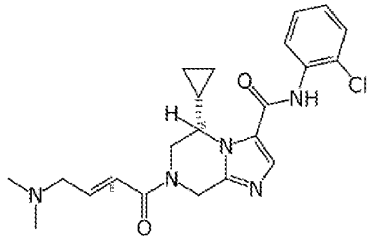
Compound No.	Structure	Compound Name
501		(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
502		(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-morpholin-3- ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
503		(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin- 3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
504		(5R)-N-(2- chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
505		(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3- ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

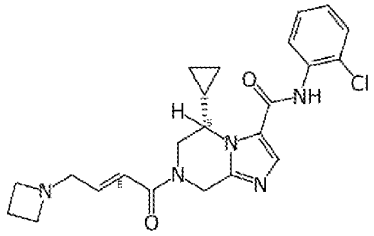
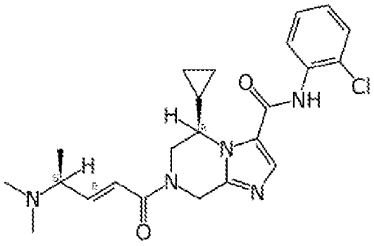
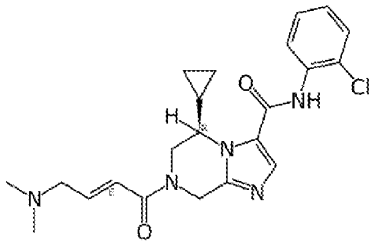
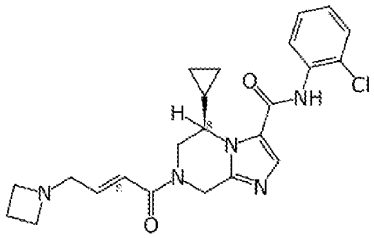
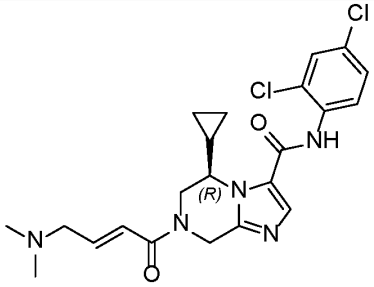
Compound No.	Structure	Compound Name
506		(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin- 3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
507		(5R)-N-(2- chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
508		(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
509		(5R)-N- (2,4-dichlorophenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
510		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

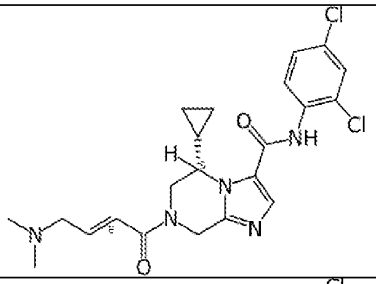
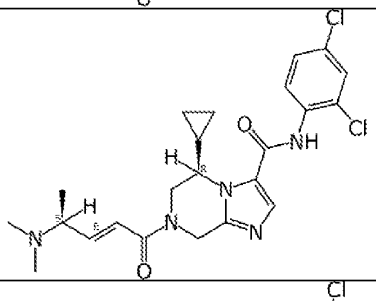
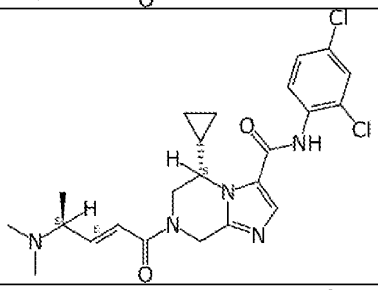
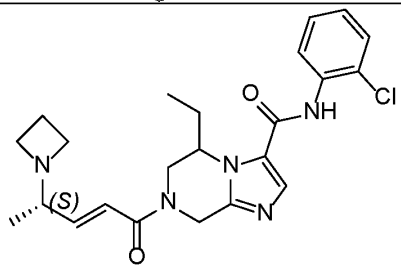
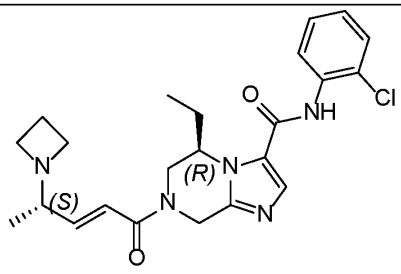
Compound No.	Structure	Compound Name
511		(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
512		(5R)-N-(2- chlorophenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
513		(5R)-7-[(E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
514		(5R)-7-[(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
515		(5R)-7-[(E,4S)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

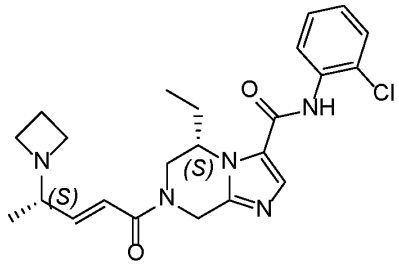
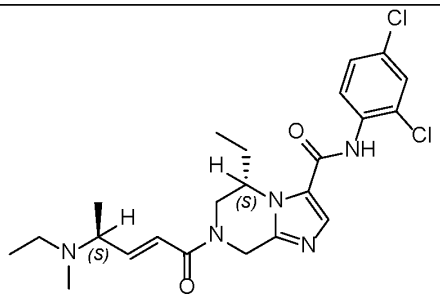
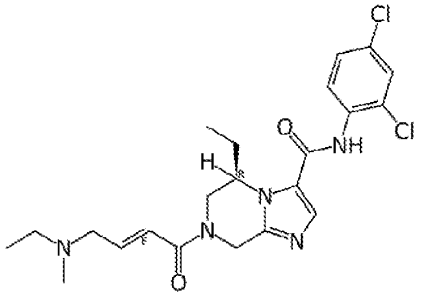
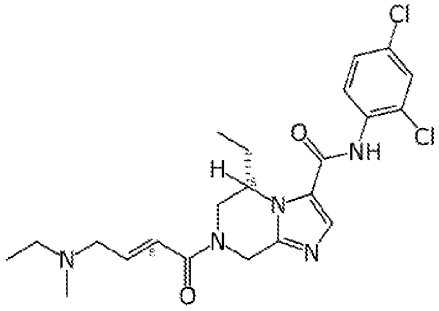
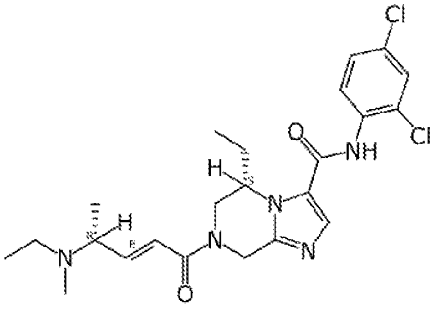
Compound No.	Structure	Compound Name
516		(5R)-7-[(E,4R)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
517		(5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
518		(6S)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
519		(6R)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
520		N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

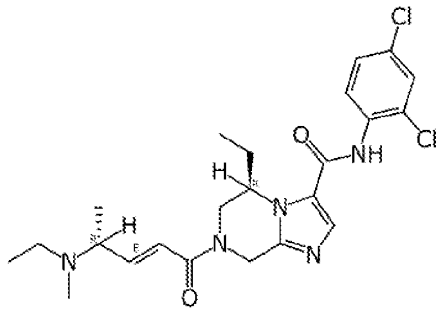
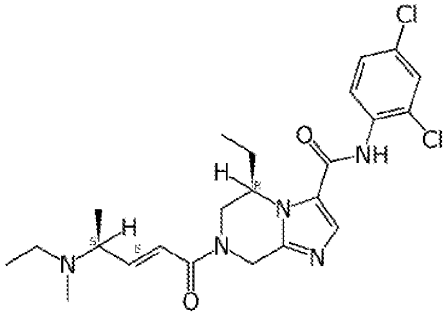
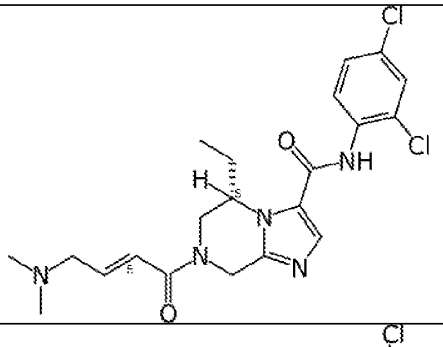
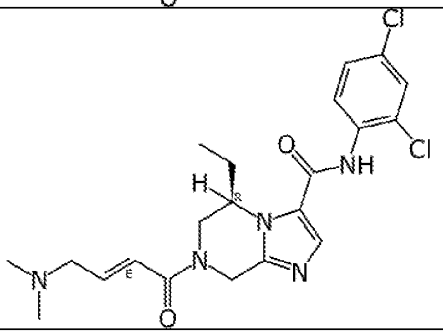
Compound No.	Structure	Compound Name
521		(5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
522		(5S)-N-(2- chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
523		7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
524		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5 -cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
525		(5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

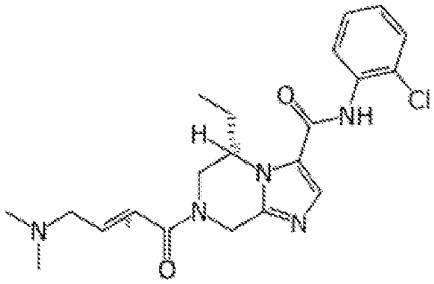
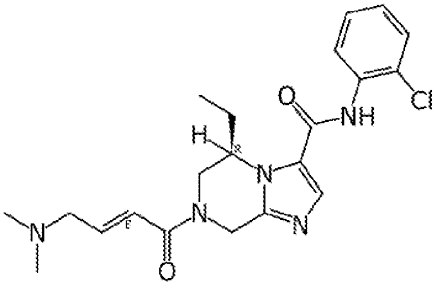
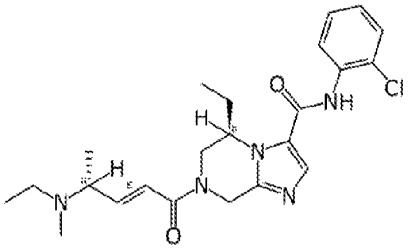
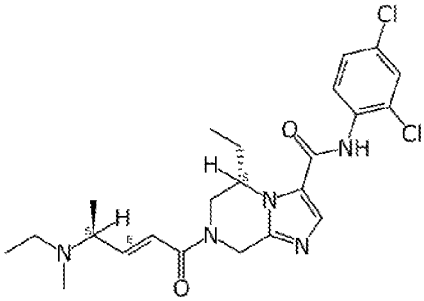
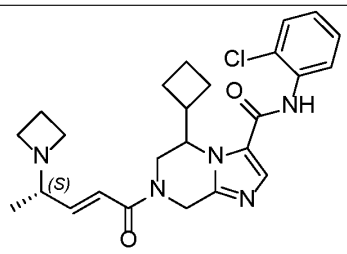
Compound No.	Structure	Compound Name
526		7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
527		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
528		(5S)-7-[(E,4R)-4- (azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
529		(S)-N-(2-chlorophenyl)-5-cyclopropyl-7-((S,E)-4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
530		(5S)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

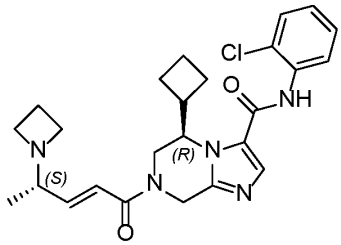
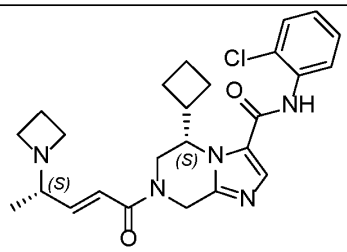
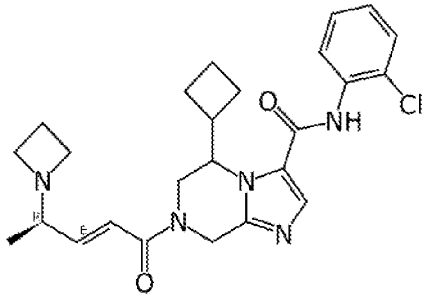
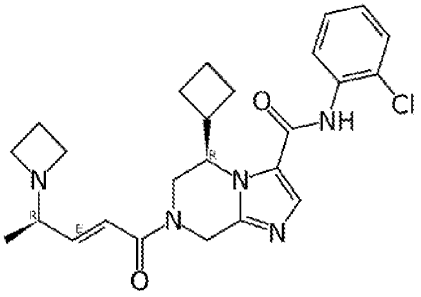
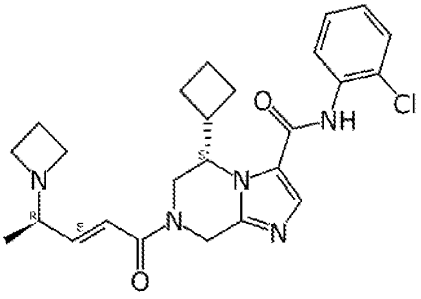
Compound No.	Structure	Compound Name
531		(5S)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
532		(5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
533		(5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
534		(5R)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
535		(5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide b

Compound No.	Structure	Compound Name
536		(5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
537		(5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
538		(5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
539		7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
540		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
541		(5S)-7-[(E,4S)-4- (azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
542		(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
543		(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
544		(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
545		(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
546		(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-((R,E)-4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
547		(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
548		(5S)-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5 -ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
549		(5R)-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl] -5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
550		(5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
551		(5R)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
552		(5R)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
553		(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
554		7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
555		(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
556		(5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
557		7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
558		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
559		(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

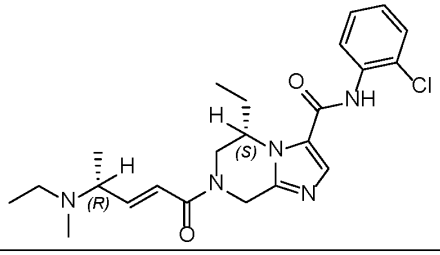
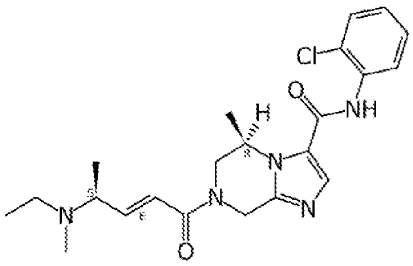
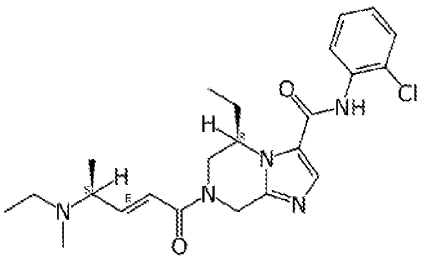
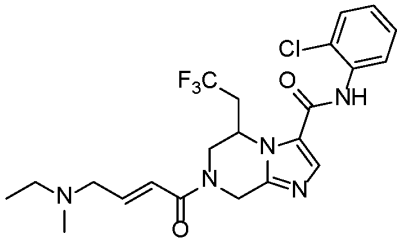
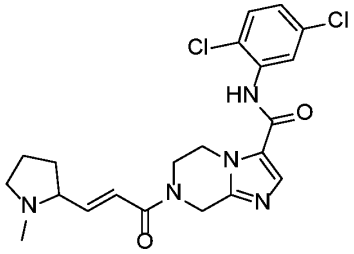
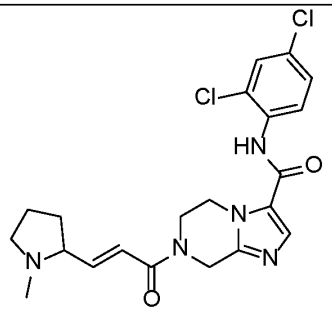
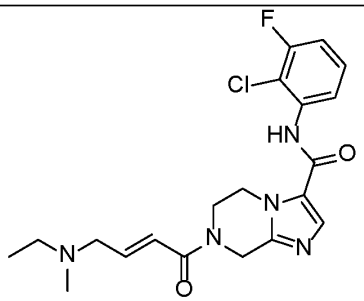
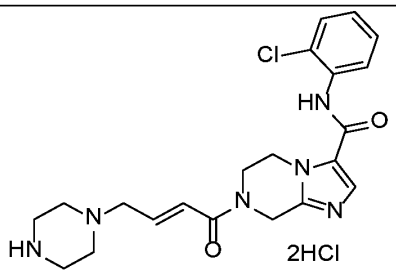
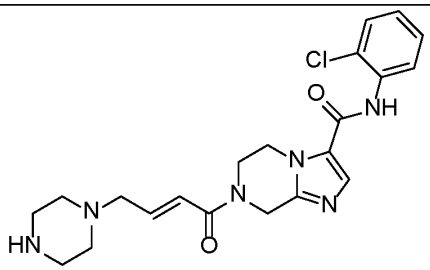
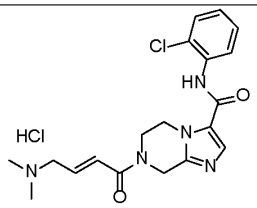
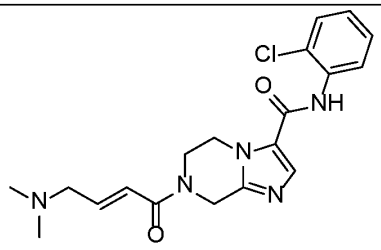
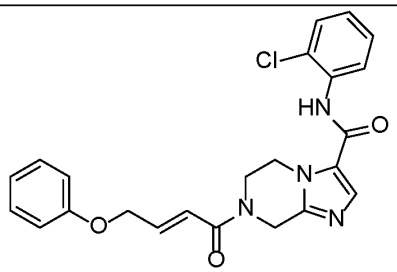
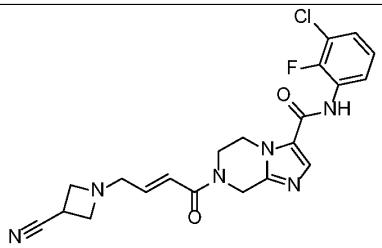
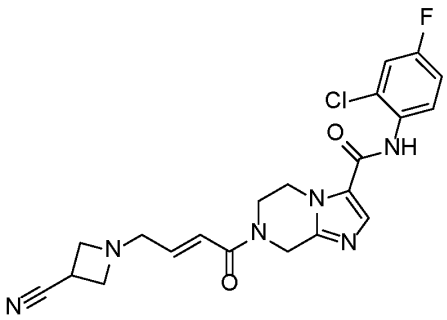
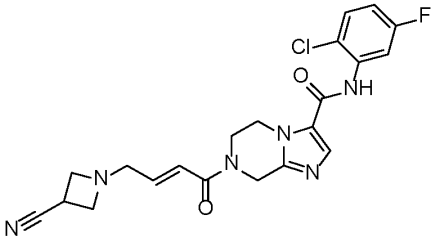
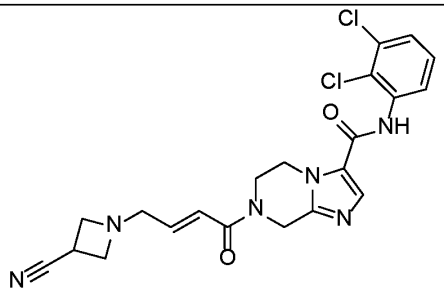
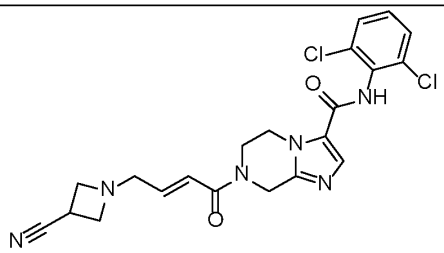
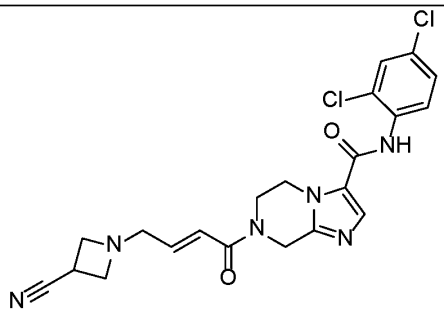
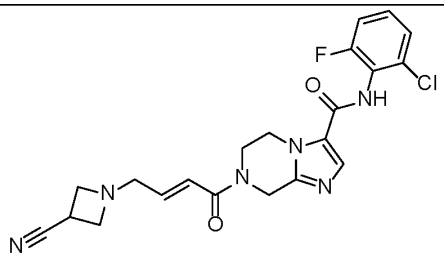
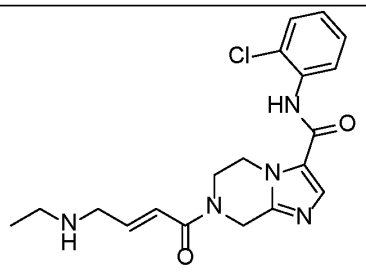
Compound No.	Structure	Compound Name
560		(5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
561		(5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-[ethyl(methyl)amino]pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
562		(5R)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
563		N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- (2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

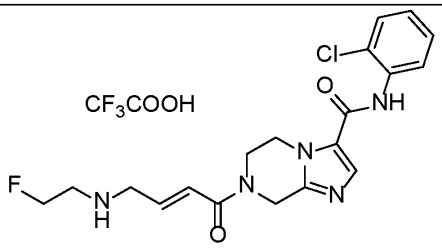
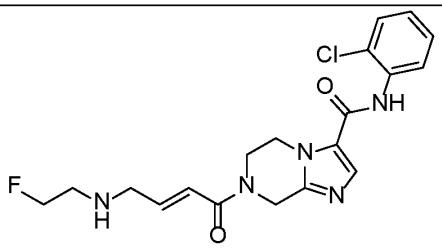
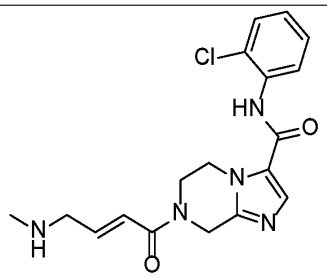
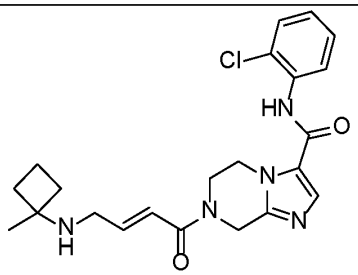
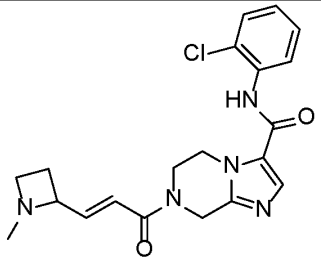
Table 3.

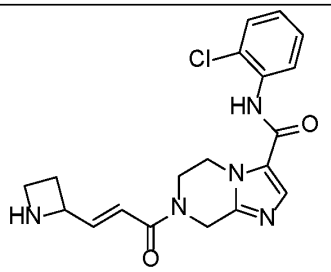
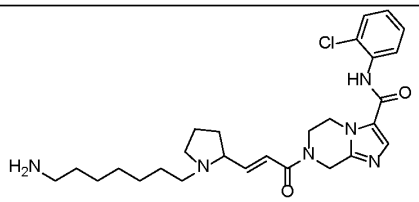
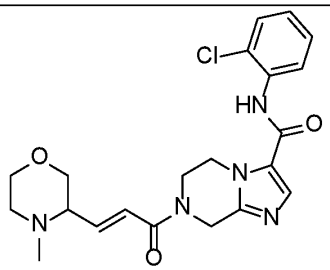
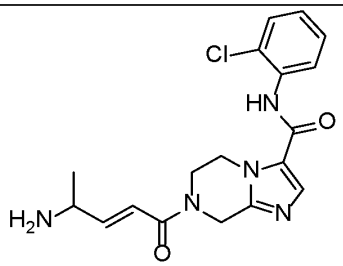
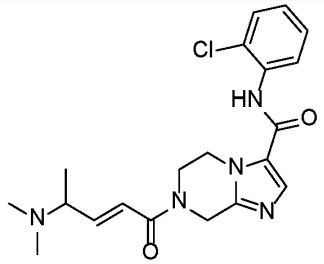
Compound No.	Structure	Compound Name
564		(E)-N-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

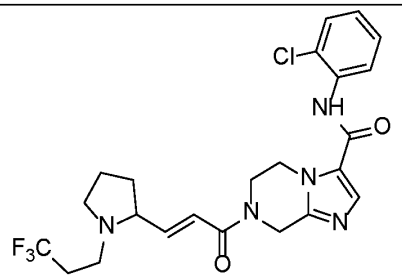
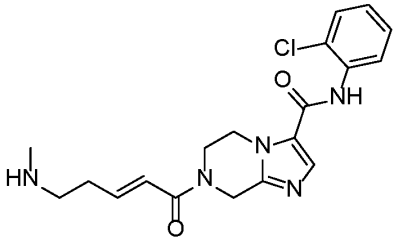
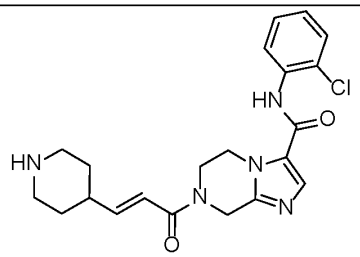
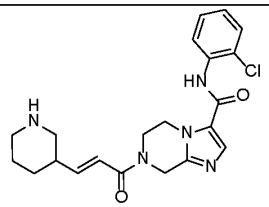
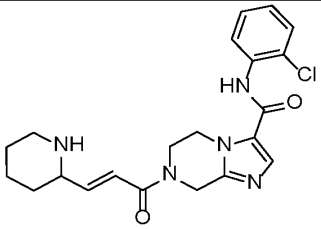
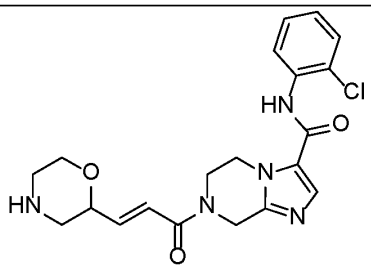
Compound No.	Structure	Compound Name
565		(E)-N-(2,4-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.
566		(E)-N-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
567		N-(2-chlorophenyl)-7-[(E)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide dihydrochloride
567a		N-(2-chlorophenyl)-7-[(E)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
568		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride

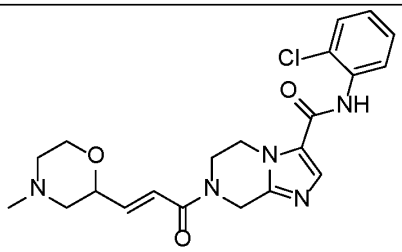
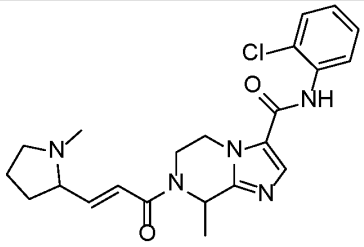
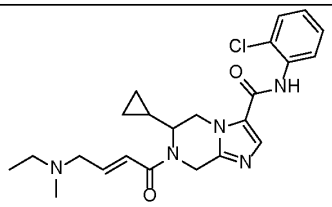
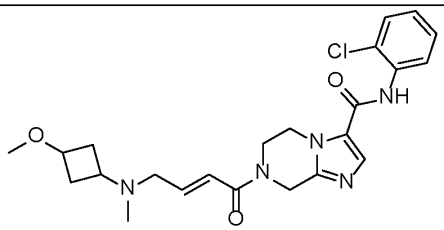
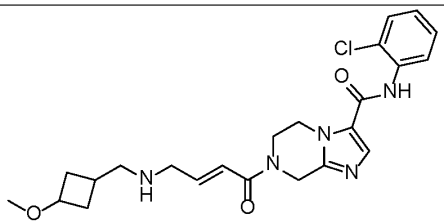
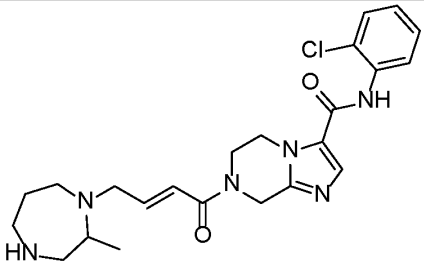
Compound No.	Structure	Compound Name
568a		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
569		N-(2-chlorophenyl)-7-[(E)-4-phenoxybut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
570		N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-(3- cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
571		N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- (3-cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
572		N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

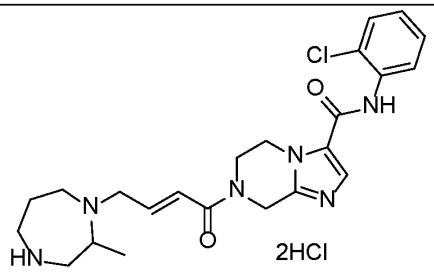
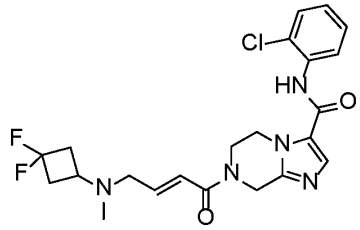
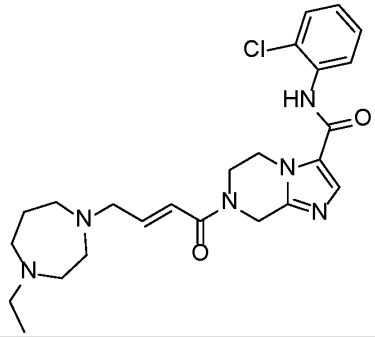
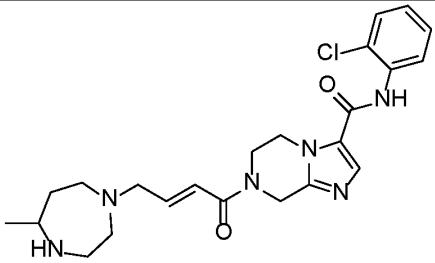
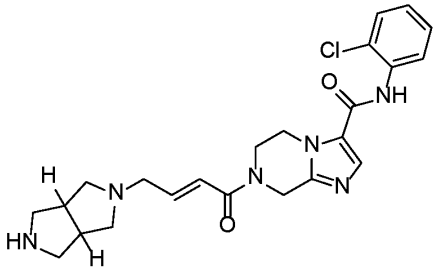
Compound No.	Structure	Compound Name
573		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,3-dichlorophenyl)-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
574		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,6-dichlorophenyl) -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
575		7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -N-(2,4-dichlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
576		N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
577		N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

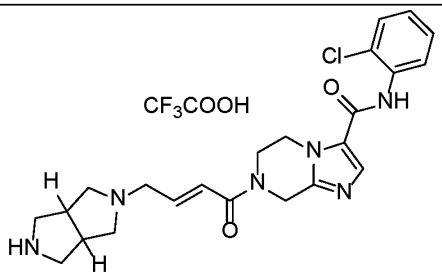
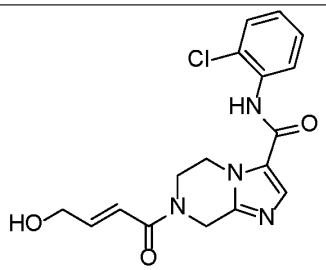
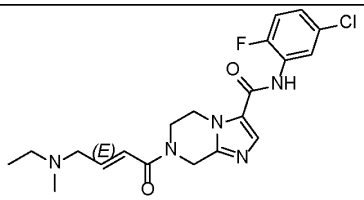
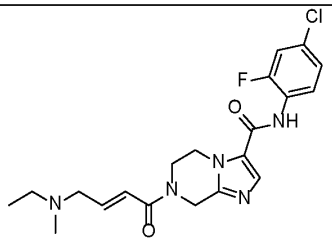
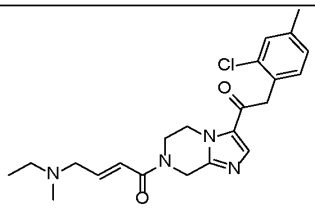
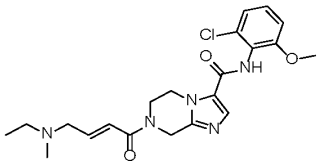
Compound No.	Structure	Compound Name
578		N-(2-chlorophenyl)-7-[(E)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide trifluoroacetic acid
578a		N-(2-chlorophenyl)-7-[(E)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
579		N-(2-chlorophenyl)-7-[(E)-4-(methylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
580		N-(2-chlorophenyl)-7-[(E)-4-[(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
581		(E)-N-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

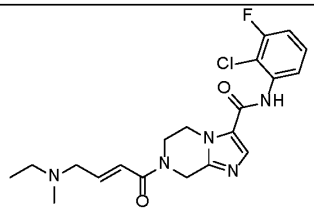
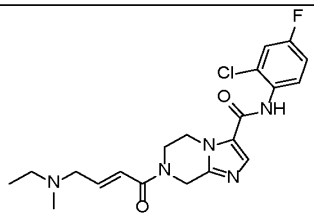
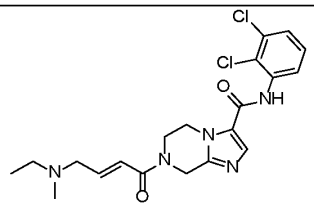
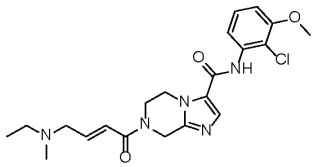
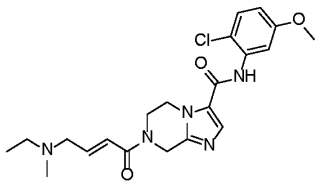
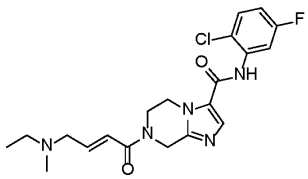
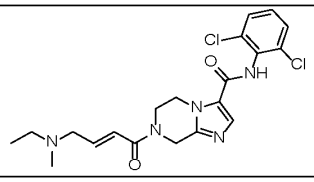
Compound No.	Structure	Compound Name
582		(E)-7-(3-(azetidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
583		(E)-7-(3-(1-(7-aminoheptyl)pyrrolidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
584		N-(2-chlorophenyl)-7-[(E)-3-(4-methylmorpholin-3-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
585		7-[(E)-4-aminopent-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
586		N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

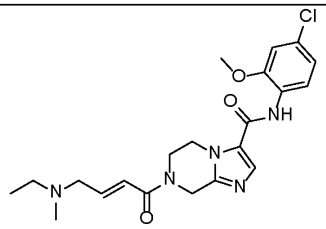
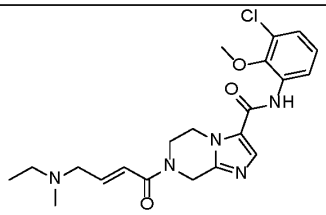
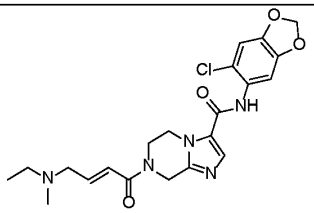
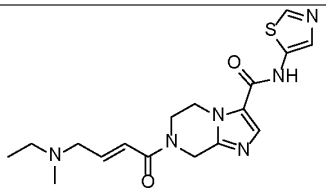
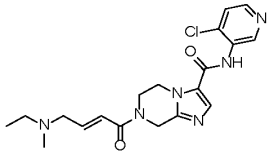
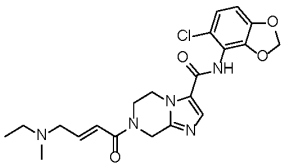
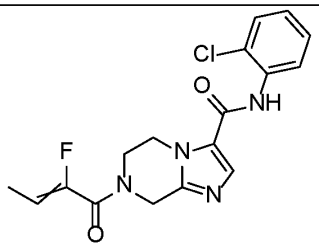
Compound No.	Structure	Compound Name
587		(E)-N-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
588		(E)-N-(2-chlorophenyl)-7-(5-(methylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
589		N-(2-chlorophenyl)-7-[(E)-3-(4-piperidyl)prop-2-enoyl]-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-3-carboxamide
590		N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide
591		N-(2-chlorophenyl)-7-[(E)-3-(2-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide
592		(E)-N-(2-chlorophenyl)-7-(3-(morpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

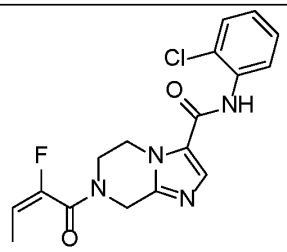
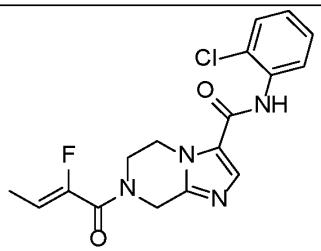
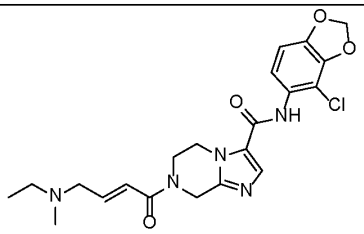
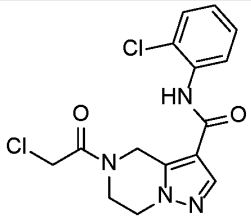
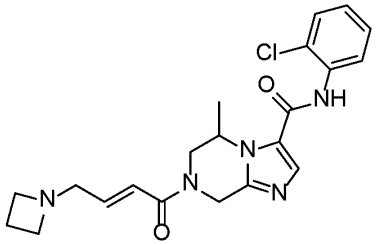
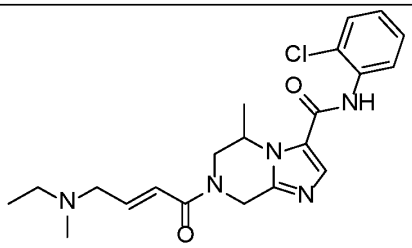
Compound No.	Structure	Compound Name
593		(E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
594		(E)-N-(2-chlorophenyl)-8-methyl-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
595		N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
596		(E)-N-(2-chlorophenyl)-7-(4-((3-methoxycyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
597		(E)-N-(2-chlorophenyl)-7-(4-(((3-methoxycyclobutyl)methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
598		(E)-N-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

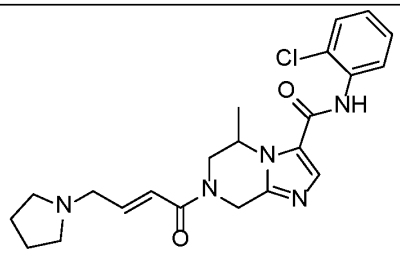
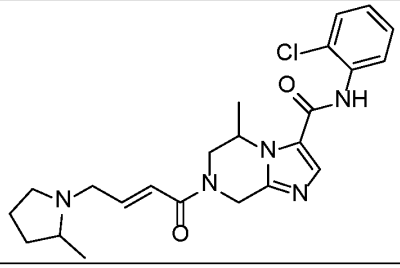
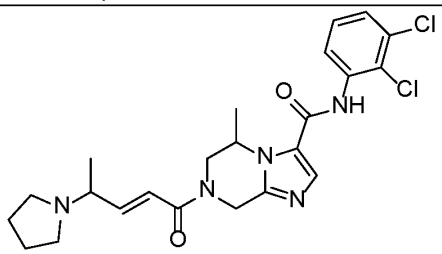
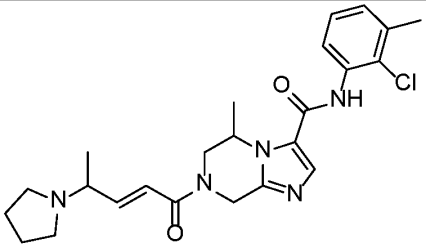
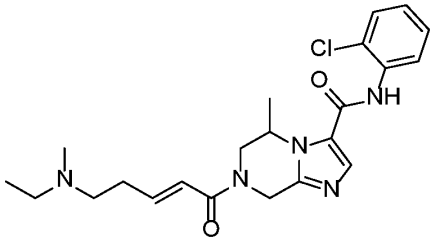
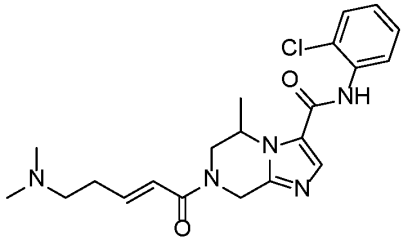
Compound No.	Structure	Compound Name
599		(E)-N-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide dihydrochloride
600		(E)-N-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
601		N-(2-chlorophenyl)-7-[(E)-4-(4-ethyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
602		(E)-N-(2-chlorophenyl)-7-(4-(5-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
603		(E)-N-(2-chlorophenyl)-7-(4-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

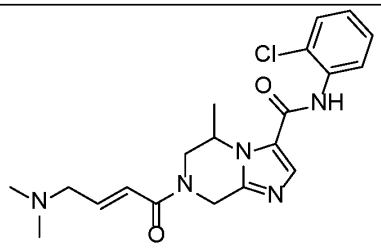
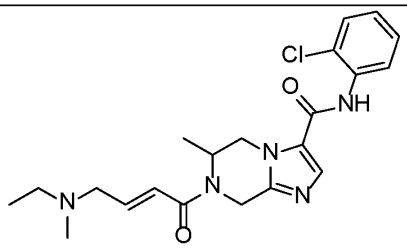
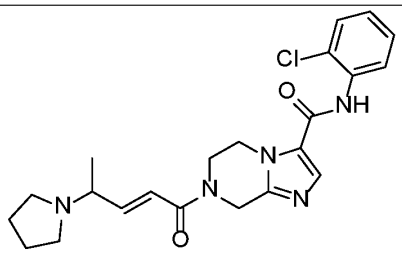
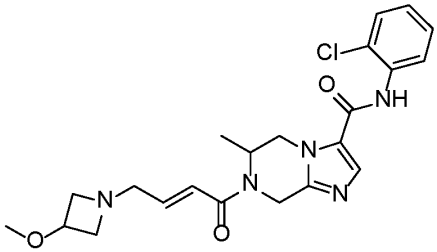
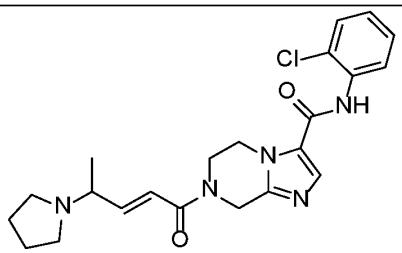
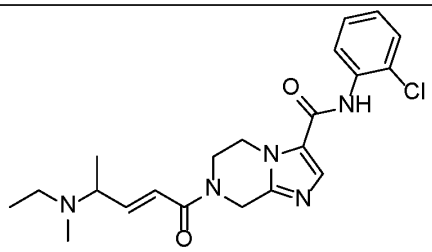
Compound No.	Structure	Compound Name
604		(E)-N-(2-chlorophenyl)-7-(4-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide 2,2,2-trifluoroacetate
605		N-(2-chlorophenyl)-7-[(E)-4-hydroxybut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
606		N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
607		N-(4-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
608		N-(2-chloro-4-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
609		N-(2-chloro-6-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

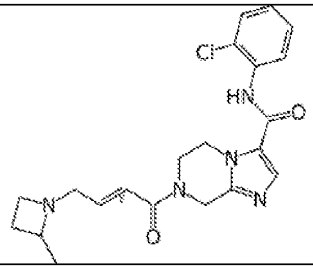
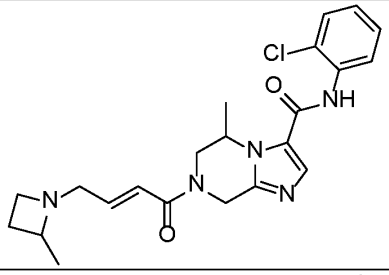
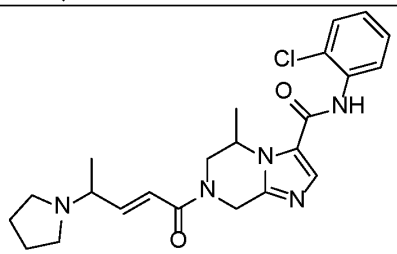
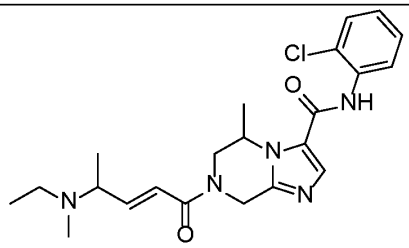
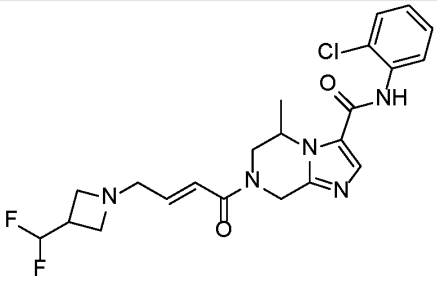
Compound No.	Structure	Compound Name
610		N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
611		N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- [ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
612		N-(2,3-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
613		N-(2-chloro-3-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
614		N-(2-chloro-5-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
615		N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
616		(E)-N-(2,6-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

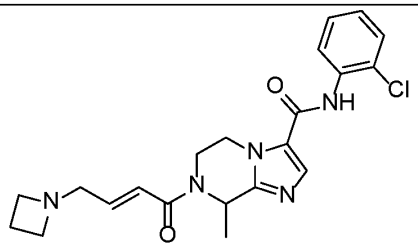
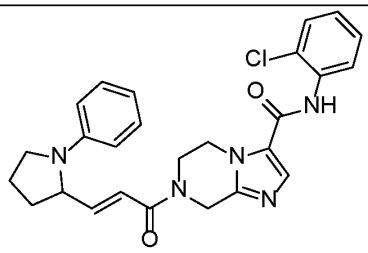
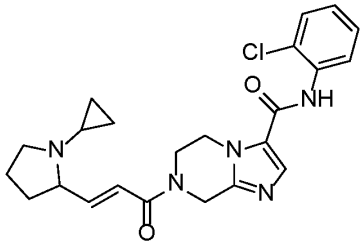
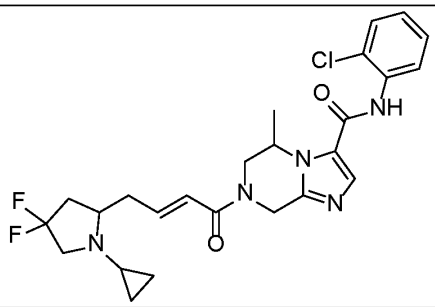
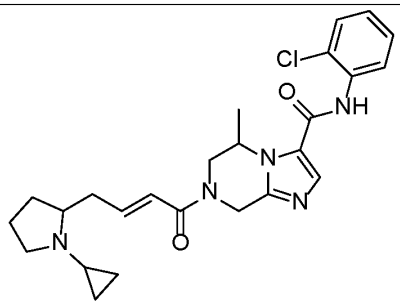
Compound No.	Structure	Compound Name
617		N-(4-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
618		N-(3-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
619		N-(6-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
620		7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxamide
621		N-(4-chloro-3-pyridyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
622		N-(5-chloro-1,3-benzodioxol-4-yl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
623		N-(2-chlorophenyl)-7-[2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide

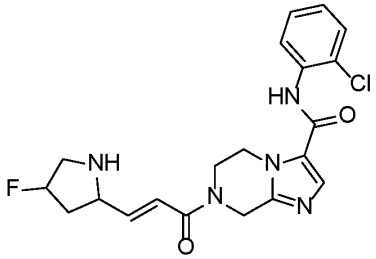
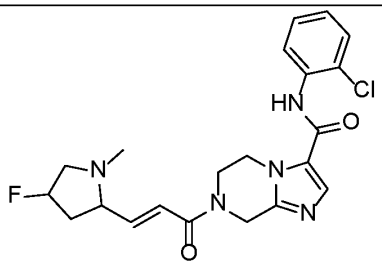
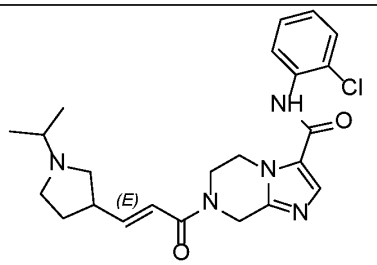
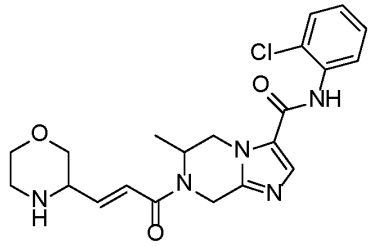
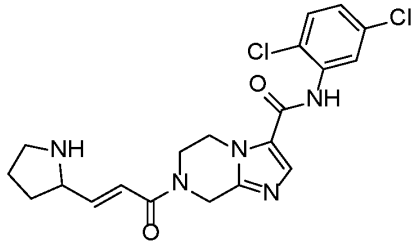
Compound No.	Structure	Compound Name
624		N-(2-chlorophenyl)-7-[(E)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
625		N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
626		N-(4-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl (methyl)amino]but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
627		5-(2-chloroacetyl)-N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide
628		N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
629		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

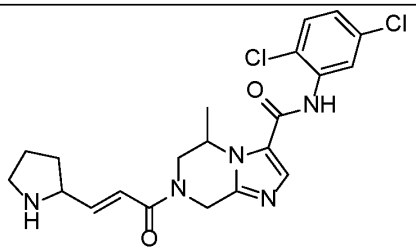
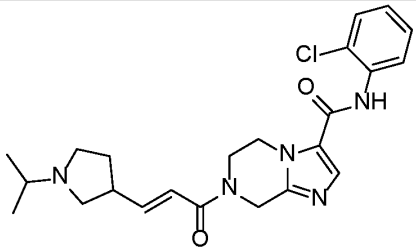
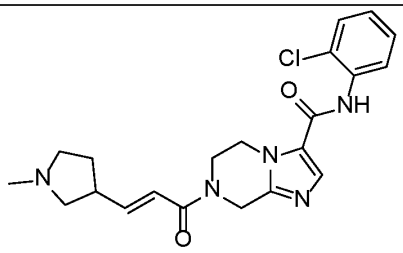
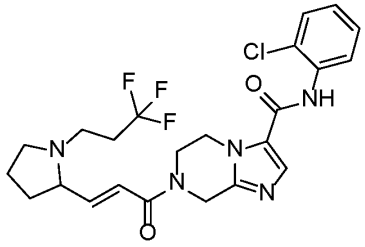
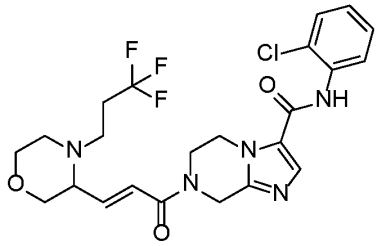
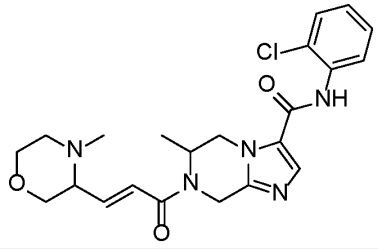
Compound No.	Structure	Compound Name
630		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
631		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(2-methylpyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
632		(E)-N-(2,3-dichlorophenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
633		(E)-N-(2-chloro-3-methylphenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
634		(E)-N-(2-chlorophenyl)-7-(5-(ethyl(methyl)amino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
635		(E)-N-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

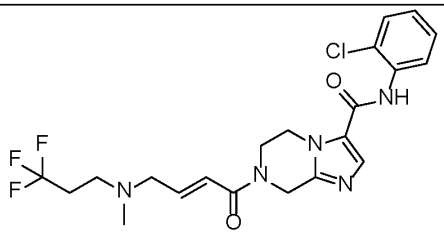
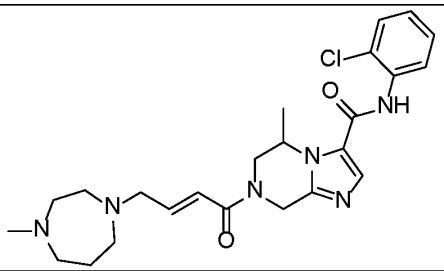
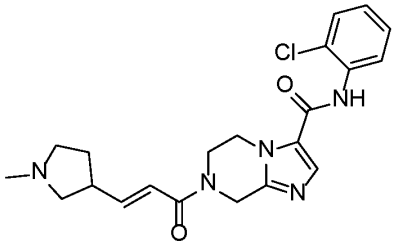
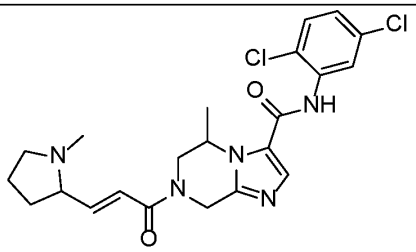
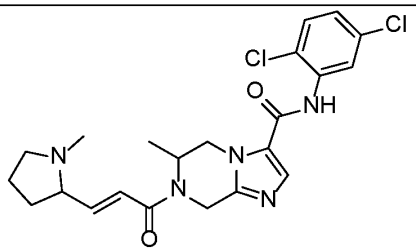
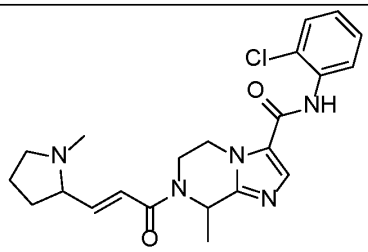
Compound No.	Structure	Compound Name
636		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
637		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
638		(E)-N-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
639		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
640		N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide
641		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

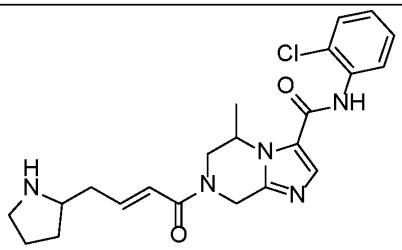
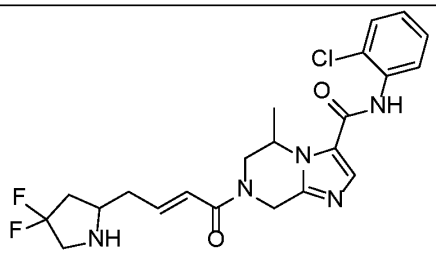
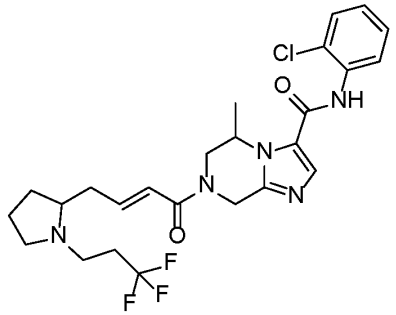
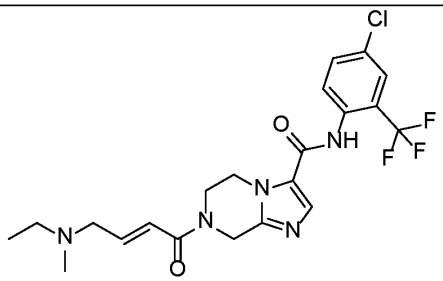
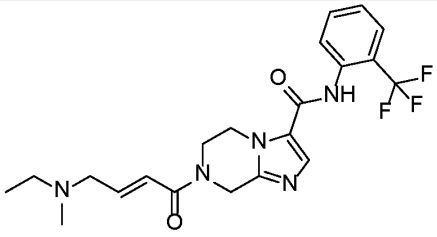
Compound No.	Structure	Compound Name
642		N-(2-chlorophenyl)-7-[(E)-4-(2-methylazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
643		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(2-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
644		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
645		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
646		(E)-N-(2-chlorophenyl)-7-(4-(3-(difluoromethyl)azetidin-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

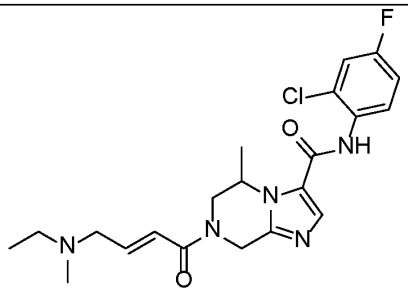
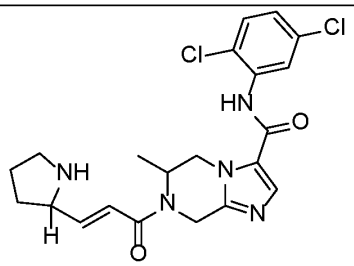
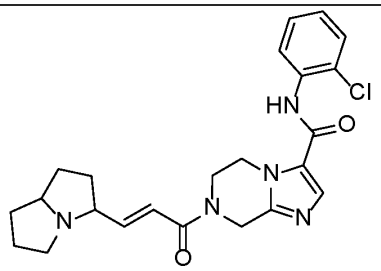
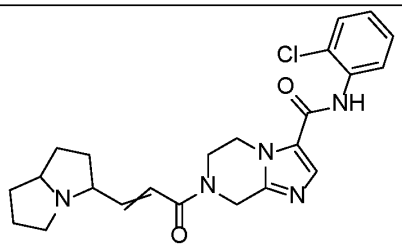
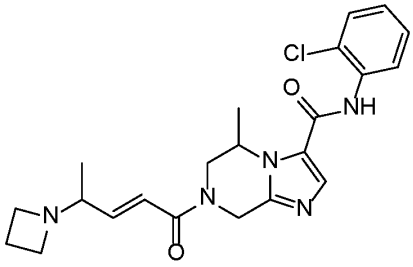
Compound No.	Structure	Compound Name
647		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
648		(E)-N-(2-chlorophenyl)-7-(3-(1-phenylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
649		(E)-N-(2-chlorophenyl)-7-(3-(1-cyclopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
650		(E)-N-(2-chlorophenyl)-7-(4-(1-cyclopropyl-4,4-difluoropyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
651		(E)-N-(2-chlorophenyl)-7-(4-(1-cyclopropylpyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

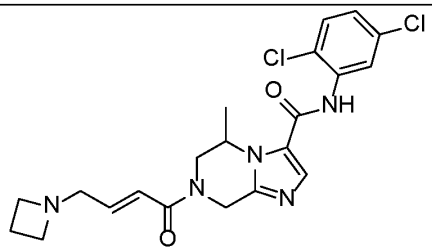
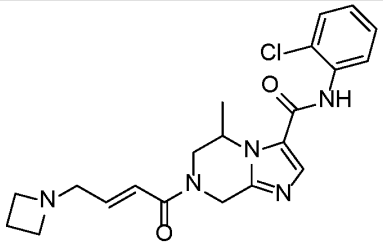
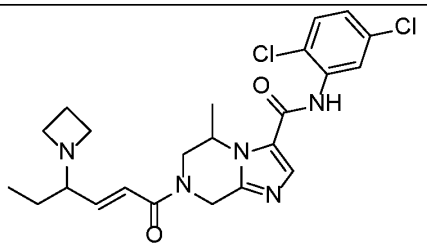
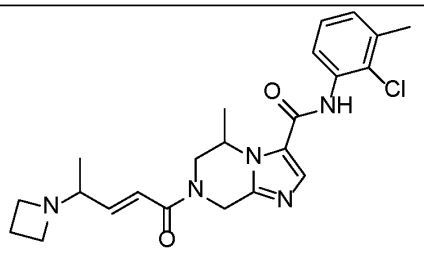
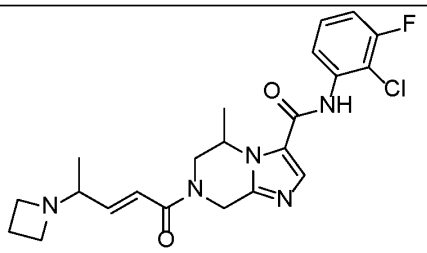
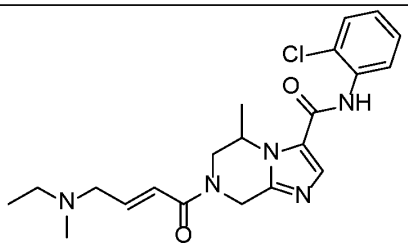
Compound No.	Structure	Compound Name
652		(E)-N-(2-chlorophenyl)-7-(3-(4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
653		(E)-N-(2-chlorophenyl)-7-(3-(4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
654		N-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
655		(E)-N-(2-chlorophenyl)-6-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
656		(E)-N-(2,5-dichlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

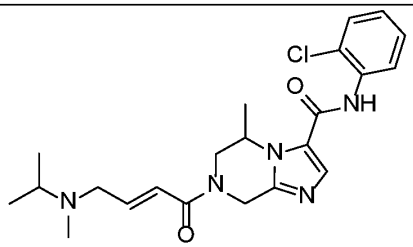
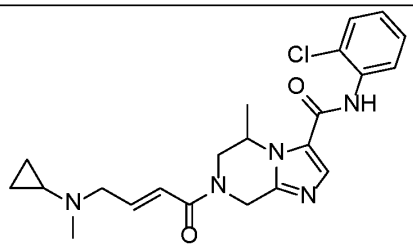
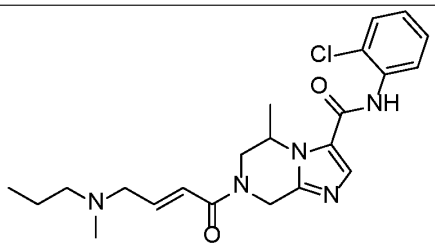
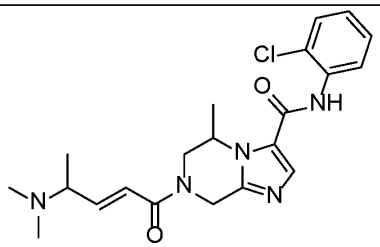
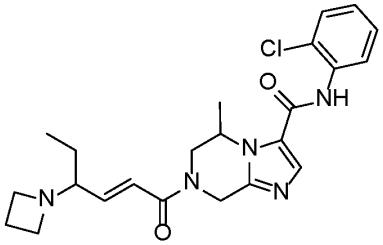
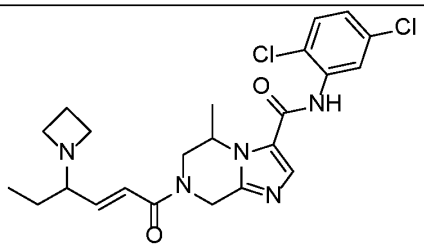
Compound No.	Structure	Compound Name
657		(E)-N-(2,5-dichlorophenyl)-5-methyl-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
658		(E)-N-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
659		N-(2-chlorophenyl)-7-[(E)-3-(1-methylpyrrolidin-3-yl)prop-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
660		(E)-N-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
661		N-(2-chlorophenyl)-7-[(E)-3-[4-(3,3,3-trifluoropropyl)morpholin-3-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
662		(E)-N-(2-chlorophenyl)-6-methyl-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

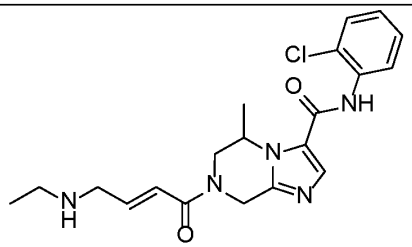
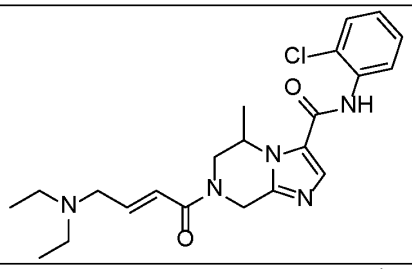
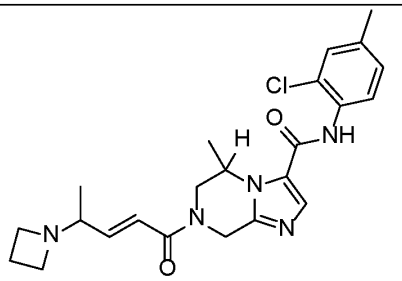
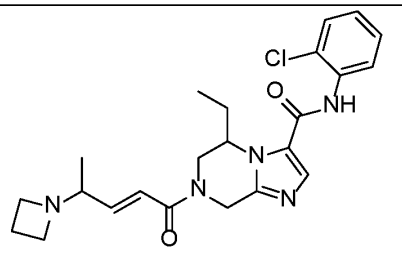
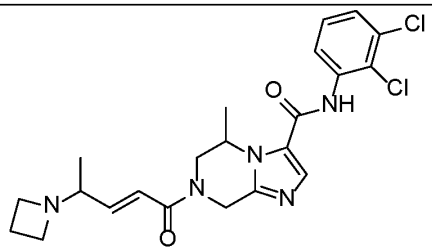
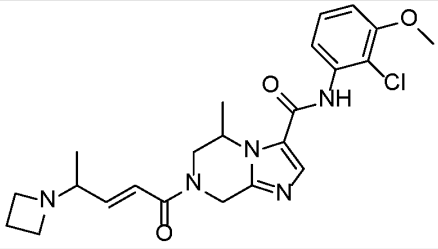
Compound No.	Structure	Compound Name
663		N-(2-chlorophenyl)-7-[(E)-4-[methyl(3,3,3-trifluoropropyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
664		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
665		(E)-N-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
666		(E)-N-(2,5-dichlorophenyl)-5-methyl-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
667		(E)-N-(2,5-dichlorophenyl)-6-methyl-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
668		N-(2-chlorophenyl)-8-methyl-7-[(E)-3-(1-methylpyrrolidin -2-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

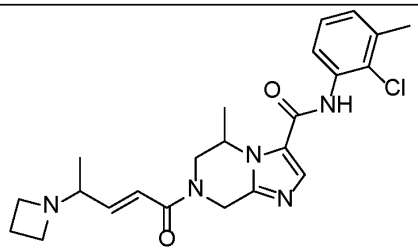
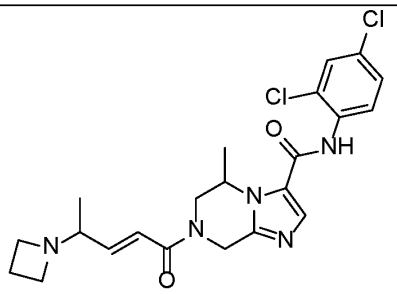
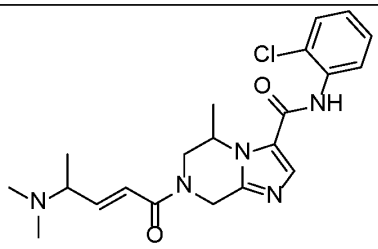
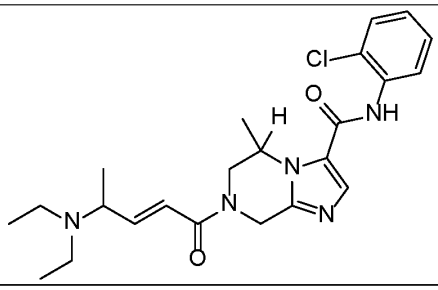
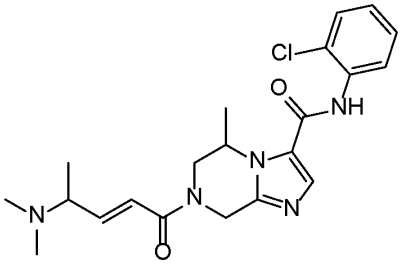
Compound No.	Structure	Compound Name
669		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
670		(5S)-N-(2-chlorophenyl)-7-((E)-4-(4,4-difluoropyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
671		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
672		N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
673		7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-[2-(trifluoromethyl)phenyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

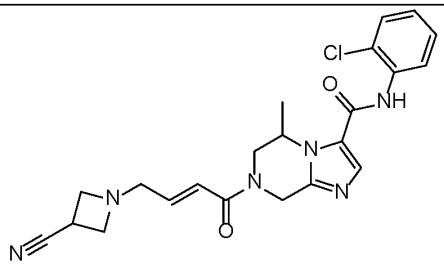
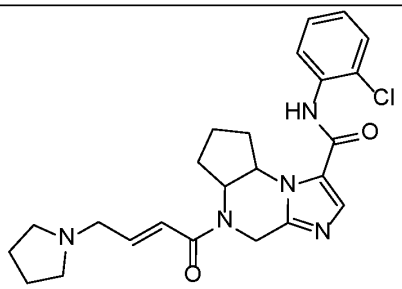
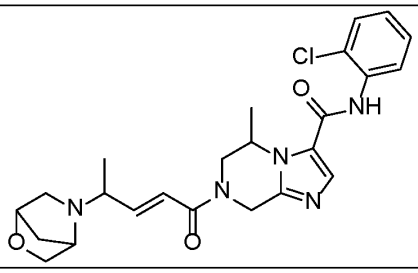
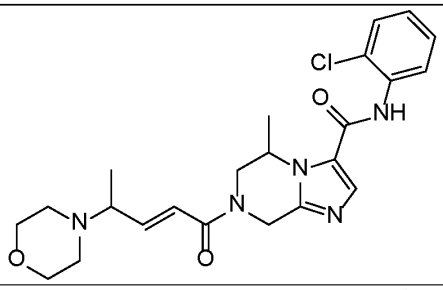
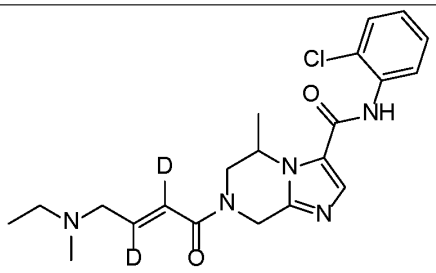
Compound No.	Structure	Compound Name
674		(E)-N-(2-chloro-4-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
675		(E)-N-(2,5-dichlorophenyl)-6-methyl-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
676		(E)-N-(2-chlorophenyl)-7-(3-(hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
677		N-(2-chlorophenyl)-7-(3-(hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
678		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

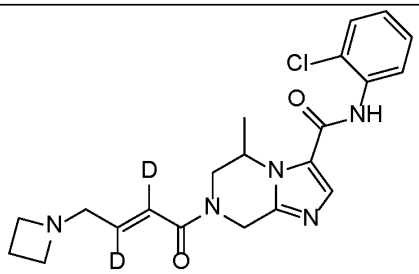
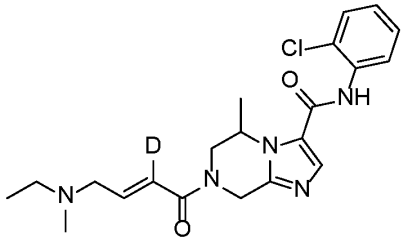
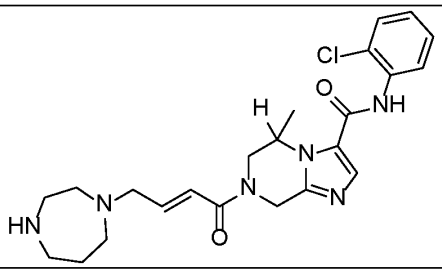
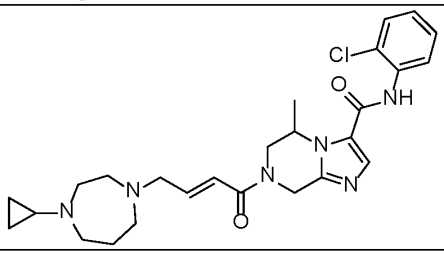
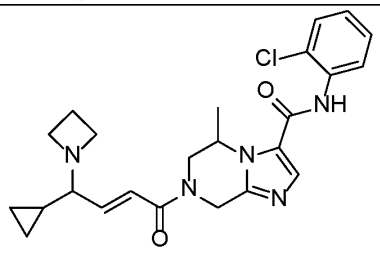
Compound No.	Structure	Compound Name
679		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2,5-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
680		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
681		(E)-7-(4-(azetidin-1-yl)hex-2-enoyl)-N-(2,5-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
682		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-3-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
683		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-3-fluorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
684		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

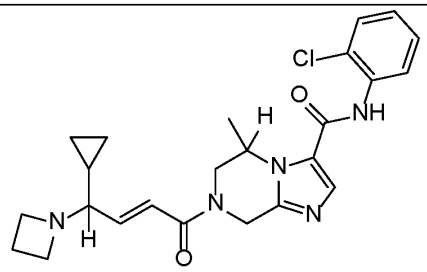
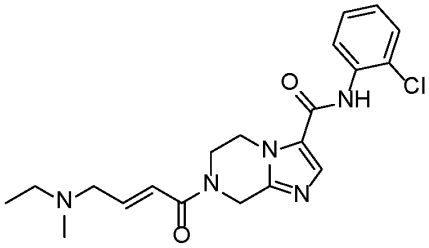
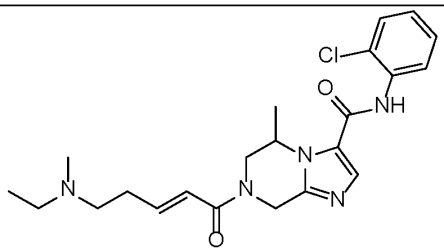
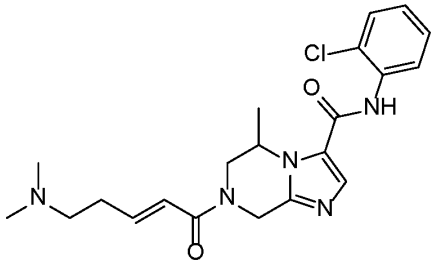
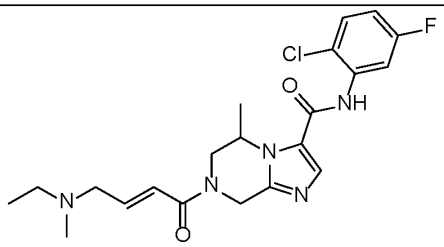
Compound No.	Structure	Compound Name
685		(E)-N-(2-chlorophenyl)-7-(4-(isopropyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
686		(E)-N-(2-chlorophenyl)-7-(4-(cyclopropyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
687		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(methyl(propyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
688		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
689		(E)-7-(4-(azetidin-1-yl)hex-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
690		(E)-7-(4-(azetidin-1-yl)hex-2-enoyl)-N-(2,5-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

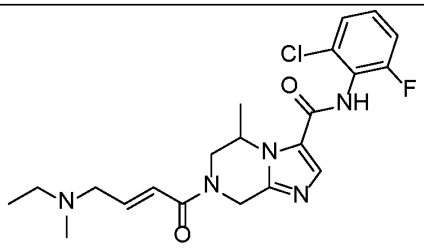
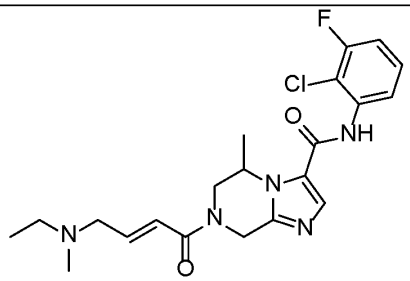
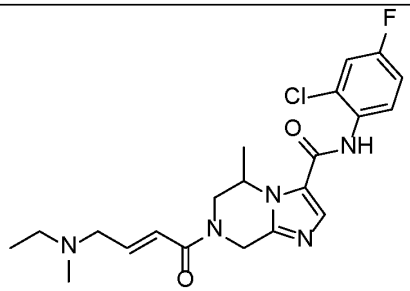
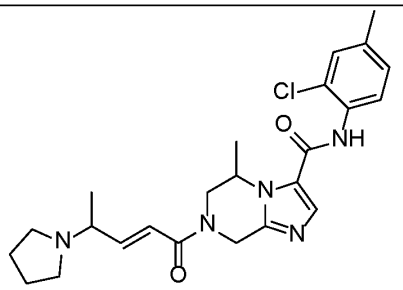
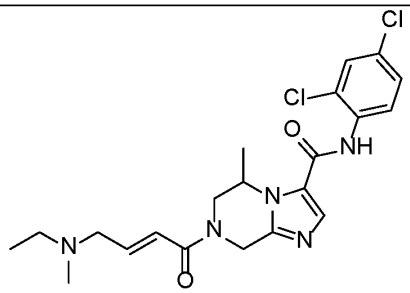
Compound No.	Structure	Compound Name
691		(E)-N-(2-chlorophenyl)-7-(4-(ethylamino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
692		(E)-N-(2-chlorophenyl)-7-(4-(diethylamino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
693		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
694		7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
695		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2,3-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
696		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chloro-3-methoxy-phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

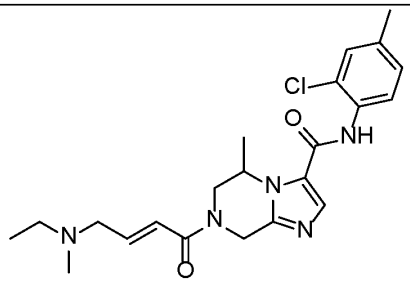
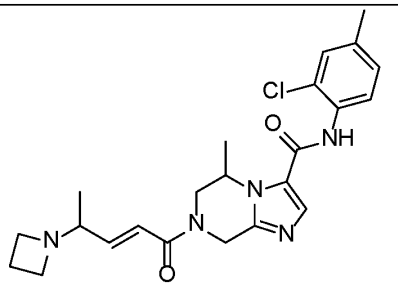
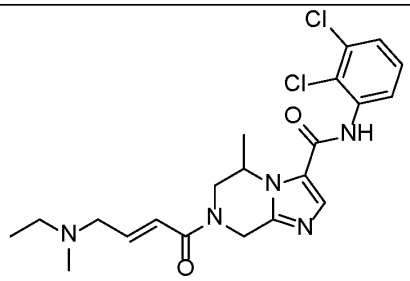
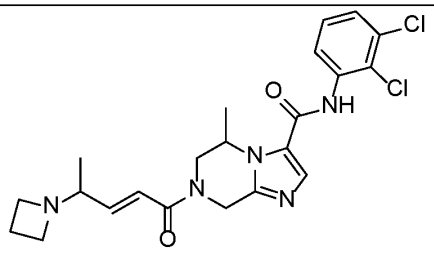
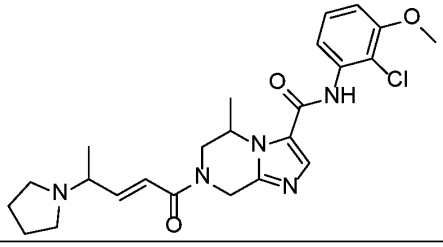
Compound No.	Structure	Compound Name
697		(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
698		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2,4-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
699		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
700		(E)-N-(2-chlorophenyl)-7-(4-(diethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
701		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

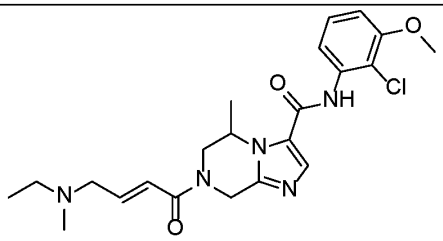
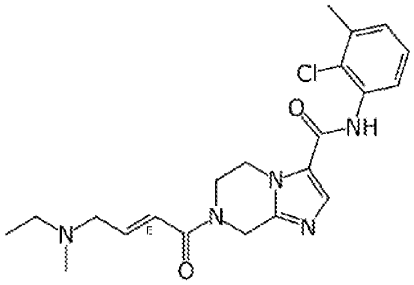
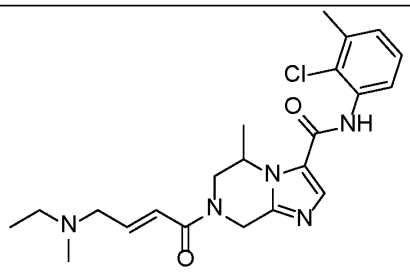
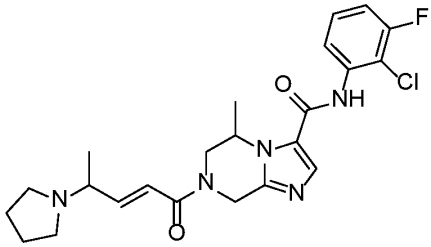
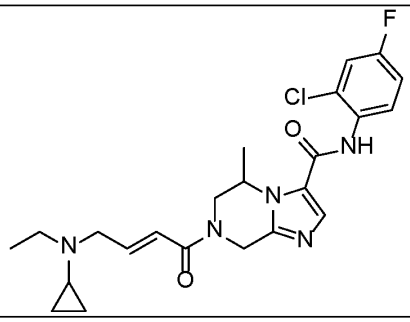
Compound No.	Structure	Compound Name
702		(E)-N-(2-chlorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
703		(E)-N-(2-chlorophenyl)-5-(4-(pyrrolidin-1-yl)but-2-enoyl)-5,5a,6,7,8,8a-hexahydro-4H-cyclopenta[e]imidazo[1,2-a]pyrazine-1-carboxamide
704		(E)-7-(4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
705		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-morpholinopent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
706		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl-2,3-d2)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

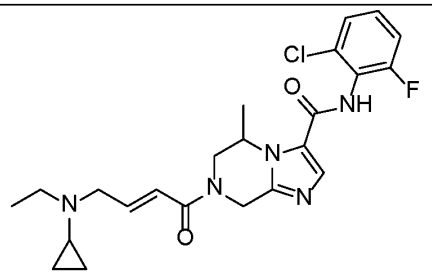
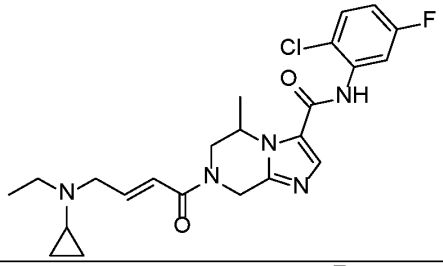
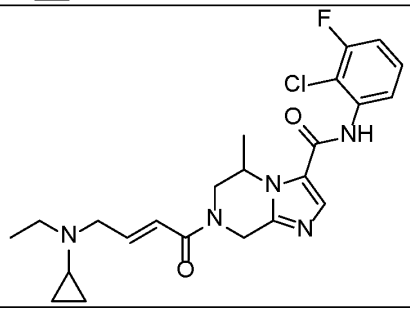
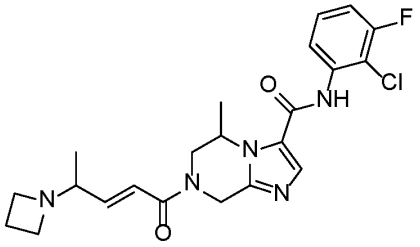
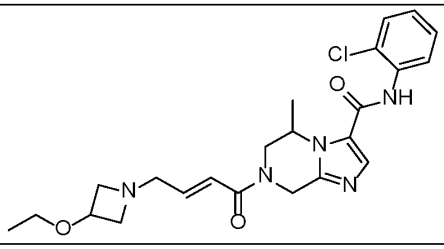
Compound No.	Structure	Compound Name
707		(E)-7-(4-(azetidin-1-yl)but-2-enoyl-2,3-d2)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
708		(E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl-2-d)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
709		(E)-7-(4-(1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
710		(E)-N-(2-chlorophenyl)-7-(4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
711		(E)-7-(4-(azetidin-1-yl)-4-cyclopropylbut-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

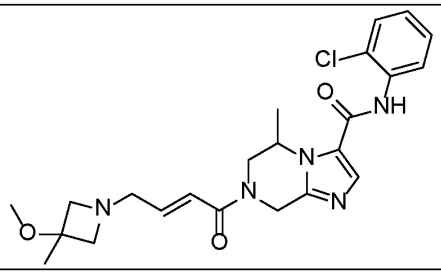
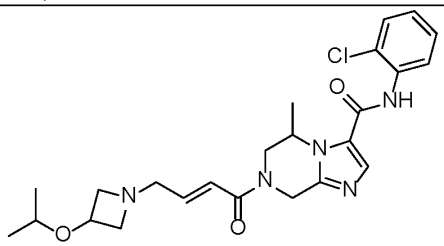
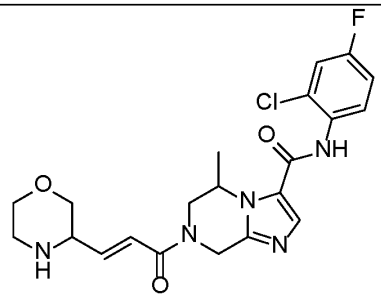
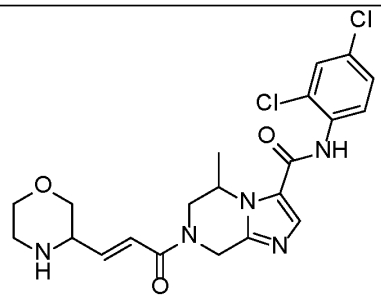
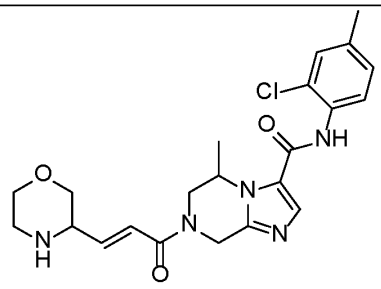
Compound No.	Structure	Compound Name
712		(E)-7-(4-(azetidin-1-yl)-4-cyclopropylbut-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
713		N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
714		(E)-N-(2-chlorophenyl)-7-(5-(ethyl(methyl)amino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
715		(E)-N-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
716		(E)-N-(2-chloro-5-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

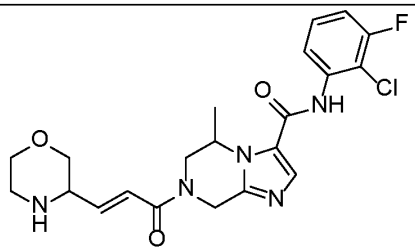
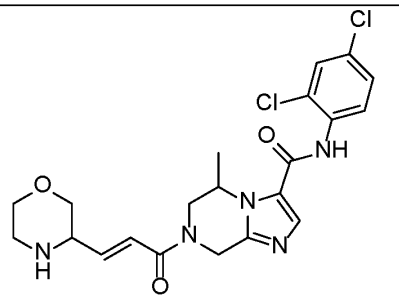
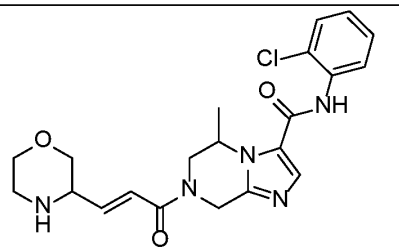
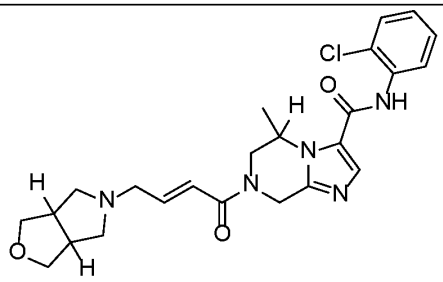
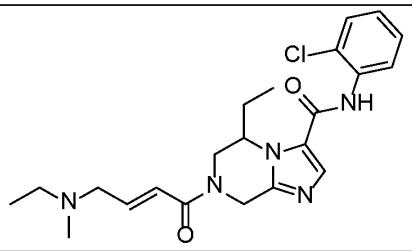
Compound No.	Structure	Compound Name
717		(E)-N-(2-chloro-6-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
718		(E)-N-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
719		(E)-N-(2-chloro-4-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
720		(E)-N-(2-chloro-4-methylphenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
721		(5R)-N-(2,4-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

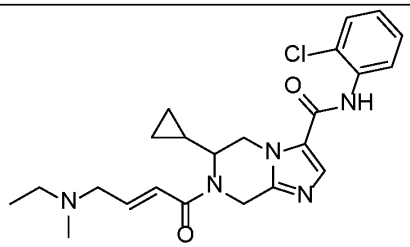
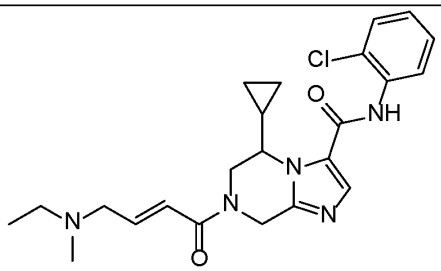
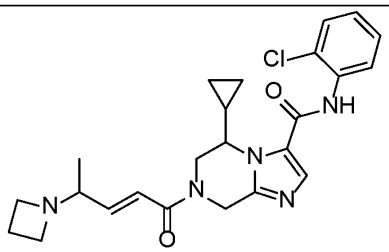
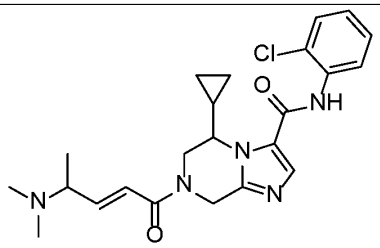
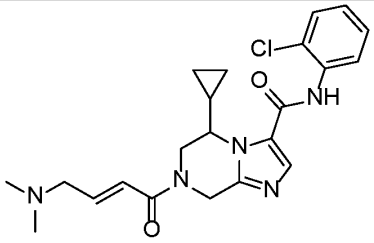
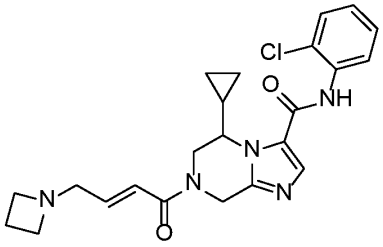
Compound No.	Structure	Compound Name
722		(E)-N-(2-chloro-4-methylphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
723		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
724		(E)-N-(2,3-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
725		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2,3-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
726		(E)-N-(2-chloro-3-methoxyphenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

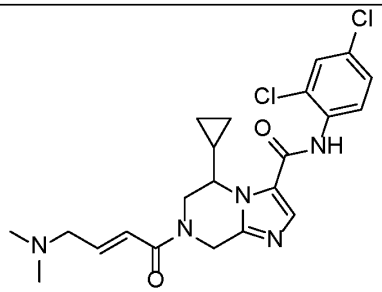
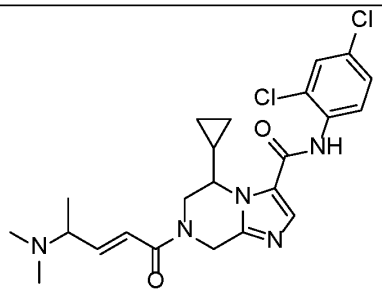
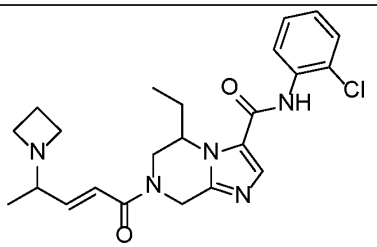
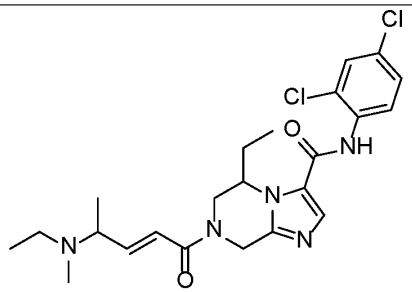
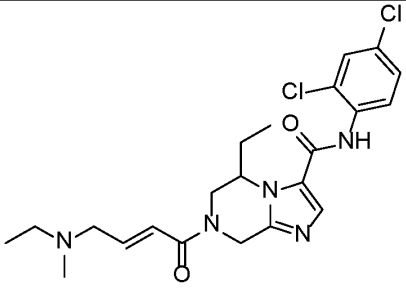
Compound No.	Structure	Compound Name
727		(E)-N-(2-chloro-3-methoxyphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
728		N-(2-chloro-3-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
729		(E)-N-(2-chloro-3-methylphenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
730		(E)-N-(2-chloro-3-fluorophenyl)-5-methyl-7-(4-(pyrrolidin-1-yl)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
731		(E)-N-(2-chloro-4-fluorophenyl)-7-(4-(cyclopropyl(ethyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

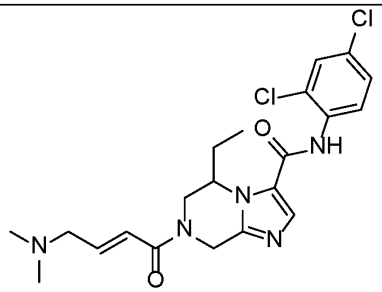
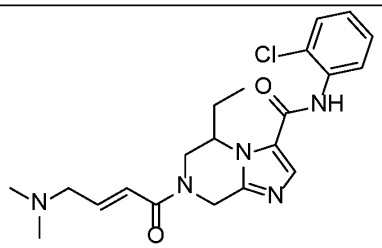
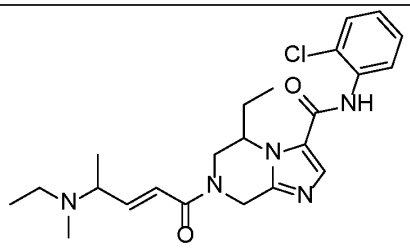
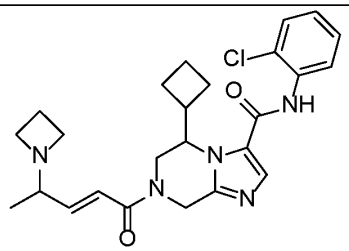
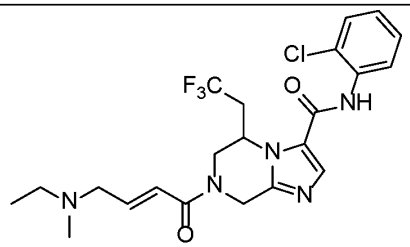
Compound No.	Structure	Compound Name
732		(E)-N-(2-chloro-6-fluorophenyl)-7-(4-(cyclopropyl(ethyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
733		(E)-N-(2-chloro-5-fluorophenyl)-7-(4-(cyclopropyl(ethyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
734		(E)-N-(2-chloro-3-fluorophenyl)-7-(4-(cyclopropyl(ethyl)amino)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
735		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-3-fluorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
736		(E)-N-(2-chlorophenyl)-7-(4-(3-ethoxyazetidin-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
737		(E)-N-(2-chlorophenyl)-7-(4-(3-methoxy-3-methylazetidin-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
738		(E)-N-(2-chlorophenyl)-7-(4-(3-isopropoxyazetidin-1-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
739		(E)-N-(2-chloro-4-fluorophenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
740		(E)-N-(2,4-dichlorophenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
741		(E)-N-(2-chloro-4-methylphenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
742		(E)-N-(2-chloro-3-fluorophenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
743		(E)-N-(2,4-dichlorophenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
744		(E)-N-(2-chlorophenyl)-5-methyl-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
745		(E)-N-(2-chlorophenyl)-5-methyl-7-(4-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
746		(E)-N-(2-chlorophenyl)-5-ethyl-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
747		(E)-N-(2-chlorophenyl)-6-cyclopropyl-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
748		N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide
749		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
750		(E)-N-(2-chlorophenyl)-5-cyclopropyl-7-(4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
751		(E)-N-(2-chlorophenyl)-5-cyclopropyl-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
752		(E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
753		(E)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
754		(E)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-(4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
755		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
756		(E)-N-(2,4-dichlorophenyl)-5-ethyl-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
757		(E)-N-(2,4-dichlorophenyl)-5-ethyl-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

Compound No.	Structure	Compound Name
758		(E)-N-(2,4-dichlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
759		(E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
760		(E)-N-(2-chlorophenyl)-5-ethyl-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
761		(E)-7-(4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide
762		N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- (2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

[0463] In some aspects, the present disclosure provides a compound being an isotopic derivative (e.g., isotopically labeled compound) of any one of the compounds of the Formulae disclosed herein.

[0464] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Tables 1, 2, and 3, or a prodrug or pharmaceutically acceptable salt thereof.

[0465] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Tables 1, 2, and 3, or a pharmaceutically acceptable salt thereof.

[0466] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Tables 1, 2, and 3.

[0467] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1, or a prodrug or pharmaceutically acceptable salt thereof.

[0468] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1, or a pharmaceutically acceptable salt thereof.

[0469] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 1.

[0470] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 2, or a prodrug or pharmaceutically acceptable salt thereof.

[0471] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 2, or a pharmaceutically acceptable salt thereof.

[0472] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 2.

[0473] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 3, or a prodrug or pharmaceutically acceptable salt thereof.

[0474] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 3, or a pharmaceutically acceptable salt thereof.

[0475] In some embodiments, the compound is an isotopic derivative of any one of the compounds described in Table 3.

[0476] It is understood that the isotopic derivative can be prepared using any of a variety of art-recognized techniques. For example, the isotopic derivative can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0477] In some embodiments, the isotopic derivative is a deuterium labeled compound.

[0478] In some embodiments, the isotopic derivative is a deuterium labeled compound of any one of the compounds of the Formulae disclosed herein.

[0479] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Tables 1, 2, and 3, or a prodrug or pharmaceutically acceptable salt thereof.

[0480] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Tables 1, 2, and 3, or a pharmaceutically acceptable salt thereof.

[0481] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Tables 1, 2, and 3.

[0482] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1, or a prodrug or pharmaceutically acceptable salt thereof.

[0483] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1, or a pharmaceutically acceptable salt thereof.

[0484] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 1.

[0485] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 2, or a prodrug or pharmaceutically acceptable salt thereof.

[0486] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 2, or a pharmaceutically acceptable salt thereof.

[0487] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 2.

[0488] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 3, or a prodrug or pharmaceutically acceptable salt thereof.

[0489] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 3, or a pharmaceutically acceptable salt thereof.

[0490] In some embodiments, the compound is a deuterium labeled compound of any one of the compounds described in Table 3.

[0491] It is understood that the deuterium labeled compound comprises a deuterium atom having an abundance of deuterium that is substantially greater than the natural abundance of deuterium, which is 0.015%.

[0492] In some embodiments, the deuterium labeled compound has a deuterium enrichment factor for each deuterium atom of at least 3500 (52.5% deuterium incorporation at each deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation),

or at least 6633.3 (99.5% deuterium incorporation). As used herein, the term "deuterium enrichment factor" means the ratio between the deuterium abundance and the natural abundance of a deuterium.

[0493] It is understood that the deuterium labeled compound can be prepared using any of a variety of art-recognized techniques. For example, the deuterium labeled compound can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a deuterium labeled reagent for a non-deuterium labeled reagent.

[0494] A compound of the invention or a pharmaceutically acceptable salt or solvate thereof that contains the aforementioned deuterium atom(s) is within the scope of the invention. Further, substitution with deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability, e.g., increased *in vivo* half-life or reduced dosage requirements.

[0495] For the avoidance of doubt, it is to be understood that, where in this specification a group is qualified by "described herein", the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

[0496] A suitable pharmaceutically acceptable salt of a compound of the disclosure is, for example, an acid-addition salt of a compound of the disclosure, which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulfuric, phosphoric, formic, citric methane sulfonate or maleic acid. In addition, a suitable pharmaceutically acceptable salt of a compound of the disclosure which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a pharmaceutically acceptable cation, for example a salt with methylamine, dimethylamine, diethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

[0497] It will be understood that the compounds of any one of the Formulae disclosed herein and any pharmaceutically acceptable salts thereof, comprise stereoisomers, mixtures of stereoisomers, polymorphs of all isomeric forms of said compounds.

[0498] As used herein, the term "isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereoisomers," and stereoisomers that are non-superimposable mirror images of each

other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture."

[0499] As used herein, the term "chiral center" refers to a carbon atom bonded to four nonidentical substituents.

[0500] As used herein, the term "chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0501] As used herein, the term "geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0502] It is to be understood that the compounds of the present disclosure may be depicted as different chiral isomers or geometric isomers. It is also to be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any isomeric forms, it being understood that not all isomers may have the same level of activity.

[0503] It is to be understood that the structures and other compounds discussed in this disclosure include all atropic isomers thereof. It is also to be understood that not all atropic isomers may have the same level of activity.

[0504] As used herein, the term "atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0505] As used herein, the term "tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerisations is called tautomerism. Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0506] It is to be understood that the compounds of the present disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present disclosure, and the naming of the compounds does not exclude any tautomer form. It will be understood that certain tautomers may have a higher level of activity than others.

[0507] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0508] The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the

separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition *J*. March, John Wiley and Sons, New York, 2001), for example by synthesis from optically active starting materials or by resolution of a racemic form. Some of the compounds of the disclosure may have geometric isomeric centers (E- and Z- isomers). It is to be understood that the present disclosure encompasses all optical, diastereoisomers and geometric isomers and mixtures thereof that possess EphB3 modulation activity.

[0509] The present disclosure also encompasses compounds of the disclosure as defined herein which comprise one or more isotopic substitutions.

[0510] It is to be understood that the compounds of any Formula described herein include the compounds themselves, as well as their salts, and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a substituted compound disclosed herein. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate.

[0511] As used herein, the term "pharmaceutically acceptable anion" refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a substituted compound disclosed herein. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion or diethylamine ion. The substituted compounds disclosed herein also include those salts containing quaternary nitrogen atoms.

[0512] It is to be understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0513] As used herein, the term "solvate" means solvent addition forms that contain either stoichiometric or non-stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water, the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

[0514] As used herein, the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0515] As used herein, the term "derivative" refers to compounds that have a common core structure and are substituted with various groups as described herein.

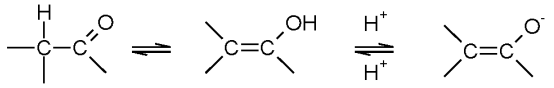
[0516] As used herein, the term "bioisostere" refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonamides, tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0517] It is also to be understood that certain compounds of any one of the Formulae disclosed herein may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. A suitable pharmaceutically acceptable solvate is, for example, a hydrate such as hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate. It is to be understood that the disclosure encompasses all such solvated forms that possess EphB3 modulation activity.

[0518] It is also to be understood that certain compounds of any one of the Formulae disclosed herein may exhibit polymorphism, and that the disclosure encompasses all such forms, or mixtures thereof, which possess EphB3 modulation activity. It is generally known that crystalline materials may be analysed using conventional techniques such as X-Ray Powder Diffraction analysis, Differential Scanning Calorimetry, Thermal Gravimetric Analysis, Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, Near Infrared (NIR) spectroscopy, solution and/or solid state nuclear magnetic resonance spectroscopy. The water content of such crystalline materials may be determined by Karl Fischer analysis.

[0519] Compounds of any one of the Formulae disclosed herein may exist in a number of different tautomeric forms and references to compounds of Formula (I), Formula (II), or Formula (III) include all such forms. For the avoidance of doubt, where a compound can exist in one of several tautomeric forms, and only one is specifically described or shown, all others are nevertheless embraced by Formula (I), Formula (II), or Formula (III). Examples of tautomeric forms include keto-, enol-, and enolate-forms, as in, for example, the following

tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



keto enol enolate

[0520] Compounds of any one of the Formulae disclosed herein containing an amine function may also form N-oxides. A reference herein to a compound of Formula (I), Formula (II), or Formula (III) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidized to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle. N-oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a peracid (e.g. a peroxycarboxylic acid), see for example Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (Syn. Comm. 1977, 7, 509-514) in which the amine compound is reacted with meta-chloroperoxybenzoic acid (mCPBA), for example, in an inert solvent such as dichloromethane.

[0521] The compounds of any one of the Formulae disclosed herein may be administered in the form of a prodrug which is broken down in the human or animal body to release a compound of the disclosure. A prodrug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the disclosure. A prodrug can be formed when the compound of the disclosure contains a suitable group or substituent to which a property-modifying group can be attached. Examples of prodrugs include derivatives containing *in vivo* cleavable alkyl or acyl substituents in a compound of the any one of the Formulae disclosed herein.

[0522] Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a prodrug thereof. Accordingly, the present disclosure includes those compounds of any one of the Formulae disclosed herein that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of any one of the Formulae disclosed herein may be a synthetically-produced compound or a metabolically-produced compound.

[0523] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein is one that is based on reasonable medical judgment as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity. Various forms of prodrug have been described, for example in the following documents: a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985); c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991); d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); e) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); f) N. Kakeya, et al., Chem. Pharm. Bull., 32, 692 (1984); g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; H. E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

[0524] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of any one of the Formulae disclosed herein containing a hydroxy group is, for example, a pharmaceutically acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically acceptable ester forming groups for a hydroxy group include C_1-C_{10} alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C_1-C_{10} alkoxycarbonyl groups such as ethoxycarbonyl, N,N-(C_1-C_6 alkyl)$_2$carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_1-C_4 alkyl)piperazin-1-ylmethyl. Suitable pharmaceutically acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

[0525] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C_{1-4}alkylamine such as methylamine, a (C_1-C_4 alkyl)$_2$amine such as dimethylamine, N-ethyl-N-methylamine

or diethylamine, a C_1-C_4 alkoxy-C_2-C_4 alkylamine such as 2-methoxyethylamine, a phenyl-C_1-C_4 alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

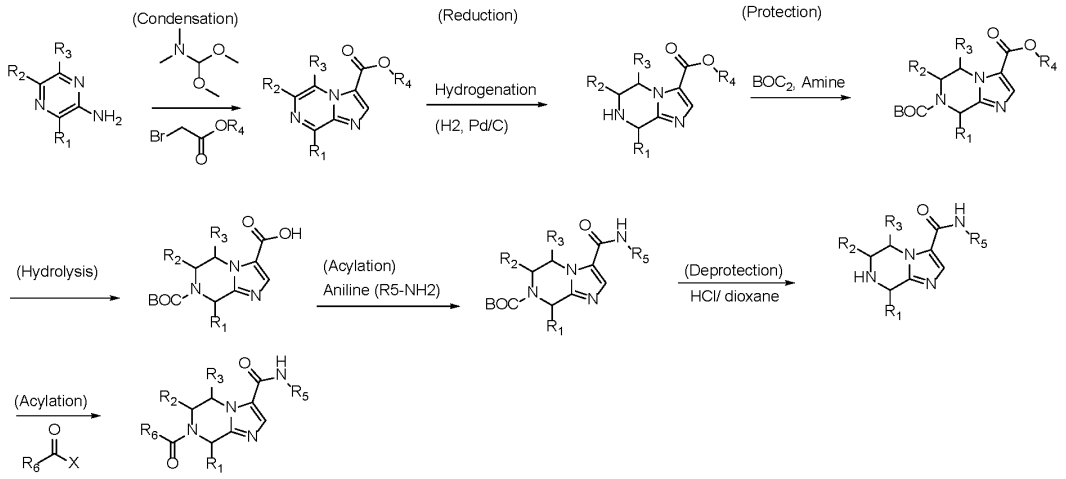
[0526] A suitable pharmaceutically acceptable prodrug of a compound of any one of the Formulae disclosed herein that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C_1-C_{10} alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_1-C_4 alkyl)piperazin-1-ylmethyl.

[0527] The *in vivo* effects of a compound of any one of the Formulae disclosed herein may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of any one of the Formulae disclosed herein. As stated hereinbefore, the *in vivo* effects of a compound of any one of the Formulae disclosed herein may also be exerted by way of metabolism of a precursor compound (a prodrug).

[0528] Suitably, the present disclosure excludes any individual compounds not possessing the biological activity defined herein.

In some aspects, compound of the present disclosure can be prepared according to the following general procedure:

Methods of Synthesis



[0529] In some aspects, the present disclosure provides a method of preparing a compound of the present disclosure.

[0530] In some aspects, the present disclosure provides a method of a compound, comprising one or more steps as described herein.

[0531] In some aspects, the present disclosure provides a compound obtainable by, or obtained by, or directly obtained by a method for preparing a compound as described herein.

[0532] In some aspects, the present disclosure provides an intermediate as described herein, being suitable for use in a method for preparing a compound as described herein.

[0533] The compounds of the present disclosure can be prepared by any suitable technique known in the art. Particular processes for the preparation of these compounds are described further in the accompanying examples.

[0534] In the description of the synthetic methods described herein and in any referenced synthetic methods that are used to prepare the starting materials, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be selected by a person skilled in the art.

[0535] It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reaction conditions utilized.

[0536] It will be appreciated that during the synthesis of the compounds of the disclosure in the processes defined herein, or during the synthesis of certain starting materials, it may be desirable to protect certain substituent groups to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed. For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with the minimum disturbance of groups elsewhere in the molecule. Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

[0537] By way of example, a suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or t-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the

choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed by, for example, hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively, an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

[0538] A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium, sodium hydroxide or ammonia. Alternatively, an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0539] A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium on carbon.

[0540] Once a compound of Formula (I), Formula (II), or Formula (III) has been synthesized by any one of the processes defined herein, the processes may then further comprise the additional steps of: (i) removing any protecting groups present; (ii) converting the compound Formula (I), Formula (II), or Formula (III) into another compound of Formula (I), Formula (II), or Formula (III); (iii) forming a pharmaceutically acceptable salt, hydrate or solvate thereof; and/or (iv) forming a prodrug thereof.

[0541] The resultant compounds of Formula (I), Formula (II), or Formula (III) can be isolated and purified using techniques well known in the art.

[0542] Conveniently, the reaction of the compounds is carried out in the presence of a suitable solvent, which is preferably inert under the respective reaction conditions. Examples of suitable

solvents comprise but are not limited to hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF), 2-methyltetrahydrofuran, cyclopentylmethyl ether (CPME), methyl tert-butyl ether (MTBE) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone, methylisobutylketone (MIBK) or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methylpyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate or methyl acetate, or mixtures of the said solvents or mixtures with water.

[0543] The reaction temperature is suitably between about -100 °C and 300 °C, depending on the reaction step and the conditions used.

[0544] Reaction times are generally in the range between a fraction of a minute and several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 minutes and 48 hours.

[0545] Moreover, by utilizing the procedures described herein, in conjunction with ordinary skills in the art, additional compounds of the present disclosure can be readily prepared. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[0546] As will be understood by the person skilled in the art of organic synthesis, compounds of the present disclosure are readily accessible by various synthetic routes, some of which are exemplified in the accompanying examples. The skilled person will easily recognize which kind of reagents and reactions conditions are to be used and how they are to be applied and adapted in any particular instance – wherever necessary or useful – in order to obtain the compounds of the present disclosure. Furthermore, some of the compounds of the present disclosure can readily be synthesized by reacting other compounds of the present disclosure under suitable conditions, for instance, by converting one particular functional group being present in a compound of the present disclosure, or a suitable precursor molecule thereof, into another one by applying standard synthetic methods, like reduction, oxidation, addition or substitution reactions; those methods are well known to the skilled person. Likewise, the skilled

person will apply – whenever necessary or useful – synthetic protecting (or protective) groups; suitable protecting groups as well as methods for introducing and removing them are well-known to the person skilled in the art of chemical synthesis and are described, in more detail, in, e.g., P.G.M. Wuts, T.W. Greene, "Greene's Protective Groups in Organic Synthesis", 4th edition (2006) (John Wiley & Sons).

[0547] Compounds of Formula (I), Formula (II), or Formula (III) can be prepared as described in the Examples.

Biological Assays

[0548] Compounds designed, selected and/or optimized by methods described above, once produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the molecules can be characterized by conventional assays, including but not limited to those assays described below, to determine whether they have a predicted activity, binding activity and/or binding specificity.

[0549] Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to rapidly screen the molecules described herein for activity, using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin (1998) *High Throughput Screening*, Marcel Dekker; and U.S. Patent No. 5,763,263. High-throughput assays can use one or more different assay techniques including, but not limited to, those described below.

[0550] Various *in vitro* or *in vivo* biological assays may be suitable for detecting the effect of the compounds of the present disclosure. These *in vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0551] In some embodiments, the biological assay is an in vitro kinase assay.

[0552] In some embodiments, the compounds of the present disclosure are prepared in a solvent and added to an enzyme solution containing EphB2 and incubated followed by termination. In some embodiments, the mixture is analyzed (e.g., at a specific excitation and emission) and the data is present as percent inhibition.

[0553] In some embodiments, the compounds of the present disclosure are prepared in a solvent and added to an enzyme solution containing EphB3 and incubated followed by termination. In some embodiments, the in vitro activity is analyzed (e.g., at a specific excitation and emission) and the data is present as percent inhibition.

[0554] In some embodiments, the biological assay is a cellular assay.

[0555] In some embodiments, the cellular assay is a target engagement assay for EphB2 or EphB3 kinase.

[0556] In some embodiments, the cellular assay measures the cellular affinity of a compound of the present disclosure by competitive displacement of a cell-permeable tracer.

[0557] In some embodiments, the compounds of the present disclosure are dosed in cells (e.g., HEK293 cells) mixed with EphB2 of EphB3 plasmid DNA followed by addition of a compound of the present disclosure and incubation. In some embodiments, the cellular activity is measured at a specific acceptor and donor emission value to calculate IC_{50}.

Pharmaceutical Compositions

[0558] In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure as an active ingredient.

[0559] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carrier, diluent, adjuvant, or excipient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table 1 or 2. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carrier, diluent, adjuvant, or excipient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table 1. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and one or more pharmaceutically acceptable carrier, diluent, adjuvant, or excipient. In some embodiments, the present disclosure provides a pharmaceutical composition comprising at least one compound selected from Table 2.

[0560] As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

[0561] The compounds of present disclosure can be formulated for oral administration in forms such as tablets, capsules (each of which includes sustained release or timed-release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of present disclosure on can also be formulated for intravenous (bolus or in-fusion), intraperitoneal, topical, subcutaneous, intra-muscular or transdermal (*e.g.*, patch) administration, all using forms well known to those of ordinary skill in the pharmaceutical arts.

[0562] The compositions of the disclosure may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular, intraperitoneal or intramuscular dosing or as a suppository for rectal dosing).

[0563] The compositions of the disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art.

[0564] An effective amount of a compound of the present disclosure for use in therapy is an amount sufficient to treat or prevent an EphB3 related condition referred to herein, slow its progression and/or reduce the symptoms associated with the condition.

[0565] The size of the dose for therapeutic or prophylactic purposes of a compound of Formula (I), Formula (II), or Formula (III) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

Methods of Use

[0566] In some aspects, the present disclosure provides a method of modulation of EphB3 activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

[0567] In some aspects, the present disclosure provides a method of inhibiting EphB3 activity (e.g., *in vitro* or *in vivo*), comprising contacting a cell with an effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof.

[0568] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0569] In some aspects, the present disclosure provides a method of treating or preventing a disease or disorder disclosed herein in a subject in need thereof, comprising administering to

the subject a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0570] In some embodiments, the disease or disorder is associated with an implicated EphB3 activity.

[0571] In some embodiments, the disease or disorder is a neurodegenerative disease or disorder.

[0572] In some aspects, the present disclosure provides a method of treating or preventing a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0573] In some aspects, the present disclosure provides a method of treating or preventing a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0574] In some aspects, the present disclosure provides a method of treating a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0575] In some aspects, the present disclosure provides a method of treating a neurodegenerative disease or disorder in a subject in need thereof, comprising administering to the subject a compound of the present disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the present disclosure.

[0576] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in modulation of EphB3 activity (e.g., *in vitro* or *in vivo*).

[0577] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a disease or disorder disclosed herein.

[0578] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating a disease or disorder disclosed herein.

[0579] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating or preventing a neurodegenerative disease or disorder in a subject in need thereof.

[0580] In some aspects, the present disclosure provides a compound of the present disclosure or a pharmaceutically acceptable salt thereof for use in treating a neurodegenerative disease or disorder in a subject in need thereof.

[0581] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for modulation of EphB3 activity (e.g., *in vitro* or *in vivo*).

[0582] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a disease or disorder disclosed herein.

[0583] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a disease or disorder disclosed herein.

[0584] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a neurodegenerative disease or disorder in a subject in need thereof.

[0585] In some aspects, the present disclosure provides use of a compound of the present disclosure or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a neurodegenerative disease or disorder in a subject in need thereof.

[0586] In some embodiments, modulation of EphB3 is inhibition of EphB3.

[0587] Effectiveness of compounds of the disclosure can be determined by industry-accepted assays/ disease models according to standard practices of elucidating the same as described in the art and are found in the current general knowledge.

[0588] In some embodiments, the neurodegenerative disease or disorder is neuromyelitis optica ("NMO"), transverse myelitis, myelin oligodendrocyte glycoprotein, acute disseminated encephalomyelitis ("ADEM"), optic neuritis, amyloidosis, Parkinson's disease, Alzheimer's disease, cerebral amyloid angiopathy, Pick's disease, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis ("ALS"), Huntington's disease, traumatic brain injury, stroke, fatty liver disease, endometriosis, paraneoplastic disorders, inflammatory demyelinating polyneuropathy, amyotrophy, fibromyalgia, multiple system atrophy, Friedrich's ataxia, or cerebellar ataxia.

[0589] In some embodiments, the disease or disorder is a psychiatric or neurodevelopmental disease or disorder.

[0590] In some embodiments, the psychiatric or neurodevelopmental disease or disorder is schizophrenia, major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia, post-traumatic stress disorder, autism spectrum disorder, cerebral palsy, Nasu Hakola disease, bipolar disorder, or substance abuse.

[0591] In some embodiments, the disease or disorder is a viral or infectious disease or disorder.

[0592] In some embodiments, the viral or infectious disease or disorder is neuro-HIV, viral encephalitis, meningitis, neurocysticercosis, neurosyphilis, neuro-Lyme disease, infectious myelopathies, COVID-19 neuroinflammation, enteroviruses, poliovirus, Epstein-Barr virus (EBV), human herpesvirus, cytomegalovirus, rabies virus, herpes simplex virus, measles, progressive multifocal leukoencephalopathy John Cunningham ("PML JC") virus, bacterial meningitis, prion disease, or Creutzfeldt Jakob disease.

[0593] In some embodiments, the disease or disorder is an autoimmune disease or disorder.

[0594] In some embodiments, the autoimmune disease or disorder is antibody-mediated encephalitis, neurological complications of connective tissue damage, neurosarcoidosid, demyelinating diseases (non-MS), idiopathic autoimmune CNS and PNS syndromes, paraneoplastic neurological disease, CNS vasculitis, type 1 diabetes, type 2 diabetes, Crohn's disease, systemic lupus erythematous ("SLE"), irritable bowel disorders, asthma, chronic obstructive pulmonary disease ("COPD"), atopic dermatitis, obesity-associated inflammation, heart disease, ulcerative colitis, psoriasis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, Sjögren's syndrome, Reiter's disease, multiple sclerosis, autoimmune encephalitis, myasthenia gravis, idiopathic pulmonary fibrosis, ankylosing spondylitis, antiphospholipid antibody syndrome, osteomyelitis, gout, Henoch-Schonlein Purpura, dermatomyositis, idiopathic arthritis, scleroderma, Kawasaki disease, mixed connective tissue damage, myositis, spondyloarthritis, undifferentiated connective tissue disease, systemic sclerosis, or autoimmune hepatitis.

[0595] In some embodiments, the disease or disorder is an eye disease or disorder.

[0596] In some embodiments, the disease or disorder is an ocular inflammatory disease.

[0597] In some embodiments, the eye disease or disorder is uveitis, keratitis, conjunctivitis, thyroid eye disease, age-related macular degeneration, glaucoma, diabetic retinopathy, diabetes-related macular edema, or scleritis.

[0598] In some embodiments, the disease or disorder is a neuronal system injury.

[0599] In some embodiments, the disease or disorder is cancer.

[0600] In some embodiments, the neurodegenerative diseases or disorder is autoimmune encephalomyelitis (AE) (including EAE), chronic inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), amyotrophic lateral sclerosis, schizophrenia, Alzheimer's disease, or Parkinson's disease.

[0601] In some embodiments, the AE is acute. In some embodiments, the AE is chronic.

[0602] In some embodiments, the MS is a late-stage MS disease. In some embodiments, the MS is in a relapsing stage.

[0603] In some embodiments, the disease or disorder is amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, or Huntington's disease.

[0604] In some embodiments, the Alzheimer's disease is Alzheimer's disease with APOE4.

[0605] In some embodiments, the multiple sclerosis is progression independent of relapses.

[0606] In some embodiments, the neurodegenerative diseases or disorder is dementia, frontotemporal lobar dementia, Huntington's disease, accessory nerve disorder, autonomic dysreflexia, peripheral neuropathy, chemotherapy-induced peripheral neuropathies, mononeuropathy, polyneuropathy, radial neuropathy, ulnar neuropathy, Villaret's syndrome, Charcot–Marie–Tooth disease, diabetic neuropathy, nerve paralysis, progressive bulbar palsy, pseudobulbar palsy, spinal bulbar muscular atrophy, myotonic dystrophy, inclusion body myositis, prion disease, seizure disorders, lysosomal storage disorders, transmissible spongiform encephalopathy, Creutzfeldt-Jacob disease (CJD), spinocerebellar ataxia, spinal muscular atrophy, and Horner's syndrome. In some embodiments, the neurodegenerative disease or condition is driven by dysregulated adaptive (T cells and B cells), or innate (monocytes, microglia and astrocytes) immune responses.

[0607] In some embodiments, the disease or disorder is adrenoleukodystrophy, macular degeneration, glaucoma, optic neuritis, Guillain-Barre syndrome, or Lewy Body syndrome.

[0608] In some embodiments, the disease or disorder is autoimmune encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia, Alzheimer's disease, Parkinson's disease, acute disseminated encephalomyelitis ("ADEM"), concentric sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, HTLV-I associated myelopathy ("HAM"), neuromyelitis optica, Schilder's disease, or transverse myelitis.

[0609] In some embodiments, the disease or disorder is a chronic autoimmune inflammatory disease.

[0610] In some embodiments, the disease or disorder is a neuronal system injury characterized by EphB3 kinase activity.

[0611] In some embodiments, the neuronal system injury is a central nervous system injury. In some embodiments, the central nervous system injury is selected from cerebral ischemia and traumatic brain injury.

[0612] In some embodiments, the disease or disorder is stroke, spinal cord injury, or traumatic brain injury.

[0613] In some embodiments, the cancer is selected from leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer.

[0614] In some embodiments, modulation of EphB3 is inhibition of EphB3 receptor signaling in an astrocyte cell of a subject.

[0615] In some embodiments, modulation of EphB3 is inhibition of EphB3 tyrosine kinase in an astrocyte cell of a subject.

[0616] In some embodiments, modulation of EphB3 is inhibition of pro-inflammatory response in an astrocyte cell of a subject.

[0617] In some embodiments, modulation of EphB3 is inhibition of production of TNF-α in an astrocyte cell of a subject.

[0618] In some embodiments, modulation of EphB3 is reduction of production of IL6 in an astrocyte cell of a subject.

[0619] In some embodiments, modulation of EphB3 is reduction of production of CCl2 in an astrocyte cell of a subject.

[0620] In some embodiments, modulation of EphB3 is inhibition of phosphorylation of AKT in astrocyte cell of a subject.

[0621] In some embodiments, modulation of EphB3 is inhibition of activation of mTOR pathway in an astrocyte cell of a subject.

[0622] In some embodiments, modulation of EphB3 is inhibition of production of mitochondrial reactive oxygen species (ROS) in an astrocyte cell of a subject.

[0623] In some embodiments, modulation of EphB3 is inhibition of pro-inflammatory response in a microglial cell of a subject.

[0624] In some embodiments, modulation of EphB3 is restoration of a homeostatic state or a normal activation state of glial cell or a neuron cell of a subject.

[0625] In some embodiments, modulation of EphB3 is inhibition of NFkB activation in a microglial cell of a subject.

[0626] In some embodiments, modulation of EphB3 is inhibition of production of TNF-α in a microglial cell of a subject.

[0627] In some embodiments, modulation of EphB3 is inhibition of demyelination of a neuron cell in a subject.

[0628] In some embodiments, modulation of EphB3 is reduction of pro-inflammatory T cells in a central nervous system of a subject.

[0629] In some embodiments, modulation of EphB3 is reduction of pro-inflammatory macrophages in a central nervous system of a subject.

[0630] In some embodiments, modulation of EphB3 is reductio of pro-inflammatory macrophages in a peripheral nervous system of a subject.

[0631] In some embodiments, modulation of EphB3 is inhibition of CNS inflammation in a subject.

[0632] In some embodiments, modulation of EphB3 is inhibition of PNS inflammation in a subject.

[0633] In some embodiments, modulation of EphB3 is inhibition of neurodegeneration in a subject.

Definitions

[0634] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

[0635] Without wishing to be limited by this statement, it is understood that, while various options for variables are described herein, the disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

[0636] It is to be understood that a compound of the present disclosure may be depicted in a neutral form, a cationic form (e.g., carrying one or more positive charges), or an anionic form (e.g., carrying one or more negative charges), all of which are intended to be included in the scope of the present disclosure. For example, when a compound of the present disclosure is depicted in an anionic form, such depiction also refers to the various neutral forms, cationic forms, and anionic forms of the compound. For another example, when a compound the present disclosure is depicted in an anionic form, such depiction also refers to various salts (e.g., sodium salt) of the anionic form of the compound.

[0637] A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to affect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0638] As used herein, "alkyl", "C_1, C_2, C_3, C_4, C_5 or C_6 alkyl" or "C_1-C_6 alkyl" is intended to include C_1, C_2, C_3, C_4, C_5 or C_6 straight chain (linear) saturated aliphatic hydrocarbon groups and C_3, C_4, C_5 or C_6 branched saturated aliphatic hydrocarbon groups. For example, C_1-C_6 alkyl is intends to include C_1, C_2, C_3, C_4, C_5 and C_6 alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl or n-hexyl. In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and in another embodiment, a straight chain or branched alkyl has four or fewer carbon atoms.

[0639] As used herein, the term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term "alkenyl" includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkenyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkenyl groups containing three to six carbon atoms.

[0640] As used herein, the term "optionally substituted alkenyl" refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0641] As used herein, the term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, "alkynyl" includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or

fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term "C_2-C_6" includes alkynyl groups containing two to six carbon atoms. The term "C_3-C_6" includes alkynyl groups containing three to six carbon atoms. As used herein, "C_2-C_6 alkenylene linker" or "C_2-C_6 alkynylene linker" is intended to include C_2, C_3, C_4, C_5 or C_6 chain (linear or branched) divalent unsaturated aliphatic hydrocarbon groups. For example, C_2-C_6 alkenylene linker is intended to include C_2, C_3, C_4, C_5 and C_6 alkenylene linker groups.

[0642] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents.

[0643] As used herein, the term "aryl" includes groups with aromaticity, including "conjugated," or multicyclic systems with one or more aromatic rings and do not contain any heteroatom in the ring structure. The term aryl includes both monovalent species and divalent species. Examples of aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl and the like.

[0644] The aryl ring can be substituted at one or more ring positions (e.g., the ring-forming carbon) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system.

[0645] As used herein, the term "substituted," means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N).

[0646] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0647] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0648] When any variable (*e.g.*, R) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R moieties, then the group may optionally be substituted with up to two R moieties and R at each occurrence is selected independently from the definition of R. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0649] As used herein, the term "hydroxy" or "hydroxyl" includes groups with an -OH or $-O^-$.

[0650] As used herein, the term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[0651] The term "haloalkyl" or "haloalkoxyl" refers to an alkyl or alkoxyl substituted with one or more halogen atoms.

[0652] As used herein, the term "alkoxy" or "alkoxyl" includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropyloxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to,

fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0653] As used herein, the expressions "one or more of A, B, or C," "one or more A, B, or C," "one or more of A, B, and C," "one or more A, B, and C," "selected from the group consisting of A, B, and C", "selected from A, B, and C", and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0654] It is to be understood that the present disclosure provides methods for the synthesis of the compounds of any of the Formulae described herein. The present disclosure also provides detailed methods for the synthesis of various disclosed compounds of the present disclosure according to the following schemes as well as those shown in the Examples.

[0655] It is to be understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated those compositions also consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0656] It is to be understood that the synthetic processes of the disclosure can tolerate a wide variety of functional groups, therefore various substituted starting materials can be used. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt thereof.

[0657] It is to be understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, *J.*, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in*

Organic Synthesis, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art.

[0658] One of ordinary skill in the art will note that, during the reaction sequences and synthetic schemes described herein, the order of certain steps may be changed, such as the introduction and removal of protecting groups. One of ordinary skill in the art will recognize that certain groups may require protection from the reaction conditions via the use of protecting groups. Protecting groups may also be used to differentiate similar functional groups in molecules. A list of protecting groups and how to introduce and remove these groups can be found in Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999.

[0659] It is to be understood that, unless otherwise stated, any description of a method of treatment includes use of the compounds to provide such treatment or prophylaxis as is described herein, as well as use of the compounds to prepare a medicament to treat or prevent such condition. The treatment includes treatment of human or non-human animals including rodents and other disease models.

[0660] As used herein, the term "subject" includes human and non-human animals, as well as cell lines, cell cultures, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[0661] As used herein, the term "subject in need thereof" refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some

embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0662] As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model. It is to be appreciated that references to "treating" or "treatment" include the alleviation of established symptoms of a condition. "Treating" or "treatment" of a state, disorder or condition therefore includes: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a human that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof (in case of maintenance treatment) or at least one clinical or subclinical symptom thereof, or (3) relieving or attenuating the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

[0663] It is to be understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0664] As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0665] It is to be understood that one skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al., Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the disclosure.

[0666] It is to be understood that the present disclosure also provides pharmaceutical compositions comprising any compound described herein in combination with at least one pharmaceutically acceptable excipient or carrier.

[0667] As used herein, the term "pharmaceutical composition" is a formulation containing the compounds of the present disclosure in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or salt, hydrate, solvate or isomer thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this disclosure include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0668] As used herein, the term "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0669] As used herein, the term "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

[0670] It is to be understood that a pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.,* intravenous, intradermal, subcutaneous, oral (*e.g.*, ingestion), inhalation, transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following

components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0671] It is to be understood that a compound or pharmaceutical composition of the disclosure can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, a compound of the disclosure may be injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, a disease or disorder disclosed herein) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0672] As used herein, the term "therapeutically effective amount," refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0673] It is to be understood that, for any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0674] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet,

time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0675] The pharmaceutical compositions containing active compounds of the present disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0676] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.*J.*) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0677] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by

incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0678] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0679] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0680] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0681] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained

commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0682] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure is dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0683] It is to be understood that the pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0684] It is to be understood that, for the compounds of the present disclosure being capable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0685] As used herein, the term "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0686] In some embodiments, the pharmaceutically acceptable salt is a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a diethylamine salt, a choline salt, a meglumine salt, a benzathine salt, a tromethamine salt, an ammonia salt, an arginine salt, or a lysine salt.

[0687] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0688] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier, excipient, adjuvant, or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0689] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0690] In the synthetic schemes described herein, compounds may be drawn with one particular configuration for simplicity. Such particular configurations are not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers; however, it will

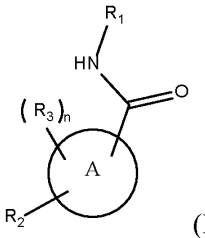
be understood that a given isomer, tautomer, regioisomer or stereoisomer may have a higher level of activity than another isomer, tautomer, regioisomer or stereoisomer.

[0691] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

[0692] As use herein, the phrase "compound of the disclosure" refers to those compounds which are disclosed herein, both generically and specifically.

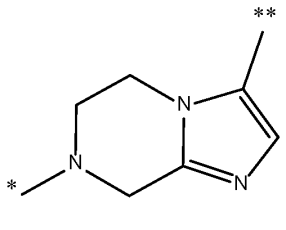
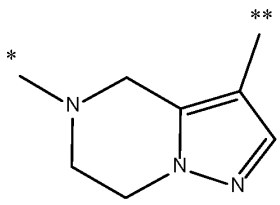
Exemplary Embodiments

[0693] Exemplary Embodiment 1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy);

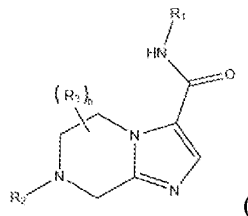
each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

[0694] Exemplary Embodiment 2. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- or 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

[0695] each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, $-NH_2$, $-NH(C_1-C_6$ alkyl), $-N(C_1-C_6$ alkyl$)_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-CO(C_1-C_6$ alkyl), or $-CO_2(C_1-C_6$ alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, $-NH-CO_2(C_1-C_6$ alkyl), or $-NH_2$;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-CO_2(R_{2g})$, $-CON(R_{2g})(R_{2h})$, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, or $-C(O)-NH(C_1-C_6$ alkyl-C_1-C_6 alkoxy);

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

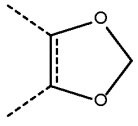
[0696] Exemplary Embodiment 3. The compound of any one of the preceding Exemplary Embodiments, wherein R_1 is phenyl optionally substituted with one or more R_{1a}.

[0697] Exemplary Embodiment 4. The compound of Exemplary Embodiment 1 or Exemplary Embodiment 2, wherein R_1 is 5- or 6-membered heteroaryl optionally substituted with one or more R_{1a}.

[0698] Exemplary Embodiment 5. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1a} is halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, or $-C(O)N(R_{1b})(R_{1c})$.

[0699] Exemplary Embodiment 6. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1a} is Cl, F, methyl, or methoxy.

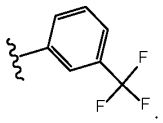
[0700] Exemplary Embodiment 7. The compound of any one of Exemplary Embodiments 1-4, wherein two R_{1a}, together with the atoms to which they are attached, form a 5- or 6-membered heterocycle.

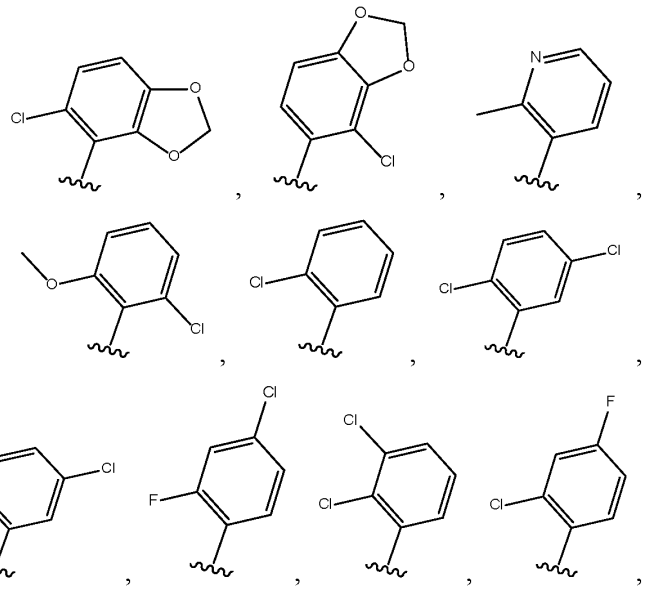
[0701] Exemplary Embodiment 8. The compound of any one of Exemplary Embodiments 1-4 or 7, wherein two R_{1a}, together with the atoms to which they are attached, form .

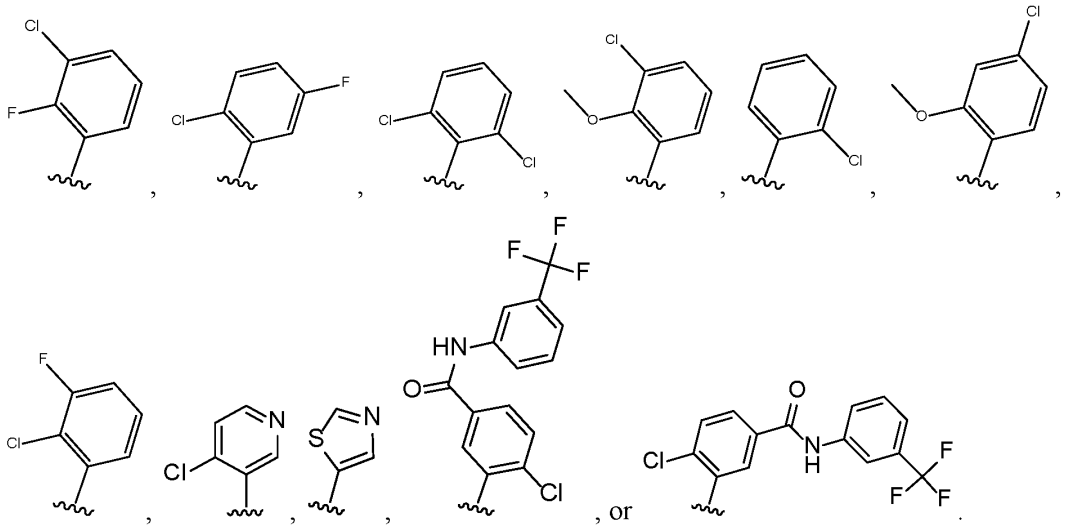
[0702] Exemplary Embodiment 9. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1b} is H.

[0703] Exemplary Embodiment 10. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1c} is C_6-C_{10} aryl optionally substituted with one or more C_1-C_6 haloalkyl.

[0704] Exemplary Embodiment 11. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1c} is phenyl optionally substituted with one or more -CF_3.

[0705] Exemplary Embodiment 12. The compound of any one of the preceding Exemplary Embodiments, wherein R_{1c} is .

[0706] Exemplary Embodiment 13. The compound of any one of the preceding Exemplary Embodiments, wherein R_1 is .



[0707] Exemplary Embodiment 14. The compound of any one of the preceding Exemplary Embodiments, wherein R_2 is -C(O)R_{2a}.

[0708] Exemplary Embodiment 15. The compound of any one of Exemplary Embodiments 1-13, wherein R_2 is C_2-C_6 alkenyl optionally substituted with one or more R_{2b}.

[0709] Exemplary Embodiment 16. The compound of any one of Exemplary Embodiments 1-14, wherein R_{2a} is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}.

[0710] Exemplary Embodiment 17. The compound of any one of Exemplary Embodiments 1-13 or 15, wherein R_{2b} is halo.

[0711] Exemplary Embodiment 18. The compound of any one of Exemplary Embodiments 1-13, 15, or 17, wherein R_{2b} is Cl.

[0712] Exemplary Embodiment 19. The compound of any one of Exemplary Embodiments 1-13 or 15, wherein R_{2b} is 4- to 10-membered heterocyclyl, -N(R_{2c})(R_{2d}), -OR_{2c}, C_6-C_{10} aryl, or -CO_2(R_{2c}), wherein the heterocyclyl or aryl is optionally substituted with one or more R_{2e}.

[0713] Exemplary Embodiment 20. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2c} is H.

[0714] Exemplary Embodiment 21. The compound of any one of Exemplary Embodiments 1-19, wherein R_{2c} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_6-C_{10} aryl, wherein the alkyl, cycloalkyl, or aryl is optionally substituted with one or more R_{2f}.

[0715] Exemplary Embodiment 22. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2d} is H, methyl, or ethyl.

[0716] Exemplary Embodiment 23. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2e} is halo, -OH, -CN, -CO(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, or -CO_2(C_1-C_6 alkyl).

[0717] Exemplary Embodiment 24. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2e} is F, -OH, -CN, -CO(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, or -CO_2(C_1-C_6 alkyl).

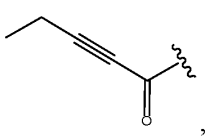
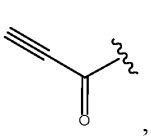
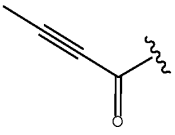
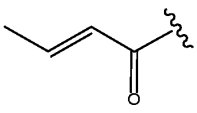
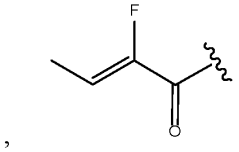
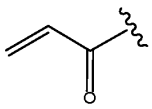
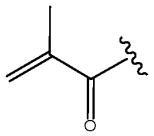
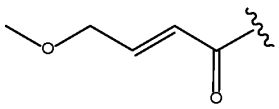
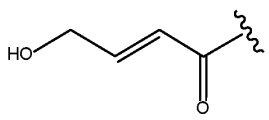
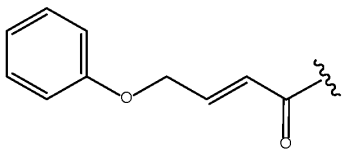
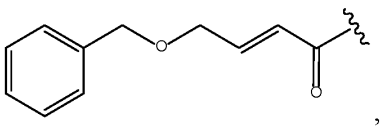
[0718] Exemplary Embodiment 25. The compound of any one of Exemplary Embodiments 1-22, wherein R_{2e} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or 5- to 10-membered heterocyclyl, wherein the alkyl, haloalkyl, alkoxy, cycloalkyl, or heterocyclyl, is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, or -NH-CO_2(C_1-C_6 alkyl).

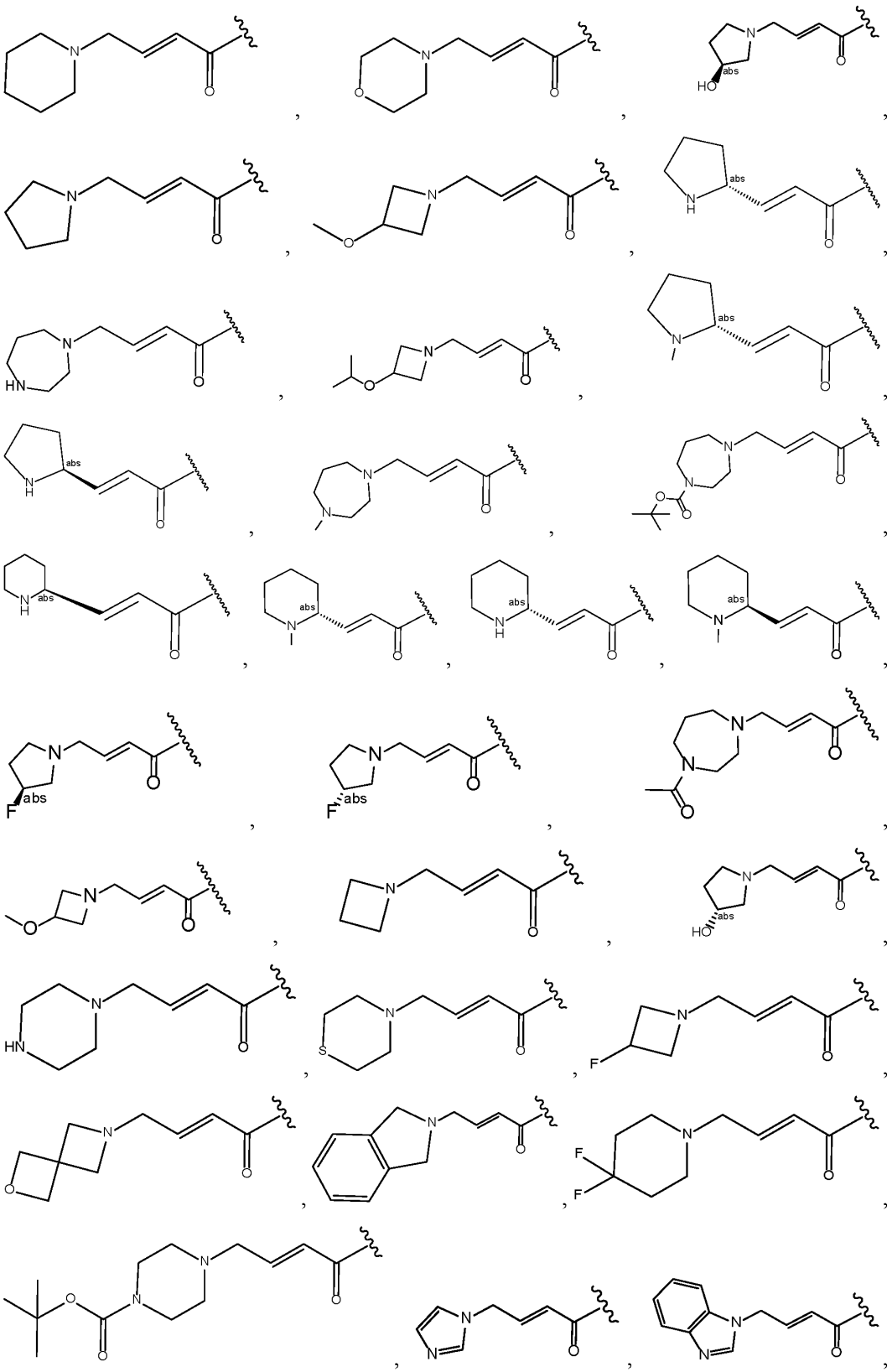
[0719] Exemplary Embodiment 26. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2f} is independently halo, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), C_3-C_6 cycloalkyl, C_6-C_{10} aryl, C_1-C_6 haloalkyl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy).

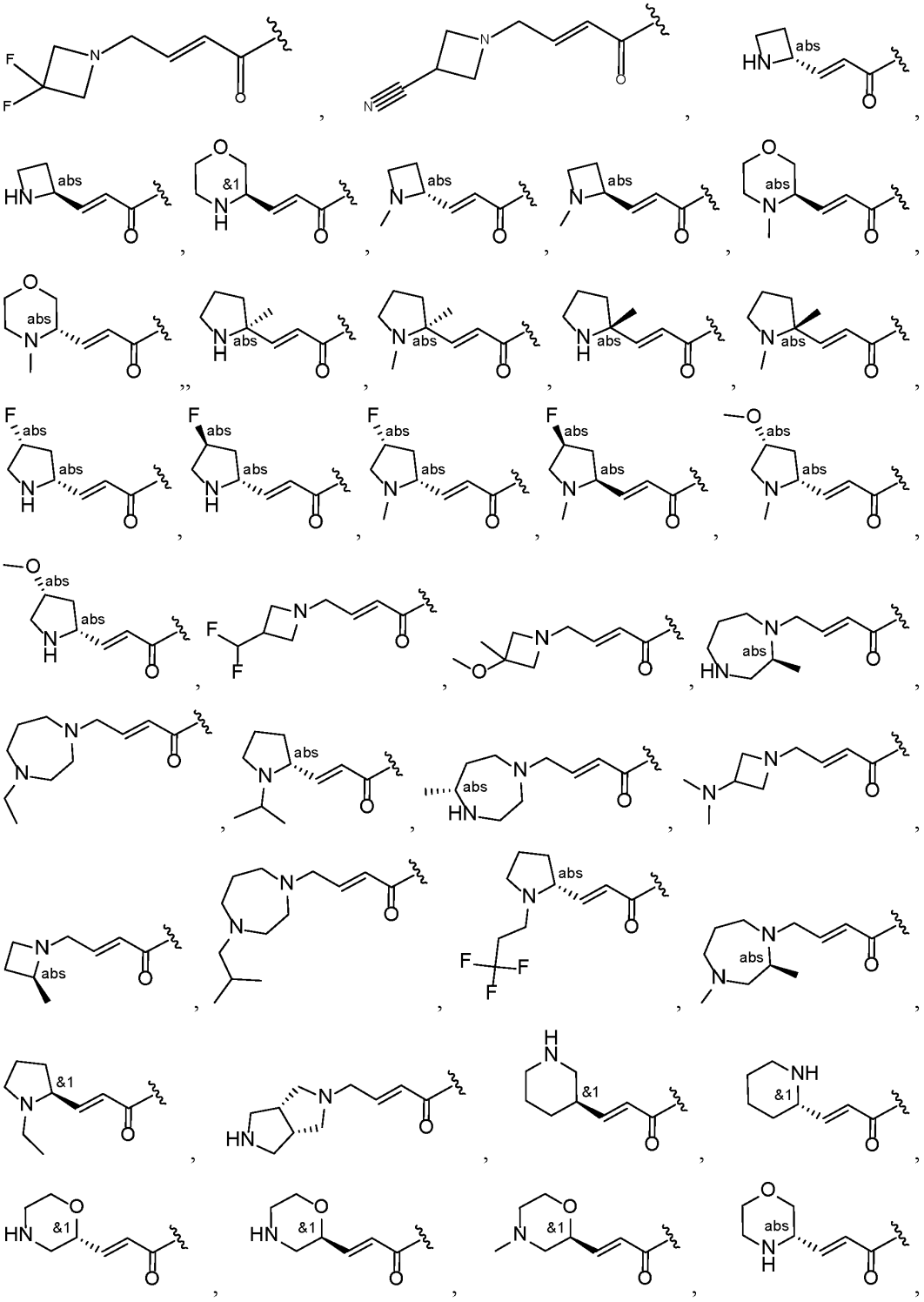
[0720] Exemplary Embodiment 27. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2f} is independently F, -CN, methyl, methoxy, phenoxy, -CO_2(R_{2g}), cyclopropyl, phenyl, -CF_3, or -C(O)-NH(ethyl-methoxy).

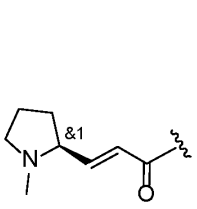
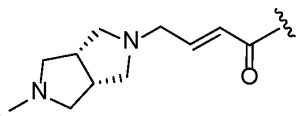
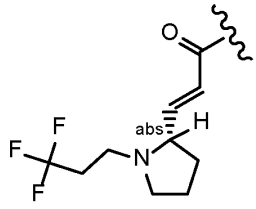
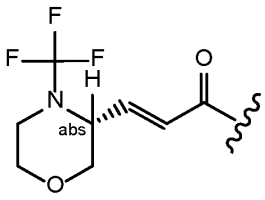
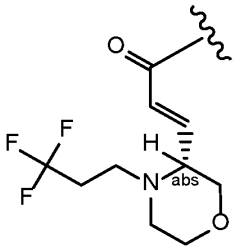
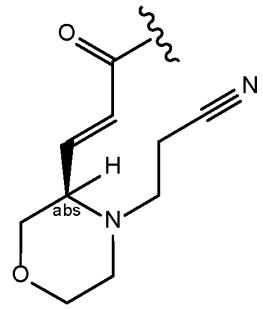
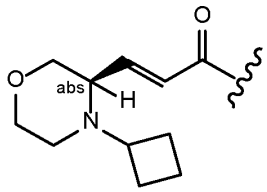
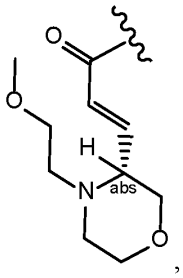
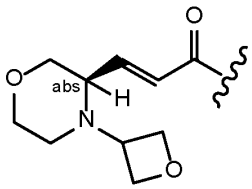
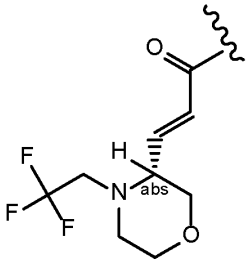
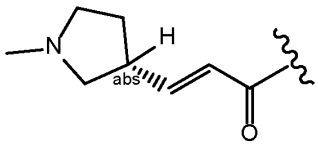
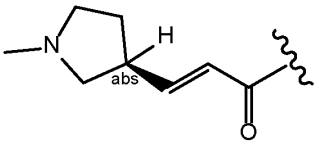
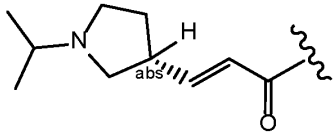
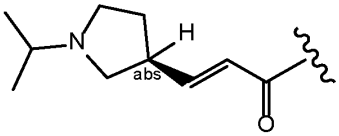
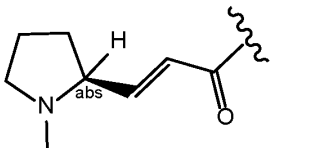
[0721] Exemplary Embodiment 28. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2g} is independently H or C_1-C_6 alkyl.

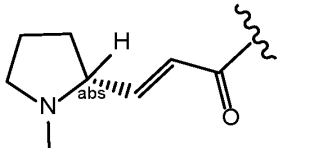
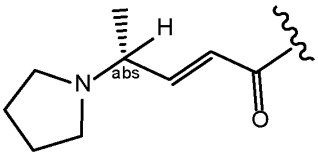
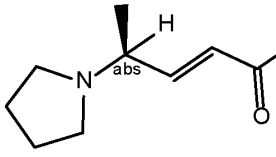
[0722] Exemplary Embodiment 29. The compound of any one of the preceding Exemplary Embodiments, wherein R_{2g} is independently H or *tert*-butyl.

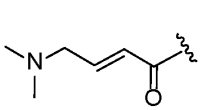
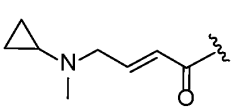
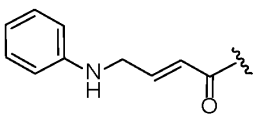
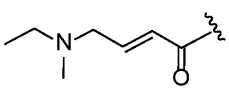
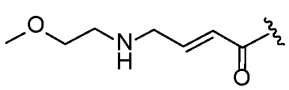
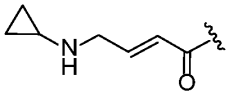
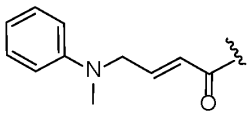
[0723] Exemplary Embodiment 30. The compound of any one of the preceding Exemplary Embodiments, wherein R_2 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,

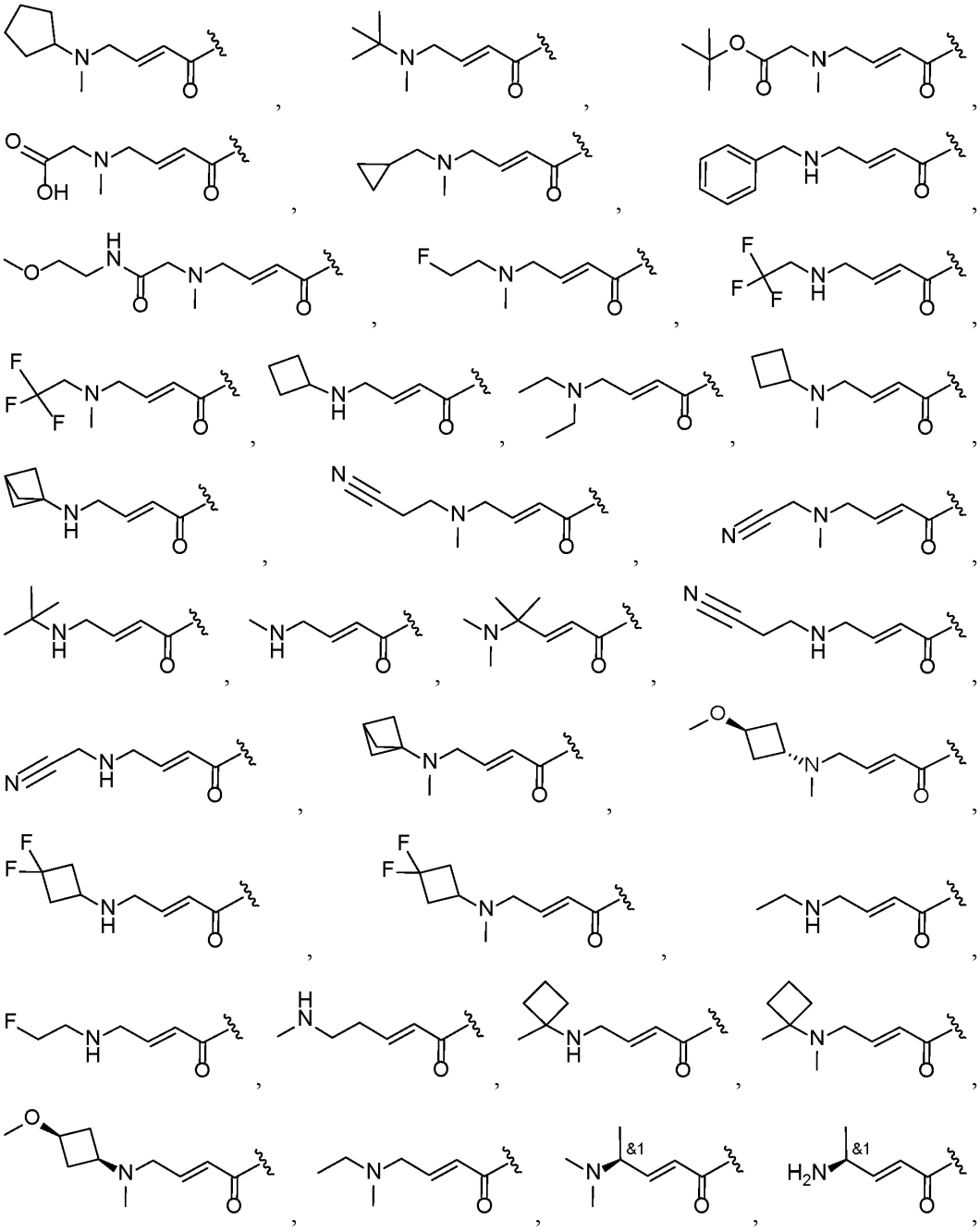


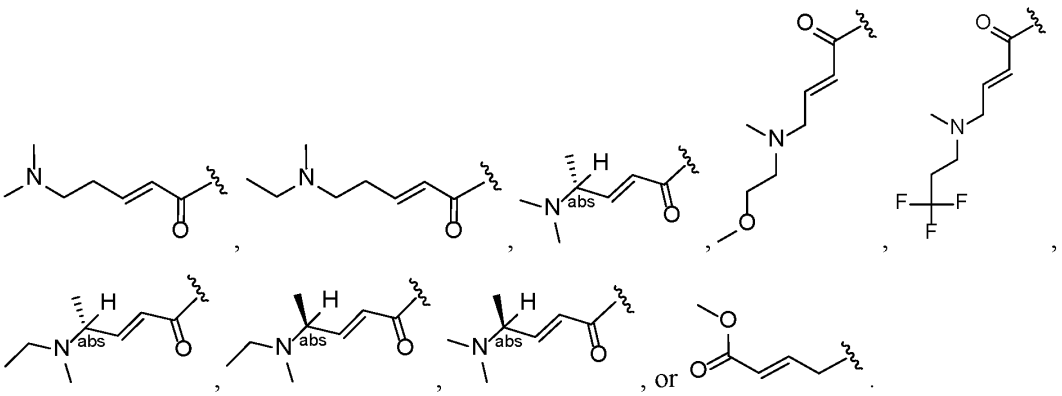


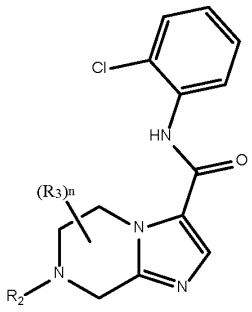




[0724] Exemplary Embodiment 31. The compound of any one of the preceding Exemplary Embodiments, wherein R_3 is C_1-C_6 alkyl or C_3-C_{10} cycloalkyl.

[0725] Exemplary Embodiment 32. The compound of any one of the preceding Exemplary Embodiments, wherein R_3 is methyl or cyclopropyl.

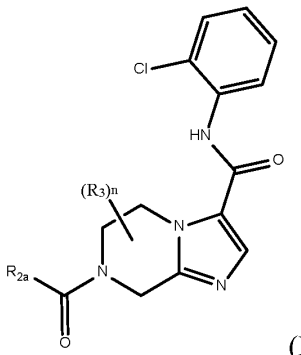
[0726] Exemplary Embodiment 33. The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (II-a)



(II-a),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

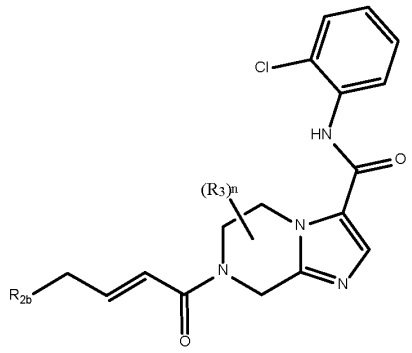
[0727] Exemplary Embodiment 34. The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (II-b)



(II-b),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

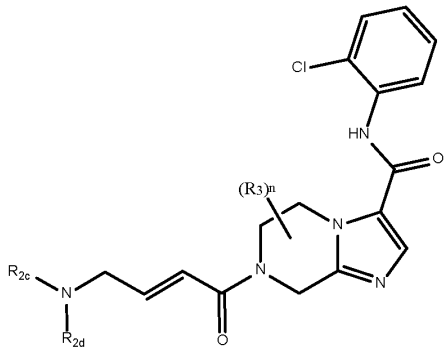
[0728] Exemplary Embodiment 35. The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (II-c)



(II-c),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

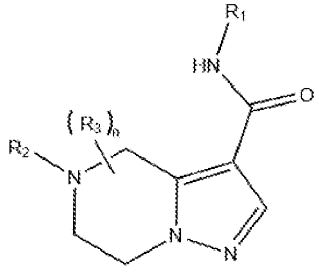
[0729] Exemplary Embodiment 36. The compound of any one of the preceding Exemplary Embodiments, wherein the compound is of Formula (II-d)



(II-d),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0730] Exemplary Embodiment 37. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is -C(O)R_{2a};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

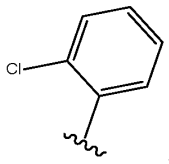
R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

[0731] Exemplary Embodiment 38. The compound of Exemplary Embodiment 1 or Exemplary Embodiment 37, wherein R_1 is phenyl optionally substituted with one or more R_{1a}.

[0732] Exemplary Embodiment 39. The compound of any one of Exemplary Embodiments 1 or 37-38, wherein R_{1a} is halo.

[0733] Exemplary Embodiment 40. The compound of any one of Exemplary Embodiments 1 or 37-39, wherein R_{1a} is Cl.

[0734] Exemplary Embodiment 41. The compound of any one of Exemplary Embodiments 1 or 37-40, wherein R_1 is 

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[0735] Exemplary Embodiment 42. The compound of any one of Exemplary Embodiments 1 or 37-41, wherein R_{2a} is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}.

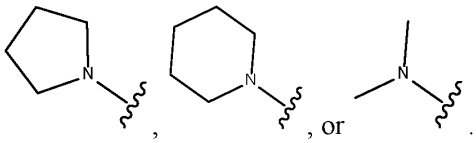
[0736] Exemplary Embodiment 43. The compound of any one of Exemplary Embodiments 1 or 37-42, wherein R_{2b} is independently -N(R_{2c})(R_{2d}) or 4- to 10-membered heterocyclyl.

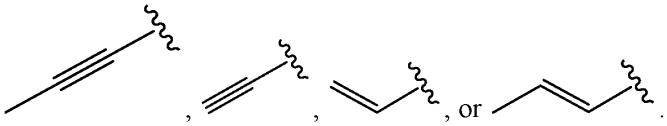
[0737] Exemplary Embodiment 44. The compound of any one of Exemplary Embodiments 1 or 37-43, wherein R_{2c} is C_1-C_6 alkyl.

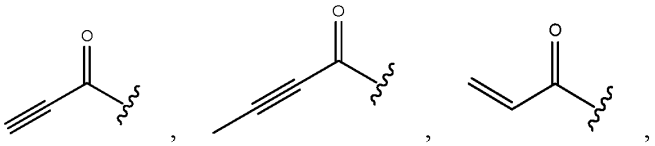
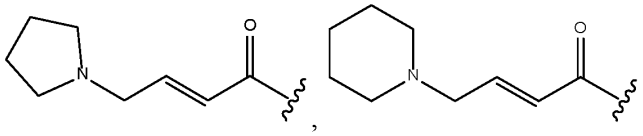
[0738] Exemplary Embodiment 45. The compound of any one of Exemplary Embodiments 1 or 37-44, wherein R_{2c} is methyl.

[0739] Exemplary Embodiment 46. The compound of any one of Exemplary Embodiments 1 or 37-45, wherein R_{2d} is C_1-C_6 alkyl

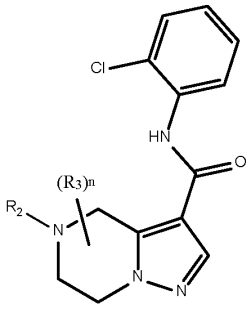
[0740] Exemplary Embodiment 47. The compound of any one of Exemplary Embodiments 1 or 37-46, wherein R_{2d} is methyl.

[0741] Exemplary Embodiment 48. The compound of any one of Exemplary Embodiments 1 or 37-47, wherein R_{2b} is .

[0742] Exemplary Embodiment 49. The compound of any one of Exemplary Embodiments 1 or 37-48, wherein R_{2a} is .

[0743] Exemplary Embodiment 50. The compound of any one of Exemplary Embodiments 1 or 37-49, wherein R_2 is , , , or .

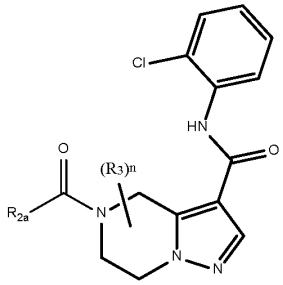
[0744] Exemplary Embodiment 51. The compound of any one of Exemplary Embodiments 1 or 37-50, wherein the compound is of Formula (III-a)



(III-a),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

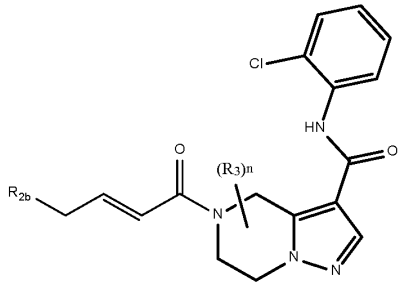
[0745] Exemplary Embodiment 52. The compound of any one of Exemplary Embodiments 1 or 37-51, wherein the compound is of Formula (III-b)



(III-b),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0746] Exemplary Embodiment 53. The compound of any one of Exemplary Embodiments 1 or 37-52, wherein the compound is of Formula (III-c)



(III-c),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0747] Exemplary Embodiment 54. The compound of any one of the preceding Exemplary Embodiments, wherein the compound is selected from the compounds described in **Table 1**, or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

[0748] Exemplary Embodiment 55. A compound being an isotopic derivative of the compound of any one of the preceding Exemplary Embodiments.

[0749] Exemplary Embodiment 56. A compound of any one of the preceding Exemplary Embodiments obtainable by, or obtained by, a method described herein.

[0750] Exemplary Embodiment 57. An intermediate obtained by a method for preparing the compound of any one of the preceding Exemplary Embodiments.

[0751] Exemplary Embodiment 58. A pharmaceutical composition comprising the compound of any one of the preceding Exemplary Embodiments and a pharmaceutical acceptable diluent or carrier.

[0752] Exemplary Embodiment 59. A method of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound of any one of the preceding Exemplary Embodiments, or the pharmaceutical composition of any one of the preceding embodiments.

[0753] Exemplary Embodiment 60. The compound or pharmaceutical composition of anyone of the preceding Exemplary Embodiments, for use in treating or preventing a disease or disorder.

[0754] Exemplary Embodiment 61. Use of the compound of any one of the preceding Exemplary Embodiments in the manufacture of a medicament for treating or preventing a disease or disorder.

[0755] Exemplary Embodiment 62. The method, compound, or use of any one of Exemplary Embodiments 59-61, wherein the disease or disorder is a neurodegenerative disease or disorder.

[0756] Exemplary Embodiment 63. The method, compound, or use of Exemplary Embodiment 62, wherein the neurodegenerative disease or disorder is neuromyelitis optica ("NMO"), transverse myelitis, myelin oligodendrocyte glycoprotein, acute disseminated encephalomyelitis ("ADEM"), optic neuritis, amyloidosis, Parkinson's disease, Alzheimer's disease, cerebral amyloid angiopathy, Pick's disease, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis ("ALS"), Huntington's disease, traumatic brain injury, stroke, fatty liver disease, endometriosis, paraneoplastic disorders, inflammatory demyelinating polyneuropathy, amyotrophy, fibromyalgia, multiple system atrophy, Friedrich's ataxia, or cerebellar ataxia.

[0757] Exemplary Embodiment 64. The method, compound, or use of any one of Exemplary Embodiments 59-61, wherein the disease or disorder is a psychiatric or neurodevelopmental disease or disorder.

[0758] Exemplary Embodiment 65. The method, compound, or use of Exemplary Embodiment 64, wherein the psychiatric or neurodevelopmental disease or disorder is schizophrenia, major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia, post-traumatic stress disorder, autism spectrum disorder, cerebral palsy, Nasu Hakola disease, bipolar disorder, or substance abuse.

[0759] Exemplary Embodiment 66. The method, compound, or use of any one of Exemplary Embodiments 59-61, wherein the disease or disorder is a viral or infectious disease or disorder.

[0760] Exemplary Embodiment 67. The method, compound, or use of Exemplary Embodiment 66, wherein the viral or infectious disease or disorder is neuro-HIV, viral encephalitis, meningitis, neurocysticercosis, neurosyphilis, neuro-Lyme disease, infectious myelopathies, COVID-19 neuroinflammation, enteroviruses, poliovirus, Epstein-Barr virus (EBV), human herpesvirus, cytomegalovirus, rabies virus, herpes simplex virus, measles, progressive multifocal leukoencephalopathy John Cunningham ("PML JC") virus, bacterial meningitis, prion disease, or Creutzfeldt Jakob disease.

[0761] Exemplary Embodiment 68. The method, compound, or use of any one of Exemplary Embodiments 59-61, wherein the disease or disorder is an autoimmune disease or disorder.

[0762] Exemplary Embodiment 69. The method, compound, or use of Exemplary Embodiment 68, wherein the autoimmune disease or disorder is antibody-mediated encephalitis, neurological complications of connective tissue damage, neurosarcoidosid, demyelinating diseases (non-MS), idiopathic autoimmune CNS and PNS syndromes, paraneoplastic neurological disease, CNS vasculitis, type 1 diabetes, type 2 diabetes, Crohn's disease, systemic lupus erythematous ("SLE"), irritable bowel disorders, asthma, chronic obstructive pulmonary disease ("COPD"), atopic dermatitis, obesity-associated inflammation, heart disease, ulcerative colitis, psoriasis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, Sjögren's syndrome, Reiter's disease, multiple sclerosis, autoimmune encephalitis, myasthenia gravis, idiopathic pulmonary fibrosis, ankylosing spondylitis, antiphospholipid antibody syndrome, osteomyelitis, gout, Henoch-Schonlein Purpura, dermatomyositis, idiopathic arthritis, scleroderma, Kawasaki disease, mixed connective tissue damage, myositis, spondyloarthritis, undifferentiated connective tissue disease, systemic sclerosis, or autoimmune hepatitis.

[0763] Exemplary Embodiment 70. The method, compound, or use of any one of Exemplary Embodiments 59-61, wherein the disease or disorder is an eye disease or disorder.

[0764] Exemplary Embodiment 71. The method, compound, or use of Exemplary Embodiment 70, wherein the eye disease or disorder is uveitis, keratitis, conjunctivitis, thyroid eye disease, age-related macular degeneration, glaucoma, diabetic retinopathy, diabetes-related macular edema, or scleritis.

[0765] Exemplary Embodiment 72. The method, compound, or use of any one of Exemplary Embodiments 59-62, wherein the disease or disorder is selected from autoimmune encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, concentric sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, HTLV-I associated myelopathy ("HAM"), Schilder's disease, dementia, frontotemporal lobar dementia, accessory nerve disorder, autonomic dysreflexia, peripheral neuropathy, chemotherapy-induced peripheral neuropathies, mononeuropathy, polyneuropathy, radial neuropathy, ulnar neuropathy, Villaret's syndrome, diabetic neuropathy, nerve paralysis, progressive bulbar palsy, pseudobulbar palsy, spinal bulbar muscular atrophy, myotonic dystrophy, inclusion body myositis, seizure disorders, lysosomal storage disorders, transmissible spongiform encephalopathy, spinocerebellar ataxia, spinal muscular atrophy, Horner's syndrome, adrenoleukodystrophy, macular degeneration, and Lewy Body syndrome.

[0766] Exemplary Embodiment 73. The method, compound, or use of Exemplary Embodiment 69 or 72, wherein the disease or disorder is autoimmune encephalomyelitis or multiple sclerosis.

[0767] Exemplary Embodiment 74. The method, compound, or use of Exemplary Embodiment 63 or 69, wherein the disease or disorder is amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, or Huntington's disease.

[0768] Exemplary Embodiment 75. The method, compound, or use of Exemplary Embodiment 63 or 74, wherein the Alzheimer's disease is Alzheimer's disease with APOE4.

[0769] Exemplary Embodiment 76. The method, compound, or use of Exemplary Embodiment 69, 73, or 74, wherein the multiple sclerosis is progression independent of relapses.

EXAMPLES

[0770] For exemplary purpose, salts of the compounds of Formula (I), Formula (II), or Formula (III) are synthesized and tested in the examples.

Synthesis of Compounds

[0771] Compounds of Formula (I), Formula (II), or Formula (III) can be prepared using the methods detailed herein. Those skilled in the art may be able to envisage alternative synthetic routes, using a variety of starting materials and reagents to prepare the disclosed compounds of Formula (I), Formula (II), or Formula (III) and to make further modifications.

[0772] In some embodiments, the stereocenters of the compounds of the present disclosure are arbitrarily assigned.

HPLC conditions

Acidic condition

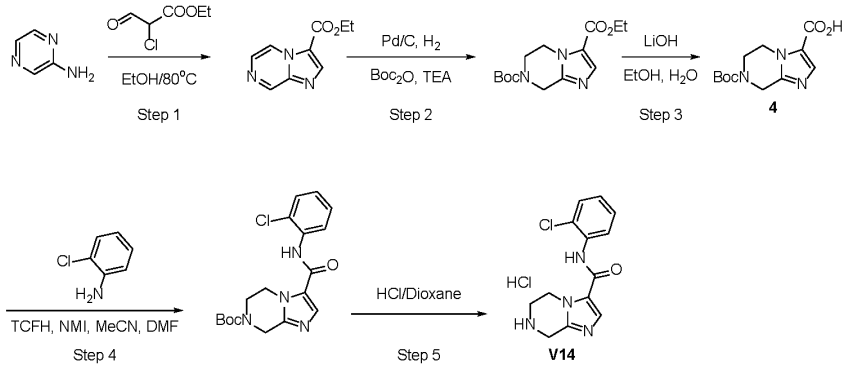
[0773] Mobile phase: A = water (0.1 % TFA), B = acetonitrile; Flow rate: 30mL\min; Gradient: B = 10-55% in 10 min, stop at 20 min; Column: Boston pHlex ODS 21.2*250mm, 10μm; Detection wavelength: 214/254 nm.

Basic condition

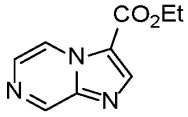
[0774] Mobile phase: A = water (10 mM NH_4HCO_3), B = acetonitrile; Flow rate: 30mL\min; Gradient: B = 10-50% in 10 min, stop at 18 min; Column: Boston pHlex ODS 21.2*250mm, 10μm; Detection wavelength: 214/254 nm.

Synthesis of Intermediates

Intermediate V14. Synthesis of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride (V14).

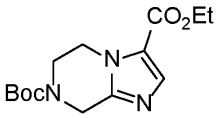


Step 1. Synthesis of ethyl imidazo[1,2-a]pyrazine-3-carboxylate



[0775] A solution of pyrazin-2-amine (30 g, 315.45 mmol) and ethyl 2-chloro-3-oxo-propanoate (56.99 g, 378.54 mmol) in Ethanol (300 mL) was stirred at 80 °C under N_2 for 16 hr. After concentration, the residue was diluted with ethyl acetate (200 ml) and filtered. The filtration was concentrated and purified by flash chromatography (EtOAc / petroleum ether = 1/1) to give ethyl imidazo[1,2-*a*]pyrazine-3-carboxylate (V14) (25.5 g, 125.38 mmol, 39.74% yield, 94% purity) as a white solid. LCMS: *m/z* 192.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 9.24 (dd, *J* = 4.6, 1.5 Hz, 1H), 9.18 (d, *J* = 1.4 Hz, 1H), 8.39 (s, 1H), 8.18 (d, *J* = 4.7 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H).

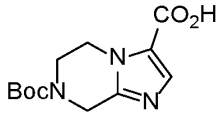
Step 2. Synthesis of 7-(tert-butyl) 3-ethyl 5,6-dihydroimidazo[1,2-a]pyrazine-3,7(8H)-dicarboxylate



[0776] To a solution of ethyl imidazo[1,2-a]pyrazine-3-carboxylate (11.7 g, 51.77 mmol) in Ethyl acetate (150 mL) was added 10% Palladium on carbon wet (4.85 g, 45.56 mmol), Et3N (10.46 g, 103.55 mmol) and Di-tert-butyl dicarbonate (16.95 g, 77.66 mmol, 17.82 mL) and the mixture was stirred at r.t. under H_2 overnight. The reaction solution was filtered and the filtration was concentrated to give yellow oil. It was purified by flash chromatography (eluting with petrol ether: ethyl acetate=0-20%) to give 7-(*tert*-butyl) 3-ethyl 5,6-dihydroimidazo[1,2-*a*]pyrazine-3,7(8*H*)-dicarboxylate (13.5 g, 36.57 mmol, 70.63% yield, 80% purity) as yellow oil. LCMS: *m/z* 296.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ

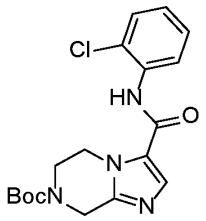
7.71 (s, 1H), 4.73 (s, 2H), 4.40 – 4.24 (m, 4H), 3.84 (t, *J* = 5.3 Hz, 2H), 1.49 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H).

Step 3. Synthesis of 7-(tert-butoxycarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid



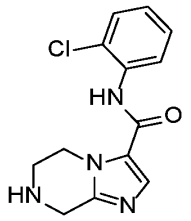
[0777] To a solution of 7-(*tert*-butyl) 3-ethyl 5,6-dihydroimidazo[1,2-*a*]pyrazine-3,7(8*H*)-dicarboxylate (20 g, 67.8 mmol) in EtOH (200 ml) was added LiOH·H_2O (8.54 g, 203.3 mmol) in H_2O (50 ml). The mixture was stirred at rt for 4 hr, and was adjusted pH 5 with 1N HCl. The pricipitate was filtered and dried to give 7-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxylic acid (15.1 g, 56.6 mmol, 83.4% yield, 96% purity) as a yellow solid. LCMS: *m/z* 268.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 7.46 (s, 1H), 4.56 (s, 2H), 4.24 (t, *J* = 5.2 Hz, 2H), 3.80 – 3.70 (m, 2H), 1.44 (s, 9H).

Step 4. Synthesis of tert-butyl 3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate



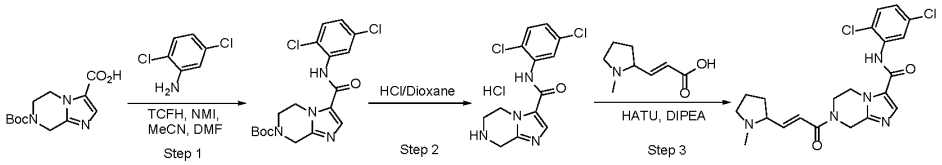
[0778] To a solution of 7-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxylic acid (3.53 g, 13.21 mmol) in DMF (30 mL) and MeCN (30 mL) were added *N,N,N',N'*-Tetramethylchloroformamidinium-hexafluorophosphate (11.12 g, 39.62 mmol) , 1-methyl-1*H*-imidazole (3.25 g, 39.62 mmol, 3.16 mL) and 2-chloroaniline (3.37 g, 26.41 mmol) . The reaction was stirred at room temperature overnight. The mixture was concentrated, diluted with water (100 mL) and extracted with ethyl acetate (100 mL x2). The extract was washed with saturated LiCl aqueous solution (100 mL x2) and brine (100 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (Biotage, 80 g silica gel column @ 80 mL/min, eluting with 80% - 100% ethyl acetate in petroleum ether, then with 0%-3% methanol in DCM) to give *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-7-carboxylate (2.16 g, 5.01 mmol, 37.90% yield, 87.33% purity) as brown gum. LCMS: *m/z* 377.0$[M+H]^+$.

Step 5. Synthesis of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride

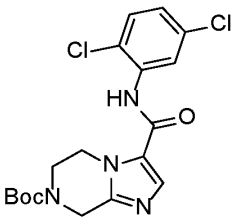


[0779] To a solution of *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-7-carboxylate (12.4 g, 32.91 mmol) in DCM (50 mL) was added 4M HCl in dioxane (60 mL) and the mixture was stirred at r.t. overnight. The reaction solution was filtered and solid collected to give N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (10.3 g, 32.56 mmol, 98.95% yield, 99% purity, HCl salt) as white solid. LCMS: *m/z* 277.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.68 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.27 – 7.22 (m, 1H), 4.60 (s, 1H), 4.34 (t, *J* = 5.6 Hz, 2H), 4.06 (s, 2H), 3.25 – 3.18 (m, 2H).

Example 1. Synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



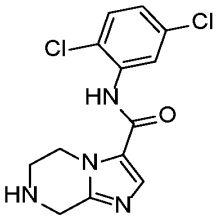
Step 1. Synthesis of tert-butyl 3-((2,5-dichlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate



[0780] To a solution of 7-(*tert*-butoxycarbonyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxylic acid (801.84 mg, 3 mmol) in DMF (15 mL) was added 2,5-dichloroaniline (583.26 mg, 3.60 mmol, 378.74 μL), *N,N,N',N'*-Tetramethylchloroformamidinium-hexafluorophosphate (2.53 g, 9.00 mmol) and 1-Methylimidazole (738.93 mg, 9.00 mmol, 716.72 μL). The resulting mixture was stirred at room temperature for 16 h. Water (20 mL)

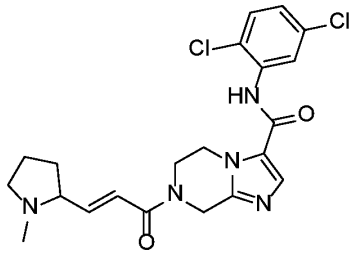
was added, extracted with EtOAc (25 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography with a gradient of EtOAc/PE (0 to 100 percent) to give *tert*-butyl 3-((2,5-dichlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate (400 mg, 972.57 μmol, 32.42% yield) as a brown solid. LCMS: *m/z* 411.0[M+H]$^+$.

Step 2. Synthesis of N-(2,5-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride



[0781] *tert*-butyl 3-((2,5-dichlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate (200 mg, 486.28 μmol) was dissolved in HCl/dioxane (4 M, 2 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to give *N*-(2,5-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (150 mg, crude, HCl salt) as a brown solid. LCMS: *m/z* 311.0[M+H]$^+$.

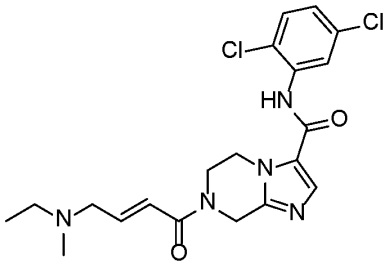
Step 3. Synthesis of (E)-N-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[0782] To a solution of *N*-(2,5-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride (90 mg, 289.23 μmol) in DMF (3 mL) was added (*R,E*)-3-(1-methylpyrrolidin-2-yl)acrylic acid (49.38 mg, 318.16 μmol), HATU (219.95 mg, 578.47 μmol) and DIPEA (112.14 mg, 867.70 μmol, 151.14 μL). The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and the residue was purified by Prep-HPLC under alkaline condition to give (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (10.2 mg, 22.75 μmol, 7.87% yield) as a white solid. LCMS: *m/z* 448.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.4 Hz, 1H), 8.09 (s, 1H), 7.64 (s, 1H), 7.34 (d, *J* = 8.4 Hz,

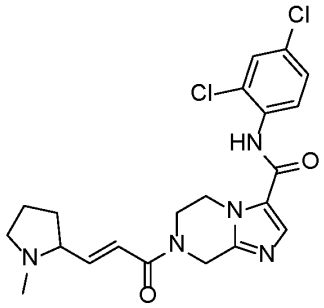
1H), 7.07 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.89 (dd, *J* = 15.2, 7.6 Hz, 1H), 6.45 (d, *J* = 15.2 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.08 (s, 2H), 3.14 (s, 1H), 2.79 (d, *J* = 8.0 Hz, 1H), 2.34- 2.20 (m, 4H), 2.08-1.98 (m, 1H), 1.90-1.76 (m, 1H), 1.71-1.65 (m, 1H).

Example 2. Synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0783] The method as described for the synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(ethyl(methyl)amino)but-2-enoic acid for (*R,E*)-3-(1-methylpyrrolidin-2-yl)acrylic acid to provide the product (*E*)-*N*-(2,5-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 436.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.0 Hz, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05-6.98 (m, 1H), 6.51 (d, *J* = 15.6 Hz, 1H), 4.96 (s, 2H), 4.51 (s, 2H), 4.10-4.02 (m, 2H), 3.21 (d, *J* = 5.6 Hz, 2H), 2.46 (q, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H).

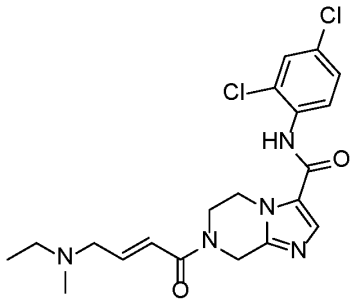
Example 3. Synthesis of (*E*)-*N*-(2,4-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0784] The method as described for the synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 2,4-dichloroaniline for 2,5-dichloroaniline to provide the product (*E*)-*N*-(2,4-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 448.1[M+H]$^+$. ^{1}H NMR (400

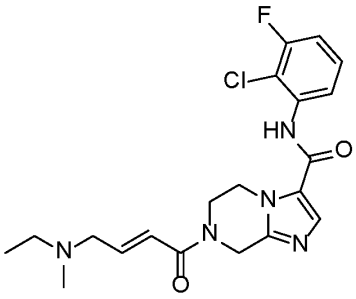
MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.9 Hz, 1H), 8.04 (s, 1H), 7.61 (d, *J* = 19.8 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.89 (dd, *J* = 15.0, 7.4 Hz, 1H), 6.45 (d, *J* = 13.9 Hz, 1H), 4.95 (s, 2H), 4.48 (s, 2H), 4.08 (s, 2H), 3.35-2.57 (m, 3H), 2.33-1.72 (m, 7H).

Example 4. Synthesis of (*E*)-*N*-(2,4-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0785] The method as described for the synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(ethyl(methyl)amino)but-2-enoic acid for (*R,E*)-3-(1-methylpyrrolidin-2-yl)acrylic acid and 2,4-dichloroaniline for 2,5-dichloroaniline to provide the product (*E*)-*N*-(2,4-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 436.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.9 Hz, 1H), 8.06 (s, 1H), 7.64 (s, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.29 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.8 Hz, 1H), 6.48 (d, *J* = 15.1 Hz, 1H), 4.94 (s, 2H), 4.48 (s, 2H), 4.09 (s, 2H), 3.19 (d, *J* = 4.8 Hz, 2H), 2.45 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H).

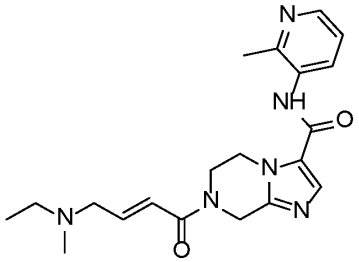
Example 5. Synthesis of (*E*)-*N*-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0786] The method as described for the synthesis of (*E*)-*N*-(2,4-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 2-chloro-3-fluoro-aniline for 2,4-dichloroaniline to provide

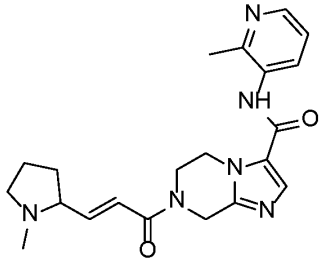
the product (*E*)-*N*-(2-chloro-3-fluorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (32.6 mg, 77.64 μmol, 45.76% yield) as white solid. LCMS: *m/z* 420.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 7.32 – 7.26 (m, 1H), 7.04 – 6.90 (m, 2H), 6.49 (d, *J* = 15.1 Hz, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.09 (s, 2H), 3.19 (d, *J* = 5.2 Hz, 2H), 2.46 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

Example 6. Synthesis of (*E*)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-*N*-(2-methylpyridin-3-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0787] The method as described for the synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(ethyl(methyl)amino)but-2-enoic acid for (,*E*)-3-(1-methylpyrrolidin-2-yl)acrylic acid and 2-methylpyridin-3-amine for 2,5-dichloroaniline to provide the product (*E*)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-*N*-(2-methylpyridin-3-yl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 383.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.37 (s, 1H), 7.21 (dd, *J* = 8.3, 4.9 Hz, 1H), 7.04 – 6.96 (m, 1H), 6.51 (d, *J* = 15.4 Hz, 1H), 4.95 (s, 2H), 4.54 – 4.44 (m, 2H), 4.13 – 3.98 (m, 2H), 3.21 (d, *J* = 6.4 Hz, 2H), 2.58 (s, 3H), 2.48 (q, *J* = 14.4, 7.3 Hz, 2H), 2.27 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H).

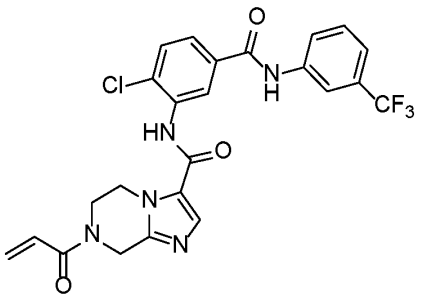
Example 7. Synthesis of (*E*)-*N*-(2-methylpyridin-3-yl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0788] The method as described for the synthesis of (*E*)-*N*-(2,5-dichlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide

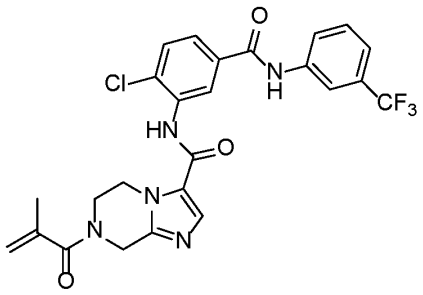
was applied with substitution of 2-methylpyridin-3-amine for 2,5-dichloroaniline to provide the (*E*)-*N*-(2-methylpyridin-3-yl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 395.2[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 3.4 Hz, 1H), 8.18 (d, *J* = 7.1 Hz, 1H), 7.62 (s, 1H), 7.43 (s, 1H), 7.21 (dd, *J* = 8.1, 4.8 Hz, 1H), 6.89 (dd, *J* = 15.1, 7.4 Hz, 1H), 6.45 (d, *J* = 14.8 Hz, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.07 (s, 2H), 3.14 (t, *J* = 8.5 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.58 (s, 3H), 2.35 – 2.23 (m, 3H), 2.09 – 1.99 (m, 1H), 1.77 (dd, *J* = 28.4, 12.6 Hz, 4H).

Example 8. Synthesis of 7-acryloyl-*N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



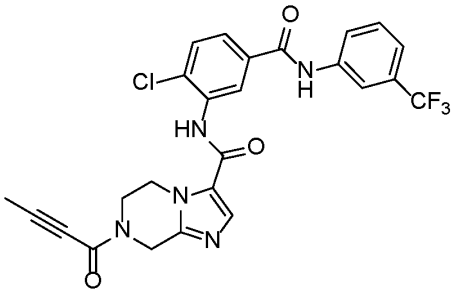
[0789] To a solution of *N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (0.125 g, 269.49 μmol) and triethylamine (54.44 mg, 538.98 μmol) in dichloromethane (5 mL) was added dropwise prop-2-enoyl chloride (32 mg, 350.34 μmol, 21.25 μL) and the mixture was stirred at room temperature for 2 hours and concentrated. The residue was purified by flash chromatography (eluting with 10mmol NH_4HCO_3: CH_3CN=0-55%) to *N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-7-prop-2-enoyl-6,8-dihydro-5H-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 518.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, *J* = 2.1 Hz, 1H), 8.14 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 6.93 – 6.82 (m, 1H), 6.31 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.85 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.96 (d, *J* = 24.1 Hz, 2H), 4.54 – 4.46 (m, 2H), 4.14 – 4.08 (m, 2H).

Example 9. Synthesis of *N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-methacryloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0790] The method as described for the synthesis of 7-acetyl-*N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of methacryloyl chloride for acetyl chloride to provide the product *N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-methacryloyl-5,6,7,8-tetrahydroimidazo [1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 532.2[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, *J* = 2.1 Hz, 1H), 8.16 – 8.12 (m, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 5.31 (d, *J* = 65.6 Hz, 2H), 4.91 (s, 2H), 4.49 (t, *J* = 5.3 Hz, 2H), 4.07 (t, *J* = 5.4 Hz, 2H), 1.99 (s, 3H).

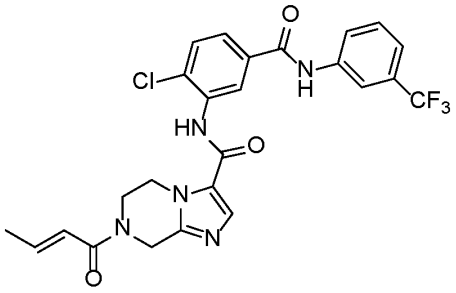
Example 10. Synthesis of 7-(but-2-ynoyl)-*N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0791] The method as described for the synthesis of 7-acetyl-*N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of but-2-ynoyl chloride for acetyl chloride to provide the product 7-(but-2-ynoyl)-*N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 530.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.30 – 8.27 (m, 1H), 8.17 – 8.13 (m, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 3.2 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 5.09 (s, 1H),

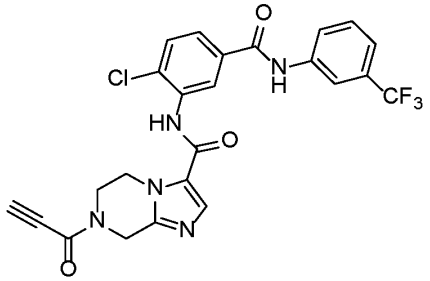
4.88 (s, 1H), 4.48 (dt, J = 35.3, 5.4 Hz, 2H), 4.16 (dt, J = 72.0, 5.5 Hz, 2H), 2.09 (d, J = 5.0 Hz, 3H).

Example 11. Synthesis of (*E*)-7-(but-2-enoyl)-*N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*] pyrazine-3-carboxamide.



[0792] The method as described for the synthesis of 7-acetyl-*N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-but-2-enoyl chloride for acetyl chloride to provide the product (*E*)-7-(but-2-enoyl)-*N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 532.2[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, J = 2.1 Hz, 1H), 8.17 – 8.12 (m, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.89 (s, 1H), 7.82 (dd, J = 8.4, 2.2 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 6.93 (dq, J = 13.7, 6.8 Hz, 1H), 6.66 – 6.49 (m, 1H), 4.99 – 4.90 (m, 2H), 4.48 (s, 2H), 4.09 (t, J = 5.0 Hz, 2H), 1.94 (dd, J = 6.8, 1.5 Hz, 3H).

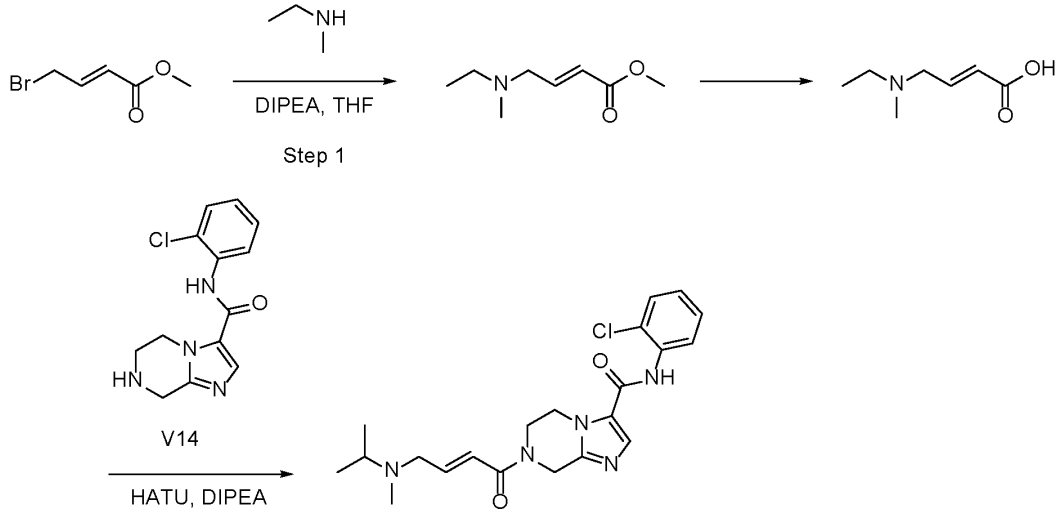
Example 12. Synthesis of *N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



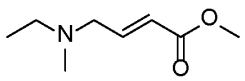
[0793] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-[2-chloro-5-[[3-(trifluoromethyl)phenyl]carbamoyl]phenyl]-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride for *N*-(2-chlorophenyl)-5,6,7,8-

tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride to provide the product *N*-(2-chloro-5-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 516.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.54 (t, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.98 (s, 1H), 4.72 (s, 1H), 4.42 – 4.24 (m, 2H), 4.17 – 3.87 (m, 2H), 2.08 (d, *J* = 7.1 Hz, 3H).

General method B

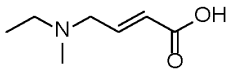


Step 1. Synthesis of Methyl (E)-4-(Ethyl(methyl)amino)but-2-enoate



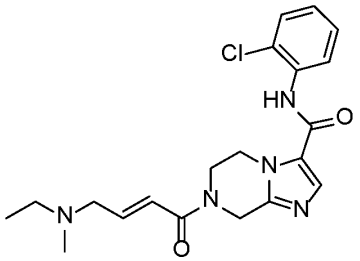
[0794] To a solution of methyl (*E*)-4-bromobut-2-enoate (8 g, 44.69 mmol) in THF (80 mL) were added *N*-methylethylamine (2.64 g, 44.69 mmol, 3.84 mL) and *N,N*-Diisopropylethylamine (11.55 g, 89.38 mmol, 15.57 mL). The reaction was stirred at room temperature for 2 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (150 mL x3). The extract was washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (Biotage, 120 g silica gel column @ 100 mL/min, eluting with 5% methanol in dichloromethane) to give methyl (*E*)-4-[ethyl(methyl)amino]but-2-enoate (**2**) (4.42 g, 28.13 mmol, 62.94% yield) as yellow oil. LCMS: *m/z* 158.1$[M+H]^+$.

Step 2. Synthesis of (E)-4-[ethyl(methyl)amino]but-2-enoic acid



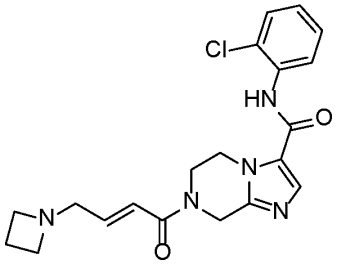
[0795] To a solution of methyl (*E*)-4-[ethyl(methyl)amino]but-2-enoate (2.2 g, 13.99 mmol) in THF (20 mL) was added a solution of NaOH (1.12 g, 27.99 mmol, 525.60 μL) in Water (10 mL). The mixture was stirred at 40 °C overnight. THF was removed under reduced pressure, the aqueous solution was acidified with 1M HCl to pH 3. The mixture was lyophilized to give (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid (3.56 g, 13.43 mmol, 95.94% yield, 54% purity) as yellow solid. The theoretical amount of product was calculated as the weight of the crude product minus theoretical amount of NaCl (1.64 g). LCMS: *m/z* 144.1[M+H]$^+$.

Step 3. Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



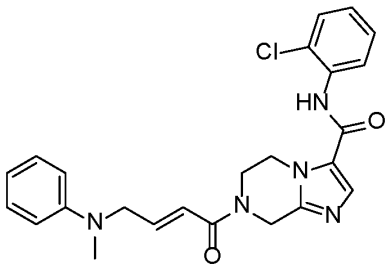
[0796] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (3 g, 9.58 mmol, CL) in DMF (60 mL) were added HATU (5.46 g, 14.37 mmol), *N*,*N*-Diisopropylethylamine (6.19 g, 47.90 mmol, 8.34 mL) and (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid (3.56 g, 13.41 mmol). The reaction was stirred at room temperature for 2 h. The mixture was diluted with water (400 mL), basified with saturated Na_2CO_3 aqueous solution (100 mL) and extracted with ethyl acetate (150 mL x3). The extract was washed with saturated LiCl aqueous solution (200 mL) and brine (200 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by Prep-HPLC basic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide (1.1 g, 2.74 mmol, 28.57% yield) as white solid. LCMS: *m/z* 400.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.8, 1.4 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.8 Hz, 1H), 6.49 (d, *J* = 15.1 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.09 (s, 2H), 3.19 (d, *J* = 5.1 Hz, 2H), 2.45 (q, *J* = 7.1 Hz, 2H), 2.25 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H).

Example 13. Synthesis of (*E*)-7-(4-(azetidin-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



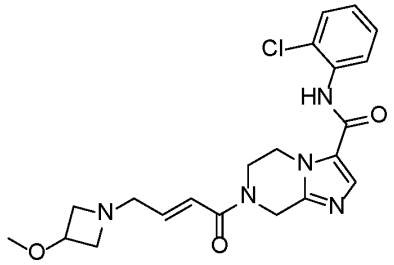
[0797] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of azetidine for *N*-ethylmethylamine to provide the product (*E*)-7-(4-(azetidin-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 400.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.79 – 6.59 (m, 2H), 4.93 (d, *J* = 30.7 Hz, 2H), 4.52 – 4.40 (m, 2H), 4.08 (t, *J* = 5.1 Hz, 2H), 3.38 (t, *J* = 7.3 Hz, 4H), 3.33 (d, *J* = 5.1 Hz, 2H), 2.21 – 2.13 (m, 2H).

Example 14. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(methyl(phenyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



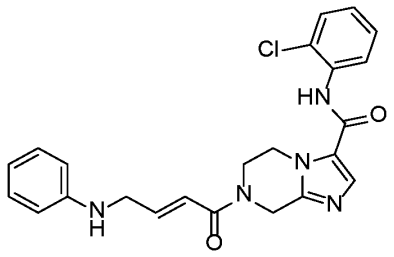
[0798] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-methylaniline for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(methyl(phenyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 450.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.68 (dd, *J* = 7.9, 1.3Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.28 – 7.15 (m, 3H), 6.90 – 6.80 (m, 1H), 6.76 (d, *J* = 8.2 Hz, 2H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.61 – 6.46 (m, 1H), 4.88 (s, 2H), 4.39 (s, 2H), 4.16 (dd, *J* = 4.7, 1.6 Hz, 2H), 3.98 (d, *J* = 48.0 Hz, 2H), 3.00 (s, 3H).

Example 15. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



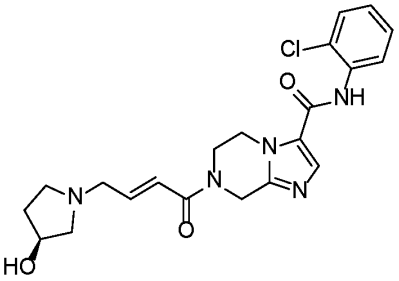
[0799] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 3-methoxyazetidine for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.69 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.74 (dd, *J* = 13.0, 7.5 Hz, 2H), 4.90 (s, 2H), 4.48 (s, 2H), 4.14 – 4.01 (m, 3H), 3.74 – 3.59 (m, 2H), 3.35 (d, J = 4.5 Hz, 2H), 3.26 (s, 3H), 3.16 – 3.02 (m, 2H).

Example 16. Synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(phenylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



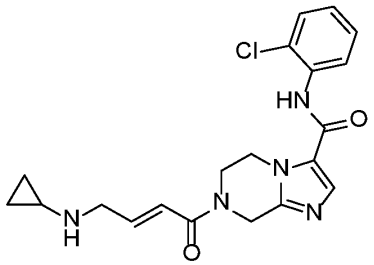
[0800] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of aniline for *N*-ethylmethylamine to provide the product (*E*)-N-(2-chlorophenyl)-7-(4-(phenylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 436.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.27 – 7.22 (m, 1H), 7.17 – 7.05 (m, 2H), 6.91 (s, 1H), 6.75 – 6.58 (m,4H), 4.88 (s, 2H), 4.39 (s, 2H), 4.09 – 3.89 (m, 4H).

Example 17. Synthesis of (*S*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



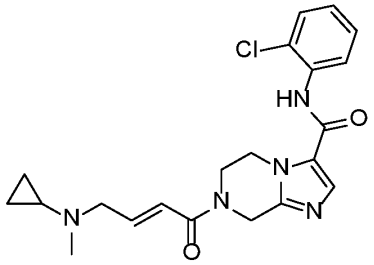
[0801] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*S*)-pyrrolidin-3-ol for *N*-ethylmethylamine to provide the product (*S*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.4 Hz, 1H), 6.97 – 6.65 (m, 2H), 4.94 (d, *J* = 26.9 Hz, 2H), 4.51 – 4.35 (m, 3H), 4.10 (s, 2H), 3.42 (s, 2H), 2.88 (s, 2H), 2.65 (s, 2H), 2.21 – 2.10 (m, 1H), 1.78 (s, 1H).

Example 18. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopropylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



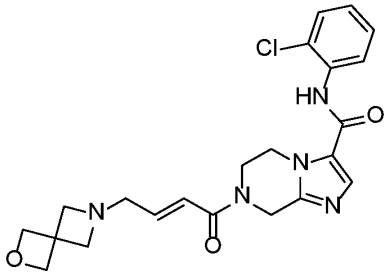
[0802] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of cyclopropanamine for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopropylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 400.0[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (dd, *J* = 12.3, 4.6 Hz, 1H), 7.25 (dd, *J* = 10.9, 4.6 Hz, 1H), 6.93 (dt, *J* = 15.3, 5.8 Hz, 1H), 6.68 (s, 1H), 4.92 (d, *J* = 16.9 Hz, 2H), 4.47 (s, 2H), 4.06 (d, *J* = 26.8 Hz, 2H), 3.57 – 3.37 (m, 2H), 2.31 – 2.16 (m, 1H), 0.61 – 0.47 (m, 2H), 0.46 – 0.35 (m, 2H).

Example 19. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopropyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



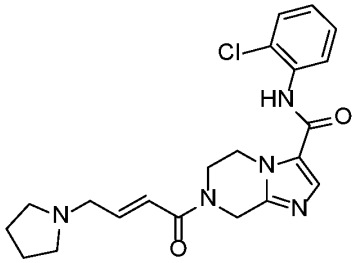
[0803] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-methylcyclopropanamine for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopropyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.0[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.69 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.25 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.90 (s, 1H), 6.73 (d, *J* = 15.0 Hz, 1H), 4.91 (s, 2H), 4.47 (s, 2H), 4.09 (t, *J* = 5.3 Hz, 2H), 3.40 (dd, *J* = 6.6, 1.0 Hz, 2H), 2.36 (d, *J* = 4.9 Hz, 3H), 1.79 (m, 1H), 0.51 (m, 2H), 0.45 (m, 2H).

Example 20. Synthesis of (*E*)-7-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



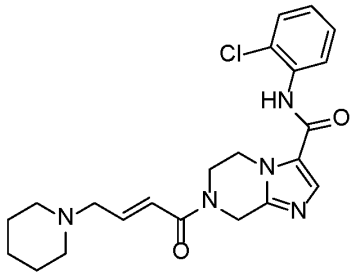
[0804] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 2-oxa-6-azaspiro[3.3]heptane for *N*-ethylmethylamine to provide the product (*E*)-7-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 442.1[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.69 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (td, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.77 – 6.58 (m, 2H), 4.98 – 4.89 (m, 2H), 4.74 (s, 4H), 4.51 – 4.41 (m, 2H), 4.11 – 4.06 (m, 2H), 3.49 (s, 4H), 3.27 (d, *J* = 5.3 Hz, 2H).

Example 21. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



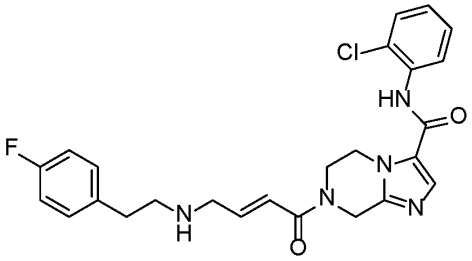
[0805] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of pyrrolidine for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(pyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 413.7[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.0, 1.3Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3Hz, 1H), 7.35 (td, *J* = 7.8, 1.44 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6Hz, 1H), 6.97 – 6.85 (m, 1H), 6.80 -6.67(m, 1H), 5.04 – 4.93 (m, 2H), 4.53 – 4.37 (m, 2H), 4.09 (t, *J* = 5.2Hz, 2H), 3.38 (dd, *J* = 6.4, 1.0 Hz, 2H), 2.66 – 2.57 (m, 4H), 1.89 (m, 4H).

Example 22. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(piperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



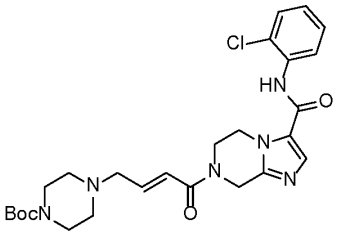
[0806] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of pyrrolidine for *N*-ethylmethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(piperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 427.7[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ7.82 (s, 1H), 7.68 (dd, *J* =7.9, 0.9 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.89 (dt, *J* = 14.8, 6.5 Hz, 1H), 6.80 -6.68 (m, 1H), 5.00 - 4.89 (m, 2H), 4.52-4.38 (m, 2H), 4.08 (t, *J* = 5.3 Hz, 2H), 3.23 (d, *J* = 5.9 Hz, 2H), 2.59 -2.41 (m, 4H), 1.67 -1.60 (m, 4H), 1.53 -1.45 (m, 2H).

Example 23. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((4-fluorophenethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



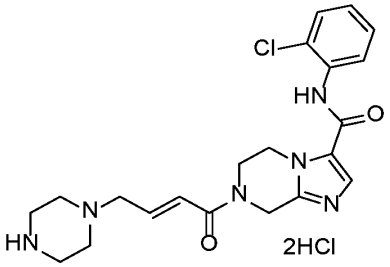
[0807] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 2-(4-fluorophenyl)ethan-1-amine for ethylamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((4-fluorophenethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 482.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 9.49 (d, *J* = 7.3 Hz, 1H), 8.49 (s, 1H), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.66 (s, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.39 (ddd, *J* = 15.3, 7.6, 1.7 Hz, 2H), 7.28 (td, *J* = 7.8, 1.6 Hz, 1H), 6.21 (s, 1H), 5.65 (s, 1H), 3.78 (s, 4H), 3.58 (d, *J* = 4.6 Hz, 2H), 3.51 (d, *J* = 4.5 Hz, 2H).

Example 24. Synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]piperazine-1-carboxylate.



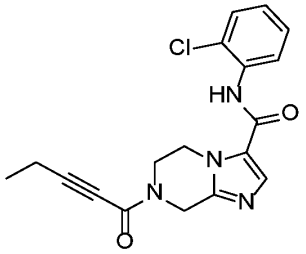
[0808] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl piperazine-1-carboxylate for *N*-ethylmethylamine to provide the product *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]piperazine-1-carboxylate. LCMS: *m/z* 529.2[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 6.84 (s, 2H), 4.91 (s, 2H), 4.48 (s, 2H), 4.09 (d, *J* = 5.5 Hz, 2H), 3.46 (s, 4H), 3.27 (d, *J* = 6.2 Hz, 2H), 2.49 (s, 4H), 1.45 (s, 9H).

Example 25. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



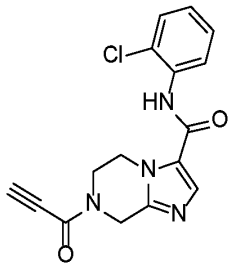
[0809] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]piperazine-1-carboxylate for *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-piperazin-1-ylbut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 429.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 (td, *J* = 7.7, 1.5 Hz, 1H), 7.31 (td, *J* = 7.8, 1.6 Hz, 1H), 7.21 (d, *J* = 14.6 Hz, 1H), 6.95 – 6.83 (m, 1H), 5.27 (d, *J* = 72.8 Hz, 2H), 4.78 – 4.53 (m, 2H), 4.30 – 4.09 (m, 4H), 3.75 – 3.58 (m, 8H).

Example 26. Synthesis of *N*-(2-chlorophenyl)-7-(pent-2-ynoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



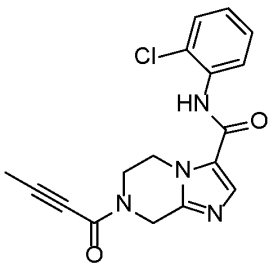
[0810] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of pent-2-ynoic acid for (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid to provide the product *N*-(2-chlorophenyl)-7-(pent-2-ynoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 357.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.34 (m, 1H), 8.13 (s, 1H), 7.66 (s, 1H), 7.42 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.34-7.29 (m, 1H), 7.09 (td, *J* = 7.8, 1.2 Hz, 1H), 5.11 (s, 1H), 4.95 (s, 1H), 4.60-4.41 (m, 2H), 4.24-4.02 (m, 2H), 2.47-2.40 (m, 2H), 1.29-1.23 (m, 3H).

Example 27. Synthesis of *N*-(2-chlorophenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



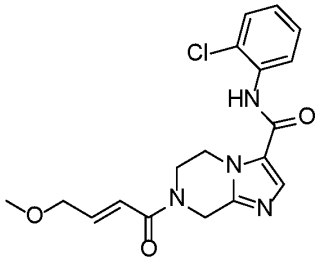
[0811] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of prop-2-ynoic acid for (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid to provide the product *N*-(2-chlorophenyl)-7-propioloyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 329.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 10.13 – 9.67 (m, 1H), 7.89 (d, *J* = 2.6 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (td, *J* = 7.6, 1.3 Hz, 1H), 5.03 – 4.67 (m, 3H), 4.44 – 4.25 (m, 2H), 4.19 – 3.92 (m, 2H).

Example 28. Synthesis of 7-(but-2-ynoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



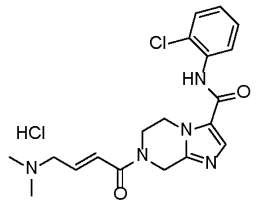
[0812] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of but-2-ynoic acid for (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid to provide the product 7-(but-2-ynoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 342.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.54 (t, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 4.98 (s, 1H), 4.72 (s, 1H), 4.42 – 4.24 (m, 2H), 4.17 – 3.87 (m, 2H), 2.08 (d, *J* = 7.1 Hz, 3H).

Example 29. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-methoxybut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



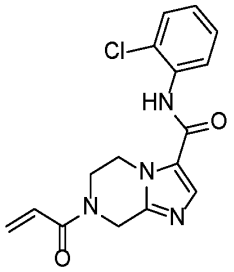
[0813] The method as described for the synthesis of (*E*)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-methoxybut-2-enoic acid for (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-methoxybut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 375.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.69 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.79 – 6.66 (m, 1H), 5.02 – 4.90 (m, 2H), 4.47 (s, 2H), 4.17 – 4.05 (m, 4H), 3.41 (s, 3H).

Example 30. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride.



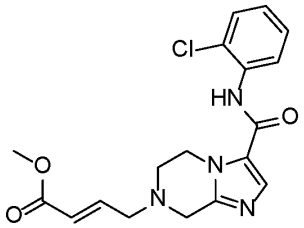
[0814] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(dimethylamino)but-2-enoic acid hydrochloride for (*E*)-4-[ethyl(methyl)amino]but-2-enoic acid to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(dimethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride. LCMS: *m/z* 388.0$[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.31 (td, *J* = 7.7, 1.5 Hz, 1H), 7.12 (d, *J* = 14.8 Hz, 1H), 6.90 – 6.78 (m, 1H), 5.38 – 5.13 (m, 2H), 4.75 – 4.54 (m, 2H), 4.30 – 4.14 (m, 2H), 4.11 – 3.97 (m, 2H), 2.98 (s, 6H).

Example 31. Synthesis of 7-acryloyl-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



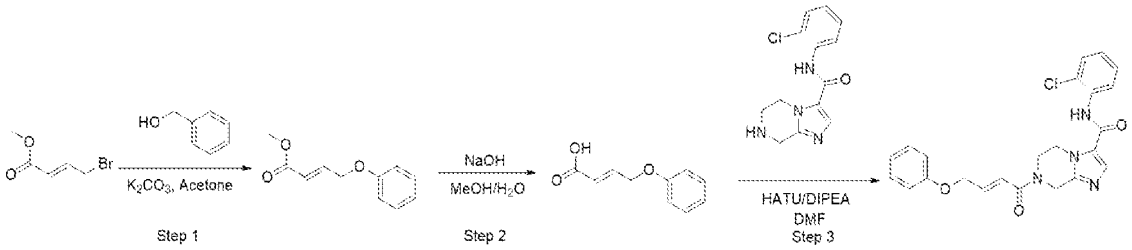
[0815] The method as described for the synthesis of 7-(2-chloroacetyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of prop-2-enoyl chloride for 2-chloroacetyl chloride to provide the product 7-acryloyl-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 331.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.97 – 6.78 (m, 1H), 6.31 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.84 (dd, *J* = 10.6, 1.6 Hz, 1H), 4.94 (d, *J* = 23.4 Hz, 2H), 4.52 – 4.41 (m, 2H), 4.10 (t, 2H).

Example 32. Synthesis of methyl (*E*)-4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)but-2-enoate.

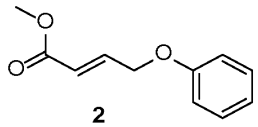


[0816] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (0.4 g, 1.45 mmol) and triethylamine (321.19 mg, 3.18 mmol) in THF (20 mL) was added methyl (*E*)-4-bromobut-2-enoate (284.64 mg, 1.59 mmol), the mixture was stirred at room temperature under N_2 overnight. Water (20 mL) was added, the aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic phase was concentrated, the residue was purified by flash chromatography (eluting with dichloromethane: methanol=0-5%) to give methyl (*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]but-2-enoate (0.32 g, 828.13 μmol, 57.29% yield, 97% purity) as white solid. LCMS: *m/z* 375.1 [M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.5 Hz, 1H), 7.24 (td, *J* = 7.8, 1.6 Hz, 1H), 6.98 (dt, *J* = 15.7, 6.1 Hz, 1H), 6.13 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.39 (t, *J* = 5.5 Hz, 2H), 3.78 (s, 2H), 3.74 (s, 3H), 3.43 (dd, *J* = 6.1, 1.5 Hz, 2H), 2.97 (t, *J* = 5.6 Hz, 2H).

Example 33. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-phenoxybut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



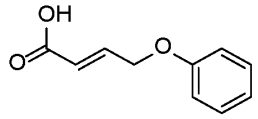
Step 1. Synthesis of methyl (E)-4-phenoxybut-2-enoate



2

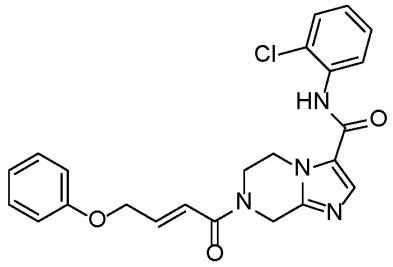
[0817] To a solution of methyl (*E*)-4-bromobut-2-enoate (2.85 g, 15.94 mmol) and phenol (1.0 g, 10.63 mmol, 933.71 μL) in acetone (20 mL) was added K_2CO_3 (2.93 g, 21.25 mmol) . The resulting mixture was stirred at 60°C overnight and concentrated. The residue was added water (20 mL) and EtOAc (20 mL), the organic phase was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Silica gel chromatography (eluting with EtOAc/petroleum ether = 1/5-1/3) to give methyl (*E*)-4-phenoxybut-2-enoate (1.2 g, 3.87 mmol, 36.43% yield, 62% purity) as a colorless oil. LCMS: *m/z* 193.3$[M+H]^+$.

Step 2. Synthesis of (E)-4-phenoxybut-2-enoic acid



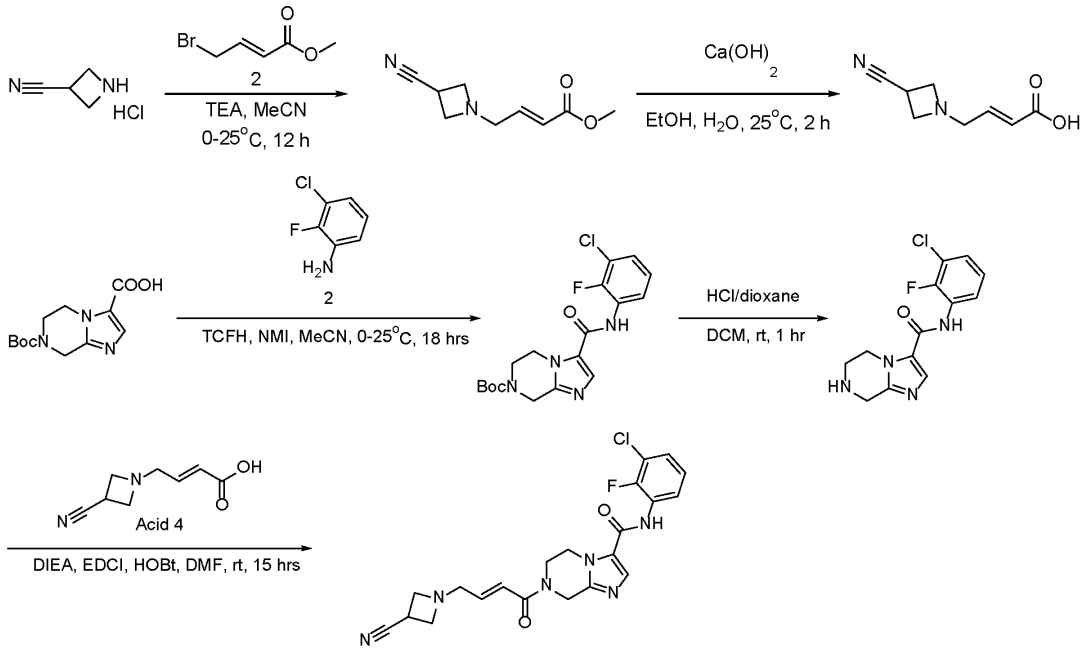
[0818] To a solution of methyl (*E*)-4-phenoxybut-2-enoate (1.2 g, 3.87 mmol) in MeOH (8 mL) was added a solution of NaOH (464.49 mg, 11.61 mmol, 218.07 μL) in water (4 mL). The resulting mixture was stirred at room temperature overnight and concentrated, the residue was diluted with water (20 mL). The aqueous phase was adjusted pH to 3-4 with 1M HCl, and extracted with EtOAc (30 mL x 3). The combined organic phase was concentrated to give (*E*)-4-phenoxybut-2-enoic acid (500 mg, 2.58 mmol, 66.69% yield, 92% purity) as a light yellow solid, which was used directly for the next step. LCMS: *m/z* 179.1$[M+H]^+$.

Step 3. Synthesis of N-(2-chlorophenyl)-7-[(E)-4-phenoxybut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

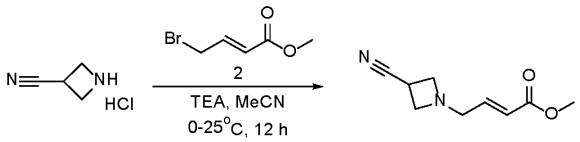


[0819] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride (60 mg, 191.58 μmol, CL) , (*E*)-4-phenoxybut-2-enoic acid (108.70 mg, 561.22 μmol) and HATU (109.27 mg, 287.37 μmol) in DMF (2.93 mL) was added DIPEA (49.52 mg, 383.16 μmol, 66.74 μL). The resulting mixture was stirred at room temperature overnight and then purified by Prep-HPLC under basic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-4-phenoxybut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (30 mg, 68.67 μmol, 35.84% yield, 100% purity) as a white solid. LCMS: *m/z* 437.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (t, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 5.6 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.13 – 7.04 (m, 2H), 7.04 – 6.92 (m, 2H), 6.75 – 6.50 (m, 1H), 4.93 (d, *J* = 4.9 Hz, 2H), 4.56 – 4.40 (m, 2H), 4.13 – 3.92 (m, 2H), 3.50 – 3.35 (m, 2H).

General Method C

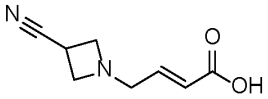


Step 1.1. General procedure for Synthesis of methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate



[0820] To a solution of azetidine-3-carbonitrile (11.92 g, 100.55 mmol, 1.2 eq, HCl) in MeCN (150 mL) was added dropwise TEA (25.44 g, 251.38 mmol, 34.99 mL, 3 eq) at 25°C and stirred at 25°C for 10 min. Then methyl (E)-4-bromobut-2-enoate (15 g, 83.79 mmol, 9.86 mL, 1 eq) was added dropwise to the reaction mixture at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 12 h. The reaction mixture was cooled to 0°C, quenched by addition ice-water (300 mL) at 0°C. The mixture was extracted with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 160 g SepaFlash® Silica Flash Column, Eluent of 0~43% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate (10 g, 55.49 mmol, 66.23% yield) as yellow oil. ^{1}H NMR ($CDCl_3$ 400 MHz) δ 6.82-6.75 (m, 1H), 5.98-5.94 (m, 1H), 3.73 (s, 3H), 3.62 (t, *J*=7.2 Hz, 2H), 3.34-3.31 (m, 2H), 3.24 (s, 1H), 3.23-3.21 (m, 2H).

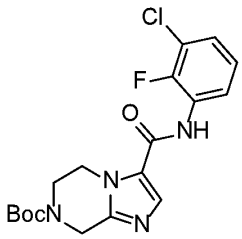
Step 1.2. General procedure for Synthesis of (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid



[0821] To a solution of methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate (6.5 g, 36.07 mmol, 1 eq) in EtOH (28 mL) and H_2O (56 mL) was added $Ca(OH)_2$ (10.69 g, 144.28 mmol, 4.77 mL, 4 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was cooled to 0°C. The reaction mixture was adjusted pH to 3 with HCl (2 N) at 0°C, then concentrated under reduced pressure to give (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid (8 g, crude) as yellow oil.

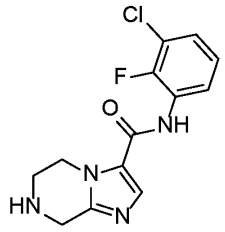
^{1}H NMR (DMSO-d6, 400 MHz) δ 6.49-6.42 (m, 1H), 5.82-5.78 (m, 1H), 3.45-3.42 (m, 3H), 3.24 (t, *J* = 4.0 Hz, 2H), 3.12 (dd, *J* = 3.6 Hz, 2.0 Hz, 2H).

Step 2.1 Synthesis of tert-butyl 3-[(3-chloro-2-fluoro-phenyl)carbamoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



[0822] To a solution of 7-tert-butoxycarbonyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (215.86 mg, 710.66 μmol, 1 eq, HCl) in MeCN (2 mL) were added NMI (175.03 mg, 2.13 mmol, 169.94 μL, 3 eq), 3-chloro-2-fluoro-aniline (155.17 mg, 1.07 mmol, 1.5 eq) and TCFH (598.19 mg, 2.13 mmol, 3 eq) in one portion at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 18 hrs. LCMS showed 7-tert-butoxycarbonyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid was consumed completely and desired mass was detected. The residue was poured into ice-water (4 mL) and stirred for 2 min at 25°C. The mixture was extracted with ethyl acetate (2 mL x 3). The combined organic phase was washed with brine (2 mL x 1), dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~42% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give tert-butyl 3-[(3-chloro-2-fluoro-phenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (300 mg, crude) as a yellow solid. LCMS: m/z 395.0 $[M+H]^+$.

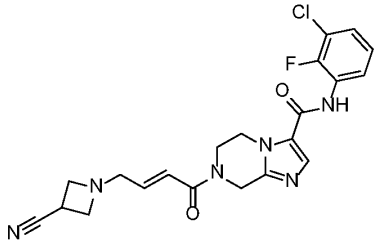
Step 2.2 Synthesis of N-(3-chloro-2-fluoro-phenyl)-5,6,7,8- tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide



[0823] To a solution of tert-butyl 3-[(3-chloro-2-fluoro-phenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (300 mg, 759.83 μmol, 1 eq) in DCM (3 mL) was added dropwise HCl/dioxane (4 M, 189.96 μL, 1 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hr. LCMS showed tert-butyl 3-[(3-chloro-2-fluoro-phenyl) carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give N-

(3-chloro-2-fluoro-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide (250 mg, crude) as a yellow solid. LCMS: m/z 295.0 $[M+H]^+$.

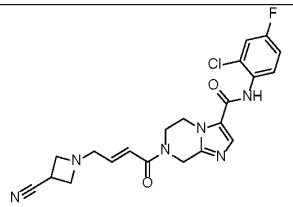
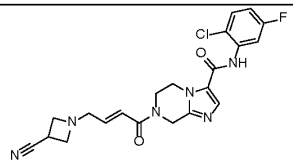
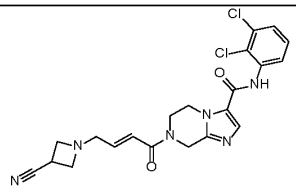
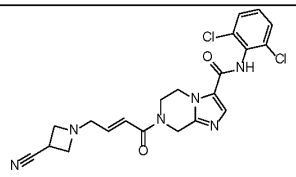
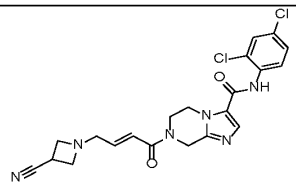
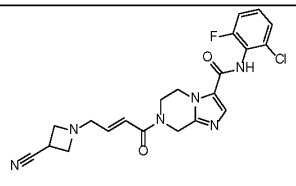
Step 3 Synthesis of N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-(3- cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[0824] To a solution of N-(3-chloro-2-fluoro-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (220 mg, 664.31 μmol, 1 eq, HCl) in DMF (3 mL) were added dropwise DIEA (257.57 mg, 1.99 mmol, 347.13 μL, 3 eq), HOBt (179.53 mg, 1.33 mmol, 2 eq), EDCI (318.37 mg, 1.66 mmol, 2.5 eq) and (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid (220.78 mg, 1.33 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 15 hrs. LCMS showed N-(3-chloro-2-fluoro-phenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100*30mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 8.0 min) to give N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (40.5 mg, 85.96 μmol, 12.94% yield, 93.98% purity) as a pale yellow solid. LCMS: m/z 443.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.09 (s, 1H), 7.85 (s, 1H), 7.52 (t, J = 6.8 Hz, 1H), 7.43 (t, J = 6.8 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 6.63-6.53 (m, 2H), 4.91-4.74 (m, 2H), 4.32-4.28 (m, 2H), 3.99-3.94 (m, 2H), 3.49 (s, 3H), 3.29 (s, 2H), 3.21 (d, J = 4.8 Hz, 2H).

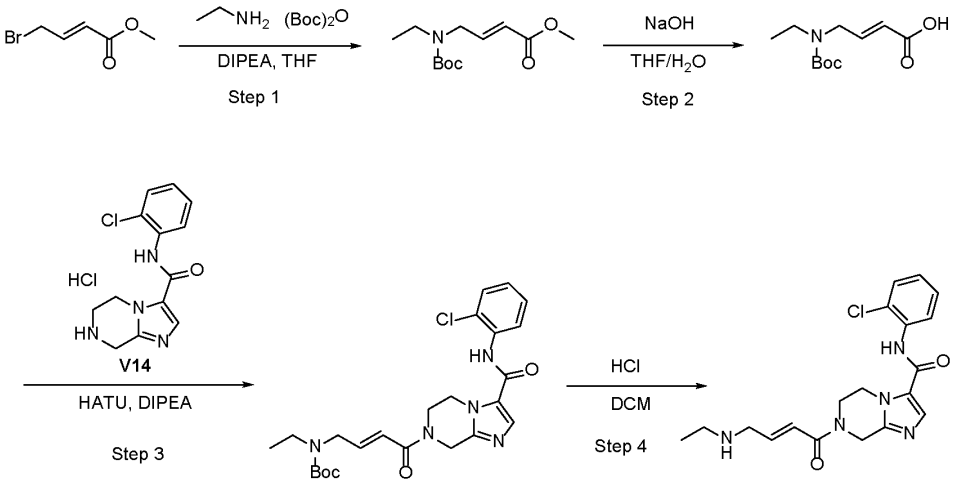
[0825] Compounds in Table A were synthesized following the procedure for N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-(3- cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table A

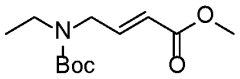
Name	Structure	NMR	LCMS
N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- (3-cyanoazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 9.87 (s, 1H), 7.84 (s, 1H), 7.55-7.52 (m, 2H), 7.28-7.25 (m, 1H), 6.63-6.56 (m, 2H), 4.90-4.73 (m, 2H), 4.32-4.28 (m, 2H), 3.99-3.94 (m, 2H), 3.49 (s, 3H), 3.29 (s, 2H), 3.21 (d, J = 8.4 Hz, 2H).	LCMS: m/z 443.2 [M+H]$^+$
N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 9.87 (s, 1H), 7.87 (s, 1H), 7.60-7.51 (m, 2H), 7.15 (td, J = 8.4 Hz, 3.2 Hz, 1H), 6.68-6.53 (m, 2H), 4.92-4.74 (m, 2H), 4.34-4.29 (m, 2H), 4.00-3.95 (m, 2H), 3.52-3.46 (m, 3H), 3.30-3.27 (m, 2H), 3.21 (d, J = 4.4 Hz, 2H).	LCMS: m/z 443.2 [M+H]$^+$
7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,3-dichlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 10.01 (s, 1H), 7.85 (s, 1H), 7.54-7.52 (m, 2H), 7.40-7.36 (m, 1H), 6.63-6.57 (m, 2H), 4.91-4.74 (m, 2H), 4.32-4.28 (m, 2H), 4.00-3.94 (m, 2H), 3.49 (s, 2H), 3.29 (s, 2H), 3.21 (d, J = 8.4 Hz, 2H).	LCMS: m/z 459.1 [M+H]$^+$
7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-N-(2,6-dichlorophenyl) -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 10.10 (s, 1H), 7.87 (s, 1H), 7.58-7.56 (m, 1H), 7.37 (t, J = 8.0 Hz, 1H), 6.67-6.54 (m, 2H), 4.91-4.74 (m, 2H), 4.32-4.28 (m, 2H), 4.00-3.95 (m, 2H), 3.49-3.47 (m, 3H), 3.30-3.29 (m, 2H), 3.21 (d, J = 4.8 Hz, 2H).	LCMS: m/z 459.1 [M+H]$^+$
7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -N-(2,4-dichlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 9.89 (s, 1H), 7.86 (s, 1H), 7.72-7.71 (m, 1H), 7.57-7.55 (m, 1H), 7.47-7.45 (m, 1H), 6.67-6.54 (m, 2H), 4.90-4.74 (m, 2H), 4.32-4.28 (m, 2H), 4.00-3.97 (m, 2H), 3.49 (s, 3H), 3.29-3.28 (m, 2H), 3.21 (d, J = 4.8 Hz, 2H).	LCMS: m/z 459.1 [M+H]$^+$
N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 9.98 (s, 1H), 7.88 (s, 1H), 7.45-7.39 (m, 2H), 7.36-7.33 (m, 1H), 6.66-6.58 (m, 2H), 4.91-4.74 (m, 2H), 4.32-4.26 (m, 2H), 4.00-3.94 (m, 2H), 3.49-3.47 (m, 3H), 3.30-3.29 (m, 2H), 3.21 (d, J = 4.8 Hz, 2H).	LCMS: m/z 443.2 [M+H]$^+$

General method D

Example 34. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.

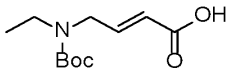


Step 1. Synthesis of methyl (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoate



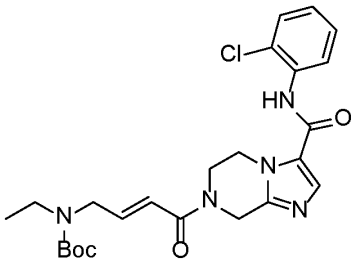
[0826] To a solution of ethylamine (901.67 mg, 20 mmol, 2 N in THF, 10 mL) and Et_3N (4.04 g, 40.00 mmol) in THF (20 mL) was added methyl (*E*)-4-bromobut-2-enoate (1.79 g, 10.00 mmol) . The resulting mixture was stirred at room temperature for 3 hours, and then *tert*-butoxycarbonyl *tert*-butyl carbonate (5.46 g, 25.00 mmol, 5.74 mL) was added. The resulting mixture was stirred at room temperature overnight. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (150 mL x3). The extract was washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (eluting with EtOAc/petroleum ether = 1/5-1/1) to give methyl (*E*)-4-[*tert*-butoxycarbonyl(ethyl)amino]but-2-enoate (0.98 g, 3.83 mmol, 38.27% yield,) as an off-white solid. LCMS: *m/z* 144.2[M+H-Boc]$^+$.

Step 2. Synthesis of (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoic acid



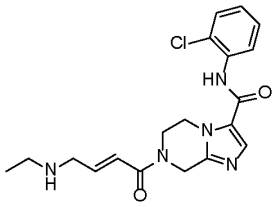
[0827] To a solution of (*E*)-4-[*tert*-butoxycarbonyl(ethyl)amino]but-2-enoate (980 mg, 4.03 mmol) in THF (8 mL) was added a solution of NaOH (480.00 mg, 12 mmol) in water (4 mL). The resulting mixture was stirred at 50°C overnight and then concentrated, the residue was added water (20 mL). The aqueous phase was acidified with 1M HCl to pH 3-4, extracted with EtOAc (30 mLx3). The combined organic phase was concentrated to give (*E*)-4-[*tert*-butoxycarbonyl(ethyl)amino]but-2-enoic acid (620 mg, crude) as a light yellow solid, which was used directly for the next step. LCMS: *m/z* 130.2 [M+H-Boc]$^+$.

Step 3. Synthesis of tert-butyl N-[(E)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-N-ethyl-carbamate



[0828] To a solution of (*E*)-4-[*tert*-butoxycarbonyl(ethyl)amino]but-2-enoic acid (160.00 mg, 697.86 μmol), *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (80 mg, 255.44 μmol, CL) and HATU (126.27 mg, 332.08 μmol) in DMF (3 mL) was added DIPEA (66.03 mg, 510.89 μmol). The resulting mixture was stirred at room temperature overnight and diluted with water (15 mL). The precipitate was filtered and dried to give *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-*N*-ethyl-carbamate (120 mg, crude) as a white solid, which was used directly for the next step. LCMS: *m/z* 488.2 $[M+H]^+$.

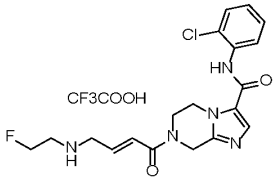
Step 4. Synthesis of N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[0829] To a solution of *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-*N*-ethyl-carbamate (120 mg, 245.91 μmol) in DCM (3 mL) was added HCl (36.46 mg, 1 mmol) at 0°C. The resulting mixture was stirred at room temperature for 3 hours, and then diluted with DCM (20 mL). The organic phase was washed with *aq. sat.* NaHCO3 (10 mL x 3), brine and concentrated. The residue was purified by Prep-HPLC under acidic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (22 mg, 43.83 μmol, 17.83% yield, TFA) as white solid. LCMS: *m/z* 388.0 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.05 (d, *J* = 23.3 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.04 – 6.87 (m, 1H), 6.86 – 6.74 (m, 1H),

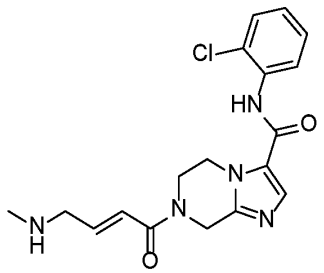
5.18 – 4.97 (m, 2H), 4.53 (d, *J* = 33.6 Hz, 2H), 4.14 (s, 2H), 3.87 (d, *J* = 6.4 Hz, 2H), 3.11 (q, *J* = 7.3 Hz, 2H), 1.33 (t, *J* = 7.3 Hz, 3H).

Example 35. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



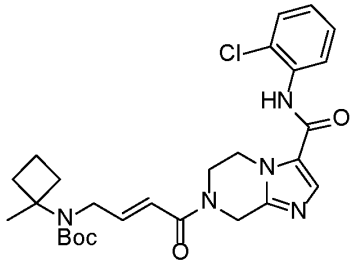
[0830] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 2-fluoroethan-1-amine for ethylamine to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-(2-fluoroethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 406.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.01 (d, *J* = 28.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.05 – 6.90 (m, 1H), 6.85 – 6.75 (m, 1H), 5.04 (d, *J* = 14.3 Hz, 2H), 4.85 – 4.66 (m, 2H), 4.52 (d, *J* = 35.9 Hz, 2H), 4.14 (s, 2H), 3.95 (d, *J* = 6.0 Hz, 2H), 3.53 – 3.38 (m, 2H).

Example 36. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(methylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



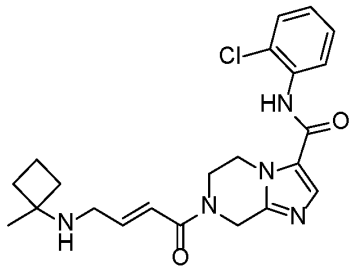
[0831] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of methylamine for ethylamine and purified under basic condition to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-(methylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 374.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.12 – 6.98 (m, 2H), 6.50 (d, *J* = 14.4 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.16 – 3.94 (m, 2H), 3.43 (d, *J* = 4.6 Hz, 2H), 2.49 (s, 3H).

Example 37. Synthesis of *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-*N*-(1-methylcyclobutyl)carbamate.



[0832] The method as described for the synthesis of *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-*N*-ethyl-carbamate was applied with substitution of 1-methylcyclobutan-1-amine for ethylamine, and purified by Prep-HPLC under basic condition to provide the product *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-*N*-(1-methylcyclobutyl)carbamate. LCMS: *m/z* 528.2[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.7 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.09 (dd, *J* = 11.0, 4.5 Hz, 1H), 7.00 (s, 1H), 6.38 (d, *J* = 15.2 Hz, 1H), 4.93 (s, 2H), 4.50 (s, 2H), 4.03 (d, *J* = 54.1 Hz, 2H), 3.81 (s, 2H), 2.23 (d, *J* = 10.9 Hz, 2H), 1.94 (s, 2H), 1.70 (s, 2H), 1.46 (s, 9H), 1.39 (s, 3H).

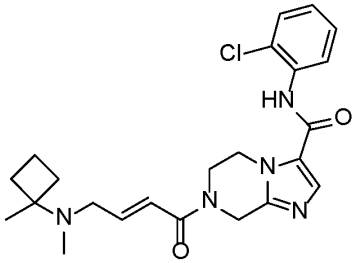
Example 38. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-[(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



[0833] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(ethylamino)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 1-methylcyclobutan-1-amine for ethylamine and purified by Prep-HPLC under basic condition to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-[(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.08

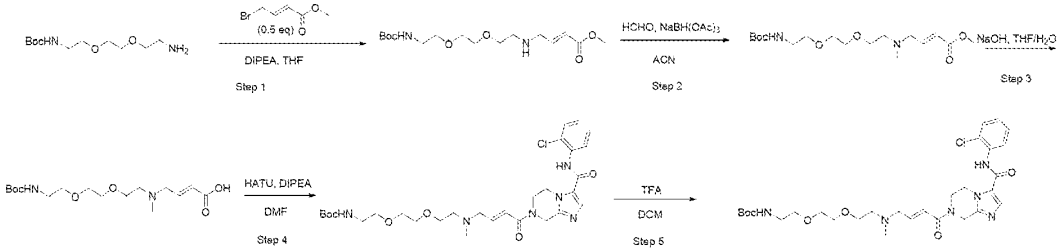
(ddd, *J* = 10.1, 5.6, 3.9 Hz, 2H), 6.53 (d, *J* = 15.1 Hz, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.08 (s, 2H), 3.40 (d, *J* = 3.6 Hz, 2H), 1.91 (dt, *J* = 10.0, 8.2 Hz, 4H), 1.80 – 1.70 (m, 2H), 1.29 (s, 3H).

Example 39. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-[methyl-(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.

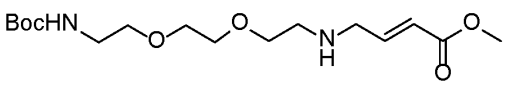


[0834] The method as described for the synthesis of (*R*,*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 1-methylcyclobutan-1-amine for *tert*-butyl 2-formylazetidine-1-carboxylate to provide *N*-(2-chlorophenyl)-7-[(*E*)-4-[methyl-(1-methylcyclobutyl)amino]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 442.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.8, 1.5 Hz, 1H), 6.96 (dt, *J* = 15.0, 5.7 Hz, 1H), 6.53 (d, *J* = 14.6 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.08 (s, 2H), 3.05 (s, 2H), 2.08 (s, 3H), 1.97 (s, 2H), 1.74 (s, 4H), 1.12 (s, 3H).

Example 40. Synthesis of 7-[(E)-4-[2-[2-(2-aminoethoxy)ethoxy]ethyl-methyl-amino]but-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

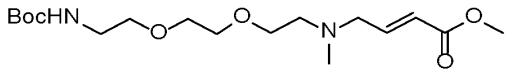


Step 1: Synthesis of methyl (E)-4-[2-[2-[2-(tert-butoxycarbonylamino)ethoxy]ethoxy]ethylamino]but-2-enoate



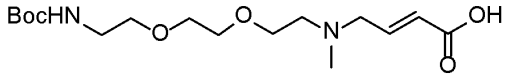
[0835] To a solution of *tert*-butyl *N*-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (4 g, 16.11 mmol) and DIPEA (6.25 g, 48.33 mmol, 8.42 mL) in THF (60 mL) was added a solution of methyl (*E*)-4-bromobut-2-enoate (2.31 g, 12.89 mmol) in THF (20 mL) at 0°C. The resulting mixture was stirred at room temperature overnight and then concentrated, the residue was purified by silica gel chromatography (eluting with EtOAc/petroleum ether = 1/5-1/1) to give methyl (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethylamino]but-2-enoate (2.9 g, 7.95 mmol, 49.37% yield, 95% purity) as an off-white solid. LCMS: *m/z* 347.2 $[M+H]^+$.

Step 2: Synthesis of methyl (E)-4-[2-[2-[2-(tert-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoate



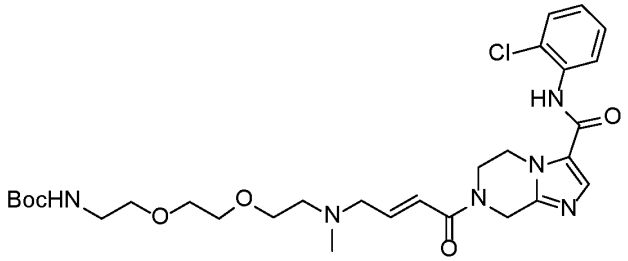
[0836] To a solution of methyl (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethylamino]but-2-enoate (2.3 g, 6.64 mmol) in ACN (50 mL) was added AcOH (2 drops) and HCHO (6.11 g, 66.39 mmol, 37% purity). The resulting mixture was stirred at room temperature for 1 hour, and then NaBH(OAc)3 (4.22 g, 19.92 mmol) was added. The mixture was stirred at room temperature overnight, filtered and purified by silica gel chromatography (eluting with EtOAc/petroleum ether = 1/5-1/1) to give methyl (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoate (2.1 g, 4.95 mmol, 74.59% yield, 85% purity) as a yellow oil. LCMS: *m/z* 361.2 $[M+H]^+$.

Step 3: Synthesis of (E)-4-[2-[2-[2-(tert-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoic acid



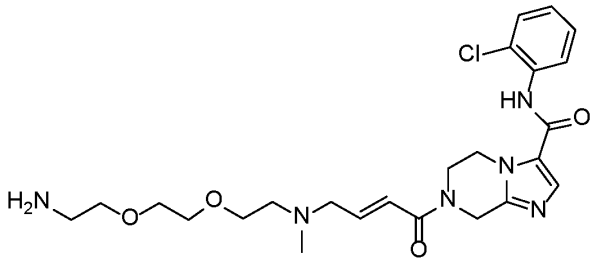
[0837] To a solution of methyl (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoate (720 mg, 2.00 mmol) in THF (10 mL) was added a solution of NaOH (239.70 mg, 5.99 mmol, 112.54 μL) in water (3 mL) The resulting mixture was stirred at 50°C overnight and then concentrated, the residue was added water (20 mL). The aqueous phase was adjusted pH to 5-6 with 1N HCl and lyophilized to give (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoic acid (900 mg, crude) as a light yellow solid, which was used directly for the next step. LCMS: *m/z* 347.2 $[M+H]^+$.

Step 4: Synthesis of tert-butyl N-[2-[2-[2-[[(E)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-methyl-amino]ethoxy]ethoxy]ethyl]carbamate



[0838] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (**V14**) (718.93 mg, 2.30 mmol, CL), (*E*)-4-[2-[2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethoxy]ethyl-methyl-amino]but-2-enoic acid (900 mg, 2.60 mmol) and DIPEA (436.50 mg, 3.38 mmol, 588.27 µL) in DMF (10 mL) was added HATU (2.96 g, 7.79 mmol). The resulting mixture was stirred at room temperature overnight and diluted with water (15 mL). The precipitate was filtered, dried and purified by Prep-HPLC under basic condition to give *tert*-butyl *N*-[2-[2-[2-[[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-methyl-amino]ethoxy]ethoxy]ethyl]carbamate (350 mg, 578.39 µmol, 22.26% yield) as a pale solid. LCMS: *m/z* 605.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.1 Hz, 1H), 8.14 (s, 1H), 7.65 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.4 Hz, 1H), 6.98 (dt, *J* = 15.1, 5.6 Hz, 1H), 6.57 (d, *J* = 14.8 Hz, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.20 – 3.92 (m, 2H), 3.72 – 3.48 (m, 8H), 3.38 – 3.20 (m, 4H), 2.63 (t, *J* = 5.5 Hz, 2H), 2.33 (s, 3H), 1.43 (s, 9H).

Step 5: Synthesis of 7-[(E)-4-[2-[2-(2-aminoethoxy)ethoxy]ethyl-methyl-amino]but-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

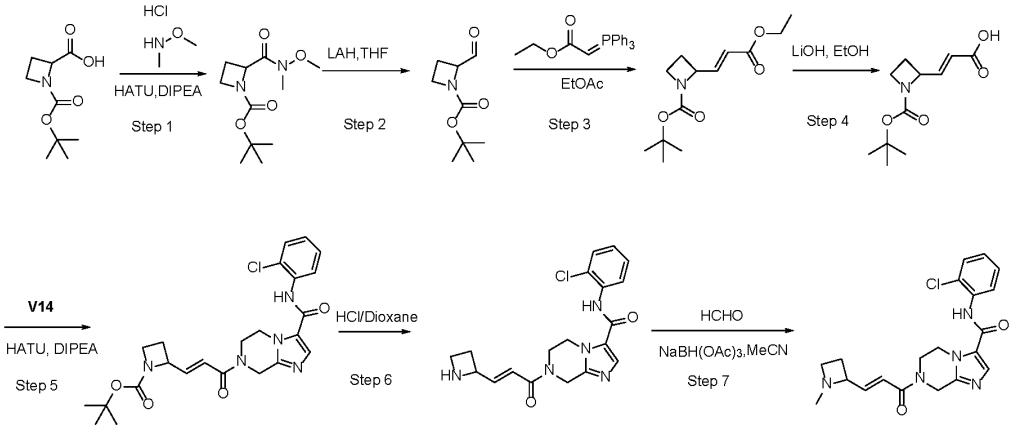


[0839] To a solution of give *tert*-butyl *N*-[2-[2-[2-[[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-methyl-amino]ethoxy]ethoxy]ethyl]carbamate (200 mg, 330.51 µmol) in DCM (3 mL) was

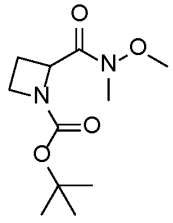
added TFA (444.00 mg, 3.89 mmol, 0.3 mL) at 0°C. The resulting mixture was stirred at room temperature overnight, and then diluted with DCM (20 mL). The organic phase was washed with *aq. sat.* NaHCO3 (10 mL x 3), brine and concentrated. The residue was purified by Prep-HPLC under basic condition to give 7-[(*E*)-4-[2-[2-(2-aminoethoxy)ethoxy]ethyl-methyl-amino]but-2-enoyl]-*N*-(2-chlorophenyl)-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (150 mg, 297.02 μmol, 89.87% yield) as white solid. LCMS: *m/z* 505.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.8 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.03 – 6.93 (m, 1H), 6.55 (d, *J* = 13.1 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.09 (s, 2H), 3.70 – 3.57 (m, 6H), 3.52 (t, *J* = 5.1 Hz, 2H), 3.26 (d, *J* = 4.6 Hz, 2H), 2.87 (t, *J* = 4.9 Hz, 2H), 2.63 (t, *J* = 5.6 Hz, 2H), 2.32 (s, 3H).

General method E

Example 41. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



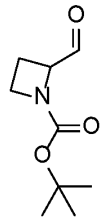
Step 1. Synthesis of tert-butyl 2-(methoxy(methyl)carbamoyl)azetidine-1-carboxylate



[0840] To a solution of 1-tert-butoxycarbonylazetidine-2-carboxylic acid (2 g, 9.94 mmol) in DMF (15 mL) were added *N*-methoxymethanamine (1.36 g, 13.92 mmol, CL), HATU (4.54 g, 11.93 mmol) and *N*-ethyl-*N*-isopropyl-propan-2-amine (3.08 g, 23.85 mmol, 4.16 mL). The mixture was stirred at room temperature for 4 h. The reaction was quenched with water and extracted with EtOAc (30 mL x 3). The extracts were washed with water (20

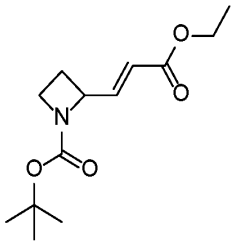
mL x2), brine (20 mL x 1), dried over Na_2SO_4 and concentrated to give *tert*-butyl (2*R*)-2-[methoxy(methyl)carbamoyl]azetidine-1-carboxylate (5.09 g, crude) as white gum. LCMS: *m/z* 145.2 $[M+H\text{-}Boc]^+$.

Step 2. Synthesis of tert-butyl 2-formylazetidine-1-carboxylate



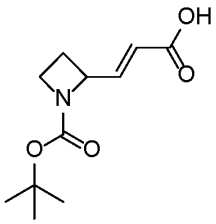
[0841] To a solution of *tert*-butyl 2-[methoxy(methyl)carbamoyl]azetidine-1-carboxylate (5.09 g, 12.50 mmol) in THF (30 mL) was added $LiAlH_4$ (1.14 g, 30.00 mmol) in portions at 0°C. The mixture was stirred at 0°C for 1 h. The reaction was quenched with Sodium sulfate decahydrate (5 g). The mixture was diluted with EtOAc (60 mL) and filtered through Celite. The filtrate was concentrated to give *tert*-butyl 2-formylazetidine-1-carboxylate (2.6 g, crude) as colorless oil which was used in next step without further purification. LCMS: *m/z* 130.1 $[M\text{-}t\text{-}Bu+H]^+$.

Step 3. Synthesis of tert-butyl (R,E)-2-(3-ethoxy-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate



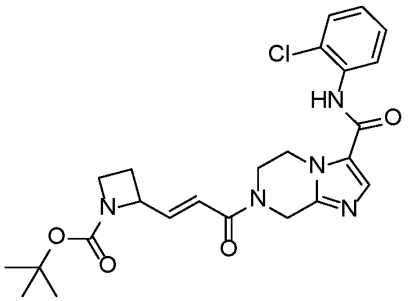
[0842] To a solution of *tert*-butyl 2-formylazetidine-1-carboxylate (2.6 g, 7.02 mmol) in EtOAc (40 mL) was added ethyl 2-(triphenyl-phosphanylidene)acetate (3.67 g, 10.53 mmol). The mixture was stirred at 25°C for 20 h. The precipitate was filtered and the filtrate was concentrated. The residue was purified on silica flash chromatography with a gradient of EtOAc/PE (0 to 25 percent, Biotage, 40 g) to give *tert*-butyl (2*R*)-2-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]azetidine-1-carboxylate (359 mg, 1.41 mmol, 20.03% yield) of colorless oil. LCMS: *m/z* 200.3 $[M\text{-}t\text{-}Bu+H]^+$.

Step 4. Synthesis of (E)-3-(1-(tert-butoxycarbonyl)azetidin-2-yl)acrylic acid



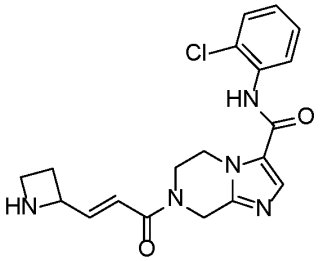
[0843] To a solution of *tert*-butyl 2-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]azetidine-1-carboxylate (359 mg, 1.41 mmol) in Ethanol (10 mL) and Water (3 mL) was added lithium hydroxide hydrate (236.01 mg, 5.62 mmol, 156.30 µL). The mixture was stirred at room temperature for 16 h. The mixture concentrated to obtain (*E*)-3-[(2*R*)-1-*tert*-butoxycarbonylazetidin-2-yl]prop-2-enoic acid (175 mg, 770.06 µmol, 54.76% yield) of colorless oil. LCMS: *m/z* 172.1 $[M\text{-t-Bu+H}]^+$.

Step 5. Synthesis of tert-butyl (E)-2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate



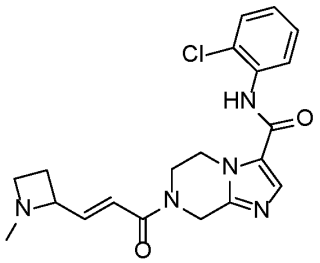
[0844] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (**V14**) (213.09 mg, 770.06 µmol), (*E*)-3-[(2*R*)-1-tert-butoxycarbonylazetidin-2-yl]prop-2-enoic acid (175 mg, 770.06 µmol), DIPEA (298.57 mg, 2.31 mmol, 402.38 µL), HATU (439.20 mg, 1.16 mmol) in DMF (6 mL). The mixture was stirred at room temperature for 16 h. The mixture was quenchded with water and extracted with DCM (20mL × 2). The organic phase washed with saturated LiCl (20 mL), concentrated and the residue was purified on silica flash chromatography with a gradient of MeOH/DCM (0 to 4 percent, Biotage, 40 g) to give *tert*-butyl (*E*)-2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(*8H*)-yl)-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate (249 mg, 512.39 µmol, 66.54% yield) of colorless oil. LCMS: *m/z* 486.1 $[M+H]^+$.

Step 6. Synthesis of (E)-7-(3-(azetidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[0845] To a solution of *tert*-butyl (*E*)-2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(*8H*)-yl)-3-oxoprop-1-en-1-yl)azetidine-1-carboxylate (36 mg, 74.08 μmol) in DCM (3.05 mL) was added TFA (16.89 mg, 148.16 μmol, 11.41 μL). The mixture was stirred at room temperature for 16 h. The mixture was concentrated to obtain (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (21.7 mg, 43.41 μmol, 58.60% yield, TFA) of white solid. LCMS: *m/z* 386.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.01 (d, *J* = 29.6 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.36 (td, *J* = 7.8, 1.4 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.03 (dd, *J* = 15.1, 6.8 Hz, 1H), 6.91 (d, *J* = 16.0 Hz, 1H), 5.23 (dd, *J* = 15.6, 7.9 Hz, 1H), 5.03 (s, 2H), 4.52 (d, *J* = 33.4 Hz, 2H), 4.20 – 4.07 (m, 3H), 3.93 (td, *J* = 10.0, 5.4 Hz, 1H), 3.25 (s, 1H), 2.79 – 2.61 (m, 2H).

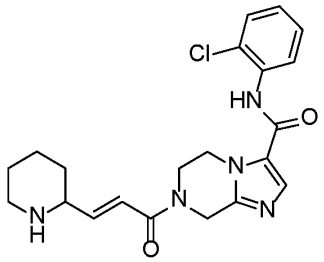
Step 7. Synthesis of (E)-N-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[0846] To a solution of formaldehyde (42.02 mg, 1.40 mmol, 38.80 μL), (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (270 mg, 699.76 μmol) in MeCN (2 mL) was added $NaBH(OAc)_3$ (296.70 mg, 1.40 mmol) and acetic acid (52.45 mg, 873.41 μmol, 0.05 mL).The mixture was stirred at room temperature for 2 h. The mixture was purified by Prep-HPLC under basic condition to obtain (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (32.7 mg, 81.78 μmol, 11.69% yield) of white solid. LCMS: *m/z* 400.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J*

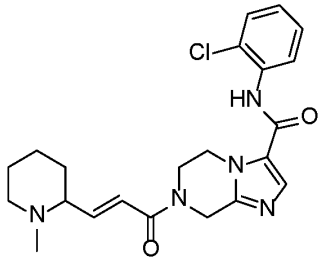
= 7.8, 1.6 Hz, 1H), 6.88 (dd, *J* = 15.2, 6.3 Hz, 1H), 6.69 (d, *J* = 14.0 Hz, 1H), 4.95 (d, *J* = 32.2 Hz, 2H), 4.47 (d, *J* = 19.3 Hz, 2H), 4.10 (s, 2H), 3.86 (s, 1H), 3.44 (t, *J* = 6.2 Hz, 1H), 3.09 – 2.98 (m, 1H), 2.38 (s, 3H), 2.33 – 2.23 (m, 1H), 2.12 (dd, *J* = 17.8, 9.2 Hz, 1H).

Example 42. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0847] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpiperidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.65 (s, 1H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35- 7.28 (m, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 7.00 (dd, *J* = 15.6, 5.2 Hz, 1H), 6.46 (d, *J* = 14.8 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.10-4.02 (m, 2H), 3.33 (d, *J* = 8.0 Hz, 1H), 3.17(d, *J* = 12.0 Hz, 1H), 2.72 (td, *J* = 11.6, 2.4 Hz, 1H), 1.88-1.80 (m, 2H), 1.67-1.64 (m, 1H), 1.51-1.39 (m, 2H), 1.29-1.19 (m, 1H).

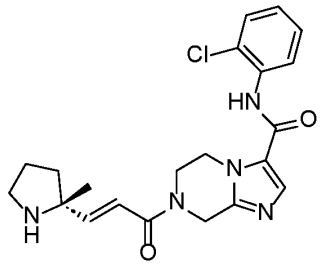
Example 43. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0848] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpiperidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

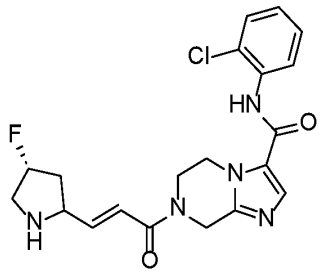
LCMS: *m/z* 428.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.65 (s, 1H), 7.43 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34-7.30 (m, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 6.98-6.91 (m, 1H), 6.44 (d, *J* = 12.8 Hz, 1H), 4.95 (s, 2H), 4.51 (s, 2H), 4.09-4.00 (m, 2H), 2.94-2.90 (m, 1H), 2.59 (t, *J* = 9.6 Hz, 1H), 2.22 (s, 3H), 2.05 (td, *J* = 11.6, 2.8 Hz, 1H), 1.79-1.63 (m, 4H), 1.53-1.42 (m, 1H), 1.37-1.25 (m, 1H).

Example 44. Synthesis of (*R,E*)-*N*-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0849] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 1-(*tert*-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid for 1*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product (*R,E*)-*N*-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.88 (s, 1H), 7.54 (td, *J* = 8.0, 1.2 Hz, 2H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.28 (td, *J* = 7.6, 1.6 Hz, 1H), 6.75 (d, *J* = 14.8 Hz, 1H), 6.59 (d, *J* = 14.8 Hz, 1H), 4.83 (d, *J* = 72.4 Hz, 2H), 4.30 (d, *J* = 14.8 Hz, 2H), 3.97 (d, *J* = 20.0 Hz, 2H), 2.95-2.78 (m, 2H), 1.77-1.49 (m, 4H), 1.21 (s, 3H).

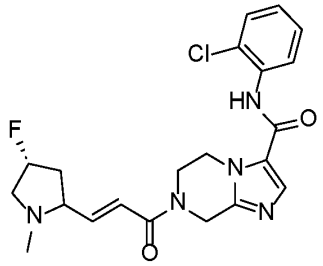
Example 45. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



[0850] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-3-((4*R*)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)acrylic acid for 1-

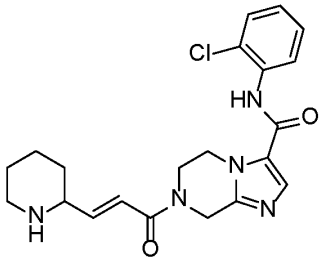
tert-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 418.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 8.0, 1.6 Hz, 2H), 7.37 (td, *J* = 8.0, 1.6 Hz, 1H), 7.28 (td, *J* = 8.0, 1.6 Hz, 1H), 6.78-6.66 (m, 2H), 5.31-5.14 (m, 1H), 4.84 (d, *J* = 70.4 Hz, 2H), 4.29 (d, *J* = 15.6 Hz, 2H), 3.97 (d, *J* = 27.2 Hz, 2H), 3.74-3.69 (m, 1H), 3.15-3.05 (m, 1H), 2.97-2.84 (m, 1H), 2.33-2.22 (m, 1H), 1.75-1.62 (m, 1H).

Example 46. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



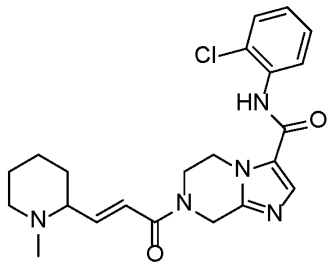
[0851] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-3-((4*R*)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidin-2-yl)acrylic acid 1-*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 432.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 7.6, 1.2 Hz, 2H), 7.37 (td, *J* = 7.6, 1.6 Hz, 1H), 7.28 (td, *J* = 8.0, 1.6 Hz, 1H), 6.75 (d, *J* = 15.2 Hz, 1H), 6.60-6.54 (m, 1H), 5.17 (d, *J* = 55.6 Hz, 1H), 4.84 (d, *J* = 70.8 Hz, 2H), 4.30 (d, *J* = 18.8 Hz, 2H), 3.98 (d, *J* = 24.4 Hz, 2H), 3.23-3.14 (m, 1H), 2.85-2.78 (m, 1H), 2.44-2.33 (m, 2H), 2.18(s, 3H), 1.80-1.64 (m, 1H).

Example 47. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



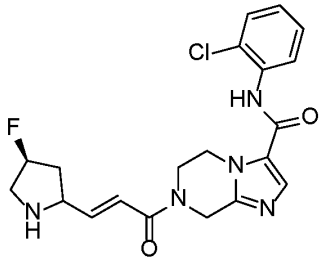
[0852] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpiperidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(piperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 414.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.11 (s, 1H), 7.63 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34-7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.99 (dd, *J* = 14.9, 5.6 Hz, 1H), 6.53-6.42 (m, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.16-3.94 (m, 2H), 3.40-3.28 (m, 1H), 3.23-3.12 (m, 1H), 2.73 (td, *J* = 11.7, 2.7 Hz, 1H), 1.90-1.77 (m, 3H), 1.45 (td, *J* = 9.1, 2.9 Hz, 2H), 1.34-1.20 (m, 1H).

Example 48. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



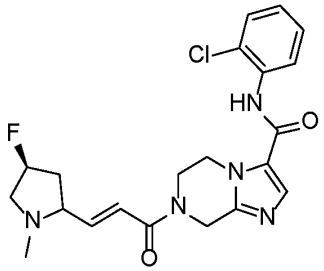
[0853] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl -2-formylpiperidine-1-carboxylate for *tert*-butyl -2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpiperidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35-7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.94 (dd, *J* = 15.0, 8.5 Hz, 1H), 6.56-6.35 (m, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.19-3.90 (m, 2H), 3.01-2.85 (m, 1H), 2.69-2.51 (m, 1H), 2.22 (s, 3H), 2.15-1.98 (m, 1H), 1.84-1.68 (m, 2H), 1.53-1.40 (m, 2H), 1.39-1.19 (m, 2H).

Example 49. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*S*)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



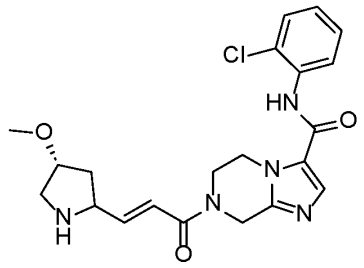
[0854] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-3-((4*S*)-4-fluoropyrrolidin-2-yl)acrylic acid for 1-*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((,4*S*)-4-fluoropyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 418.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.58 – 7.48 (m, 2H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.29 (td, *J* = 7.7, 1.6 Hz, 1H), 6.82 – 6.63 (m, 2H), 5.35 – 5.10 (m, 1H), 4.98 – 4.66 (m, 2H), 4.38 – 4.21 (m, 2H), 4.06 – 3.87 (m, 2H), 3.80 – 3.67 (m, 1H), 3.19 – 3.04 (m, 1H), 3.01 – 2.84 (m, 1H), 2.41 – 2.19 (m, 1H), 1.79 – 1.61 (m, 1H), 1.47 (s, 1H).

Example 50. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*S*)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



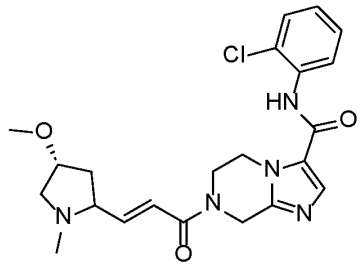
[0855] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid for (2*R*)-1-*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((4*S*)-4-fluoro-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 432.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.88 (s, 1H), 7.54 (t, *J* = 9.3 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.85 – 6.48 (m, 2H), 5.28 – 4.70 (m, 3H), 4.43 – 4.19 (m, 2H), 4.13 – 3.82 (m, 2H), 3.24 – 3.11 (m, 1H), 2.84 – 2.73 (m, 1H), 2.42 – 2.24 (m, 1H), 2.16 (s, 3H), 1.84 – 1.40 (m, 2H).

Example 51. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-methoxypyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0856] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (4*R*)-1-(*tert*-butoxycarbonyl)-4-methoxypyrrolidine-2-carboxylic acid for 1-*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((,4*R*)-4-methoxypyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.62 – 7.47 (m, 2H), 7.42 – 7.21 (m, 2H), 6.81 – 6.52 (m, 2H), 4.99 – 4.67 (m, 2H), 4.48 – 4.25 (m, 2H), 4.08 – 3.69 (m, 4H), 3.24 – 3.06 (m, 4H), 2.96 – 2.83 (m, 1H), 2.30 – 2.12 (m, 1H), 2.10 – 1.80 (m, 1H), 1.60 – 1.38 (m, 1H).

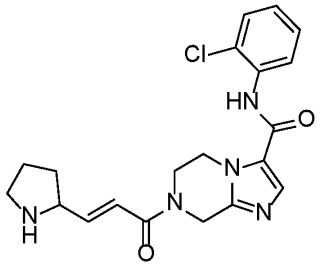
Example 52. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-3-((4*R*)-4-methoxy-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0857] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of (4*R*)-1-(*tert*-butoxycarbonyl)-4-methoxypyrrolidine-2-carboxylic acid for 1-*tert*-butoxycarbonylazetidine-2-carboxylic acid to provide the product *N*-(2-chlorophenyl)-7-((*E*)-3-((,4*R*)-4-methoxy-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 444.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.59 – 7.50 (m, 2H), 7.33 (dtd, *J* = 35.5, 7.7, 1.5 Hz, 2H), 6.75 (t, *J* = 14.9 Hz, 1H), 6.60 – 6.46 (m, 1H), 4.99 – 4.67 (m, 2H), 4.41 – 4.21

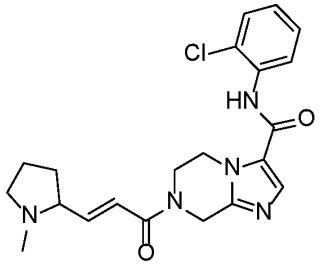
(m, 2H), 4.06 – 3.82 (m, 3H), 3.17 (d, J = 8.6 Hz, 3H), 3.11 – 2.92 (m, 1H), 2.42 – 1.48 (m, 7H).

Example 53. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0858] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpyrrolidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 400.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.74 – 9.33 (m, 1H), 7.90 (s, 1H), 7.57 – 7.49 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 14.8 Hz, 1H), 6.84 – 6.73 (m, 1H), 5.02 – 4.70 (m, 2H), 4.43 – 3.84 (m, 5H), 3.29 – 3.15 (m, 2H), 2.23 – 2.11 (m, 1H), 2.04 – 1.72 (m, 3H).

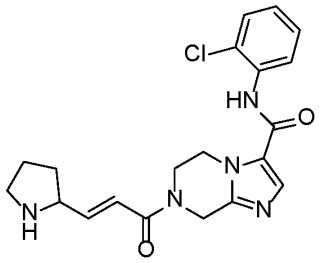
Example 54. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0859] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl -2-formylpyrrolidine-1-carboxylate for *tert*-butyl -2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.54 (t, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.73 – 6.70 (m, 1H),

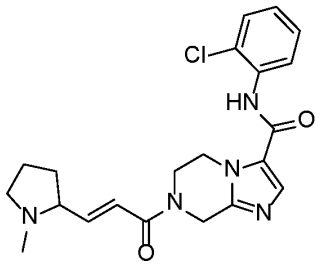
6.55 (dd, *J* = 15.0, 8.0 Hz, 1H), 4.92 (s, 1H), 4.75 (s, 1H), 4.38 – 4.23 (m, 2H), 4.06 – 3.88 (m, 2H), 3.05 – 2.94 (m, 1H), 2.86 – 2.70 (m, 1H), 2.20 – 2.13 (m, 4H), 2.02 – 1.88 (m, 1H), 1.76 – 1.67 (m, 2H), 1.61 – 1.47 (m, 1H).

Example 55. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0860] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpyrrolidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*R*,*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 400.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-*d*6) δ 9.88 (s, 1H), 9.09 – 8.96 (m, 1H), 8.82 – 8.61 (m, 1H), 7.89 (s, 1H), 7.57 – 7.48 (m, 2H), 7.38 (td, *J* = 7.7, 1.3 Hz, 1H), 7.29 (td, *J* = 7.8, 1.6 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.79 – 6.73 (m, 1H), 4.96 (s, 1H), 4.78 (s, 1H), 4.37 – 4.19 (m, 3H), 4.08 – 3.92 (m, 2H), 2.22 – 2.14 (m, 1H), 2.04 – 1.75 (m, 4H).

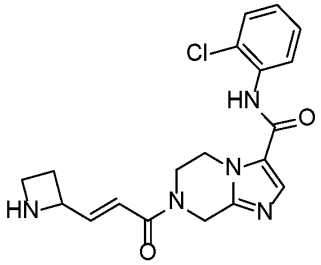
Example 56. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0861] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpyrrolidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.54

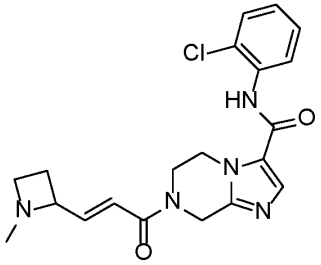
(td, *J* = 8.2, 2.7 Hz, 2H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.29 (td, *J* = 7.7, 1.6 Hz, 1H), 6.74 – 6.70 (m, 1H), 6.55 (dd, *J* = 15.0, 8.0 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.81 – 4.66 (m, 1H), 4.40 – 4.18 (m, 2H), 4.10 – 3.89 (m, 2H), 3.08 – 2.96 (m, 1H), 2.86 – 2.71 (m, 1H), 2.17 – 2.14 (m, 4H), 2.03 – 1.90 (m, 1H), 1.77 – 1.67 (m, 2H), 1.62 – 1.45 (m, 1H).

Example 57. Synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0862] The method as described for the synthesis of (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid for 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid to provide the product (*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 386.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.12 (d, *J* = 12.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.37 (td, *J* = 7.8, 1.1 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.04 (dd, *J* = 14.9, 6.5 Hz, 1H), 6.91 (d, *J* = 15.6 Hz, 1H), 5.24 (dd, *J* = 15.6, 8.1 Hz, 1H), 5.07 (s, 2H), 4.60 (dd, *J* = 35.5, 19.0 Hz, 2H), 4.13 (dd, *J* = 19.2, 9.0 Hz, 3H), 3.93 (td, *J* = 10.0, 5.4 Hz, 1H), 2.81 – 2.62 (m, 2H).

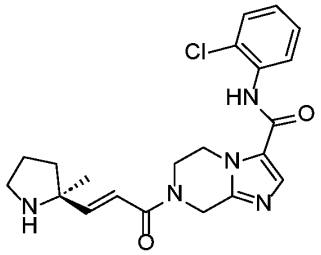
Example 58. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0863] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid for 1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid to provide the product (*E*)-3-(1-methylazetidin-2-

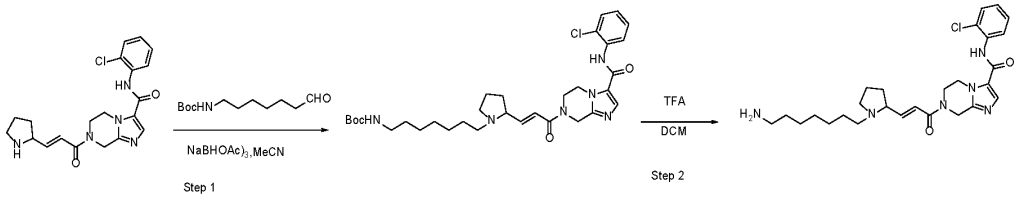
yl)acrylaldehyde for (*E*)-3-(1-methylazetidin-2-yl)acrylaldehyde to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylazetidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 400.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.88 (dd, *J* = 15.2, 6.3 Hz, 1H), 6.70 (d, *J* = 15.4 Hz, 1H), 4.95 (d, *J* = 31.2 Hz, 2H), 4.46 (d, *J* = 21.5 Hz, 2H), 4.10 (s, 2H), 3.89 (d, *J* = 7.2 Hz, 1H), 3.46 (t, *J* = 7.9 Hz, 1H), 3.07 (d, *J* = 7.9 Hz, 1H), 2.40 (s, 3H), 2.29 (dd, *J* = 16.1, 8.2 Hz, 1H), 2.14 (dd, *J* = 18.7, 9.2 Hz, 1H).

Example 59. Synthesis of (*S,E*)-*N*-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

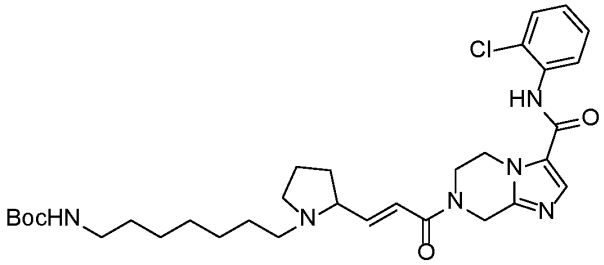


[0864] The method as described for the synthesis of (*R,E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl 2-formylpyrrolidine-1-carboxylate for *tert*-butyl 2-formylazetidine-1-carboxylate to provide the product (*S,E*)-*N*-(2-chlorophenyl)-7-(3-(2-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 414.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 8.03 – 7.92 (m, 1H), 7.72 – 7.66 (m, 1H), 7.53 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.38 (td, *J* = 7.8, 1.2 Hz, 1H), 7.30 (dd, *J* = 11.7, 4.7 Hz, 1H), 7.02 – 6.82 (m, 2H), 5.03 (d, *J* = 19.8 Hz, 2H), 4.60 – 4.44 (m, 2H), 4.16 (s, 2H), 3.51 – 3.41 (m, 2H), 2.30 – 2.07 (m, 4H), 1.64 (s, 3H).

Example 60. Synthesis of (*E*)-7-(3-(1-(7-aminoheptyl)pyrrolidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

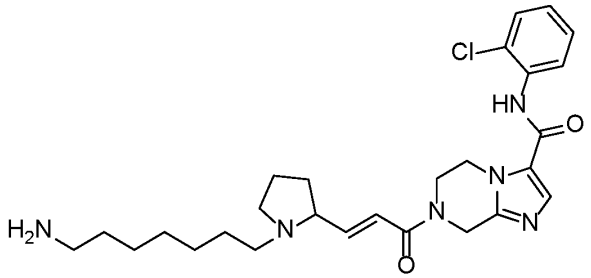


Step 1. Synthesis of tert-butyl (E)-(7-(2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-3-oxoprop-1-en-1-yl)pyrrolidin-1-yl)heptyl)carbamate



[0865] To a solution of (*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (430 mg, 1.08 mmol) in MeCN (5 mL) was added *tert*-butyl-*N*-(7-oxoheptyl)carbamate (493.18 mg, 2.15 mmol) and $NaBH(OAc)_3$ (683.72 mg, 3.23 mmol) and two drops of acetic acid. Then the mixture was stirred at 25°C for 1 h. The mixture was purified by Prep-HPLC under basic condition to give *tert*-butyl (*E*)-(7-(2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-3-oxoprop-1-en-1-yl)pyrrolidin-1-yl)heptyl)carbamate (200 mg, 326.16 μmol, 30.33% yield) as white solid. LCMS: *m/z* 613.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.57 – 7.50 (m, 2H), 7.33 (dtd, J = 17.0, 7.6, 1.5 Hz, 2H), 6.93 – 6.40 (m, 3H), 4.99 – 4.67 (m, 2H), 4.37 – 4.22 (m, 2H), 4.08 – 3.88 (m, 2H), 3.13 – 2.83 (m, 3H), 2.16 – 2.00 (m, 2H), 1.98 – 1.86 (m, 1H), 1.81 – 1.67 (m, 2H), 1.56 – 1.12 (m, 22H).

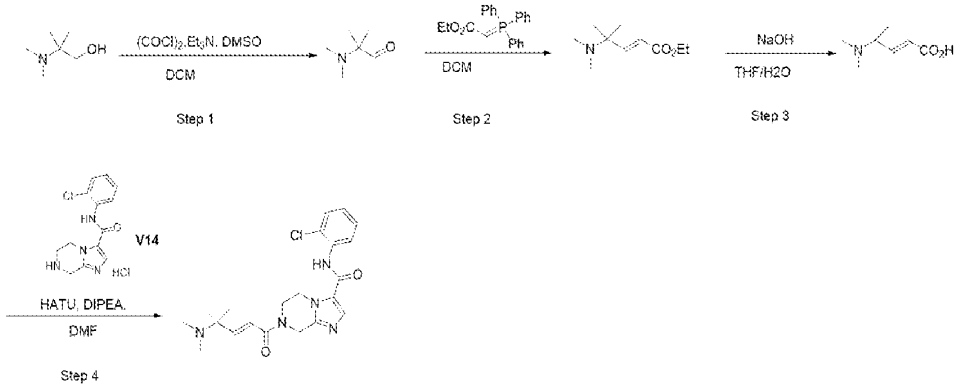
Step 2. Synthesis of (E)-7-(3-(1-(7-aminoheptyl)pyrrolidin-2-yl)acryloyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

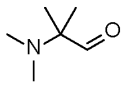


[0866] To a solution of *tert*-butyl (*E*)-(7-(2-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-3-oxoprop-1-en-1-yl)pyrrolidin-1-yl)heptyl)carbamate (180 mg, 293.55 μmol) in DCM (4 mL) was added TFA (100.41 mg, 880.64 μmol). Then the mixture was stirred at 25°C for 4 h. The mixture was neutralized with aqueous sodium bicarbonate. The resulting solution was concentrated and the residue was purified by Prep-HPLC under basic condition to give (*E*)-7-(3-(1-(7-aminoheptyl)pyrrolidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (100 mg, 194.90 μmol, 66.40% yield) as white solid. LCMS: *m/z* 513.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.60 – 7.43 (m, 2H), 7.33 (dtd, *J* = 35.5, 7.6, 1.5 Hz,

2H), 6.80 – 6.43 (m, 2H), 5.03 – 4.65 (m, 2H), 4.45 – 4.15 (m, 2H), 4.09 – 3.87 (m, 2H), 3.14 – 2.80 (m, 3H), 2.18 – 1.01 (m, 19H).

Example 61. Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)-4-methylpent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

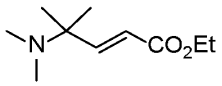




Step 1. Synthesis of 2-(dimethylamino)-2-methylpropanal

[0867] To a solution of DMSO (3.12 g, 39.94 mmol, 2.83 mL) in DCM (10 mL) was added a solution of (COCl)2 (3.77 g, 29.95 mmol) in DCM (10 mL) at -78° C. The mixture was stirred at the same temperature for 30 minutes, and then a solution of 2-(dimethylamino)-2-methyl-propan-1-ol (1.17 g, 9.98 mmol) in DCM (10 mL) was added. The resulting mixture was stirred at the same temperature for 20 minutes, Et3N (6.55 g, 64.90 mmol) was added, and the mixture was stirred at the same temperature for 40 minutes. The reaction mixture was warmed to room temperature, and then diluted with DCM (20 mL) The organic layer was washed with *sat. aq.* sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate and concentrated to give 2-(dimethylamino)-2-methyl-propanal (1.2 g, crude) as a yellow oil. LCMS: *m/z* 116.1 $[M+H]^+$.

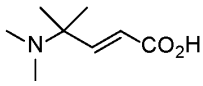
Step 2. Synthesis of ethyl (E)-4-(dimethylamino)-4-methylpent-2-enoate



[0868] To a solution of 2-(dimethylamino)-2-methyl-propanal (1.15 g, 10 mmol) in DCM (20 mL) was added ethyl 2-(triphenyl-phosphanylidene)acetate (5.23 g, 15.00 mmol). The resulting mixture was stirred at 40°C overnight and concentrated, the residue was purified by SGC (eluting with Petroleum ether/EtOAc = 3/1-1/2) to give ethyl (*E*)-4-(dimethylamino)-4-

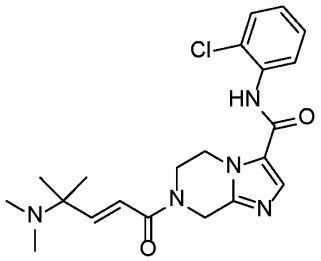
methyl-pent-2-enoate (400 mg, 1.30 mmol, 12.95% yield, 60% purity) as a yellow oil. LCMS: *m/z* 186.1 $[M+H]^+$.

Step 3. Synthesis of (E)-4-(dimethylamino)-4-methylpent-2-enoic acid



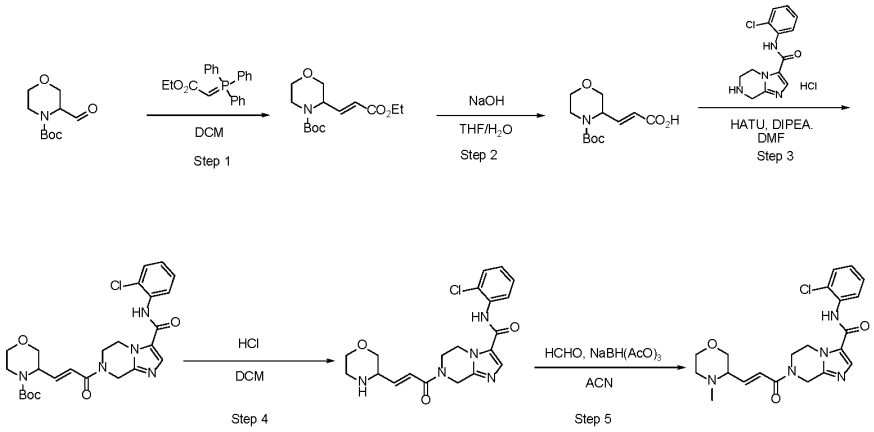
[0869] To a solution of ethyl (*E*)-4-(dimethylamino)-4-methyl-pent-2-enoate (400 mg, 2.16 mmol) in THF (6 mL) was added a solution of NaOH (240.00 mg, 6 mmol, 112.68 μL) in water (2.00 mL). The resulting mixture was stirred at 50°C overnight and then concentrated, the residue was added water (20 mL). The aqueous phase was acidified with 1M HCl to pH 3-4 and lyophilized to give (*E*)-4-(dimethylamino)-4-methyl-pent-2-enoic acid (800 mg, crude) as a light yellow solid, which was used directly for the next step. LCMS: *m/z* 158.1 $[M+H]^+$.

Step 4. Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(dimethylamino)-4-methylpent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

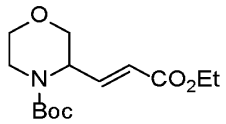


[0870] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (60 mg, 216.82 μmol CL), (*E*)-4-(dimethylamino)-4-methyl-pent-2-enoic acid (200 mg, 1.27 mmol) and HATU (82.44 mg, 216.82 μmol) in DMF (3 mL) was added DIPEA. (27.97 mg, 216.82 μmol). The resulting mixture was stirred at room temperature overnight and then purified by Prep-HPLC under basic condition to give (*E*)-*N*-(2-chlorophenyl)-7-(4-(dimethylamino)-4-methylpent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (40 mg, 92.33 μmol, 42.58% yield, 96% purity) as a white solid. LCMS: *m/z* 416.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.7 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.8, 1.5 Hz, 1H), 7.02 (d, *J* = 15.4 Hz, 1H), 6.46 – 6.25 (m, 1H), 4.96 (s, 2H), 4.50 (s, 2H), 4.10 (brs, 2H), 2.28 (s, 6H), 1.23 (s, 6H).

Example 62. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-(4-methylmorpholin-3-yl)prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.

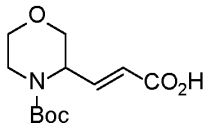


Step 1: Synthesis of tert-butyl -3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]morpholine-4-carboxylate



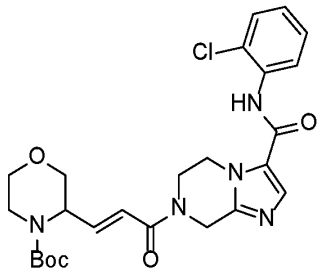
[0871] To a solution of ethyl 2-(triphenyl-phosphanylidene)acetate (2.43 g, 6.97 mmol) in DCM (30 mL) was added *tert*-butyl -3-formylmorpholine-4-carboxylate (1.0 g, 4.65 mmol) . The mixture was stirred at 40 °C overnight, and the precipitate was filtered and the filtrate was concentrated. The residue was purified on silica flash chromatography (eluting with EtOAc/petroleum ether 0 to 1/1) to give *tert*-butyl -3-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]morpholine-4-carboxylate (1.2 g, 3.90 mmol, 84.01% yield, 92.8% purity) as colorless oil. LCMS: *m/z* 186.2 $[M+H-Boc]^+$.

Step 2: Synthesis of (E)-3-(4-(tert-butoxycarbonyl)morpholin-3-yl)acrylic acid



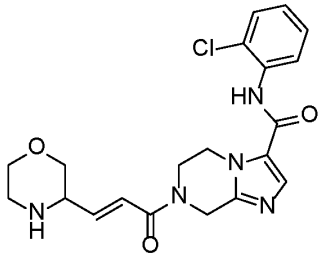
[0872] To a solution of *tert*-butyl 3-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]morpholine-4-carboxylate (1.3 g, 4.21 mmol) in THF (30 mL) was added a solution of NaOH (504.63 mg, 12.62 mmol, 236.91 μL) in water (10 mL) The resulting mixture was stirred at 50°C overnight and then concentrated, the residue was added water (20 mL). The aqueous phase was adjusted pH to 5-6 with 1N HCl, and extracted with EtOAc (30 mL * 3). The combined organic phase was concentrated to give (*E*)-3-(4-(*tert*-butoxycarbonyl)morpholin-3-yl)acrylic acid (0.75 g, 2.92 mmol, 69.32% yield) as a light yellow solid, which was used directly for the next step. LCMS: *m/z* 158.2 $[M+H-Boc]^+$.

Step 3: Synthesis of tert-butyl (E)-3-(3-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-3-oxoprop-1-en-1-yl)morpholine-4-carboxylate



[0873] To a solution of (*E*)-3-[(3*S*)-4-tert-butoxycarbonylmorpholin-3-yl]prop-2-enoic acid (260 mg, 1.01 mmol) , *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (210.99 mg, 673.71 μmol, CL) and HATU (307.40 mg, 808.45 μmol) in DMF (5 mL) was added DIPEA (113.19 mg, 875.82 μmol, 152.55 μL) . The resulting mixture was stirred at room temperature overnight and diluted with water (15 mL). The precipitate was filtered, dried and then purified by Prep-HPLC under basic condition to give *tert*-butyl -3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (200 mg, 387.61 μmol, 57.53% yield, 100% purity) as a white solid. LCMS: *m/z* 516.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.30 (m, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.16 – 6.97 (m, 2H), 6.45 (d, *J* = 15.0 Hz, 1H), 5.00 – 4.76 (m, 2H), 4.68 – 4.42 (m, 3H), 4.12 – 3.52 (m, 7H), 3.23 – 3.08 (m, 1H), 1.46 (s, 9H).

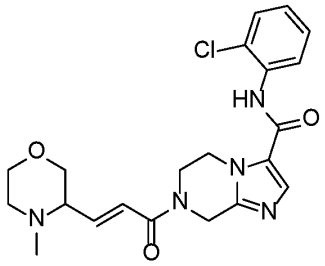
Step 4: Synthesis of (E)-N-(2-chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[0874] To a solution of *tert*-butyl -3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (200 mg, 387.61 μmol) in DCM (5 mL) was added HCl (145.84 mg, 4 mmol, 1 mL) at 0°C. The resulting mixture was stirred at room temperature for 3 hours, and then diluted with DCM (20 mL). The organic phase was washed with *aq. sat.* NaHCO3 (10 mL x 3), brine and concentrated. The residue was purified by Prep-HPLC under basic condition to give (*E*)-*N*-(2-

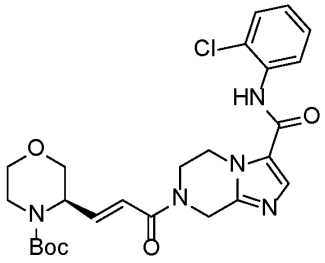
chlorophenyl)-7-(3-(morpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (95 mg, 228.44 μmol, 58.93% yield, 100% purity) as white solid. LCMS: *m/z* 416.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.13 – 7.05 (m, 1H), 6.89 (dd, *J* = 15.1, 5.2 Hz, 1H), 6.57 (d, *J* = 15.0 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.10 (s, 2H), 3.94 – 3.80 (m, 2H), 3.69 – 3.48 (m, 2H), 3.30 – 3.19 (m, 1H), 3.10 – 2.92 (m, 2H).

Step 5: Synthesis of (E)-N-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



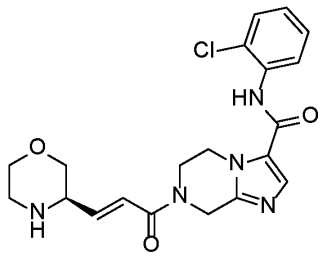
[0875] To a solution of *N*-(2-chlorophenyl)-7-[(*E*)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide (65 mg, 156.30 μmol) in ACN (5 mL) was added AcOH (2 drops) and HCHO (143.88 mg, 1.56 mmol, 37% purity). The resulting mixture was stirred at room temperature for 1 hour, and then $NaBH(OAc)_3$ (99.41 mg, 468.89 μmol) was added. The mixture was stirred at room temperature overnight, filtered and purified by Prep-HPLC under basic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-4-methylmorpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (16 mg, 37.22 μmol, 23.81% yield, 100% purity) as a white solid. LCMS: *m/z* 430.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.7 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.46 – 7.39 (m, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.80 (dd, *J* = 15.3, 8.4 Hz, 1H), 6.55 (d, *J* = 14.6 Hz, 1H), 4.93 (s, 2H), 4.50 (s, 2H), 4.20 – 3.90 (m, 2H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.68 (t, *J* = 12.4 Hz, 2H), 3.43 – 3.25 (m, 1H), 2.91 – 2.68 (m, 2H), 2.36 – 2.29 (m, 1H), 2.24 (s, 3H).

Example 63. Synthesis of *tert*-butyl (3*R*)-3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate.



[0876] The method as described for the synthesis of *tert*-butyl (3*S*)-3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate was applied with substitution of *tert*-butyl (3*R*)-3-formylmorpholine-4-carboxylate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product *tert*-butyl (3*R*)-3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate. LCMS: *m/z* 516.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 6.93 (dd, *J* = 15.4, 5.8 Hz, 1H), 6.63 (d, *J* = 16.8 Hz, 1H), 4.99 – 4.91 (m, 1H), 4.86 – 4.83 (m, 1H), 4.69 – 4.36 (m, 3H), 4.12 – 3.81 (m, 4H), 3.75 – 3.66 (m, 2H), 3.49 (t, *J* = 10.4 Hz, 1H), 3.25 – 3.16 (m, 1H), 1.50 – 1.42 (m, 9H).

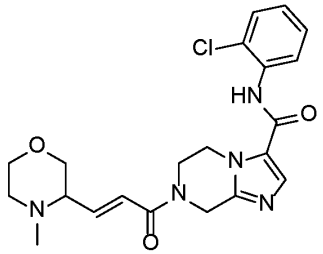
Example 64. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*R*)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



[0877] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (3*R*)-3-formylmorpholine-4-carboxylate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide, after chiral SFC, the product *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*R*)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 416.1[M+H]$^+$.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.89 (dd, *J* = 15.0, 5.0 Hz, 1H), 6.57 (d, *J* = 14.8 Hz, 1H), 4.94 (s,

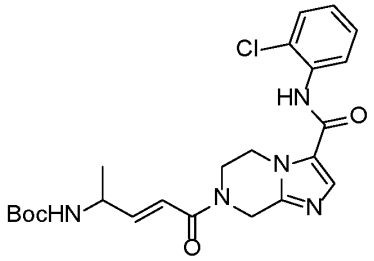
2H), 4.50 (s, 2H), 4.21 – 3.77 (m, 4H), 3.67 – 3.49 (m, 2H), 3.30 – 3.18 (m, 1H), 3.12 – 2.87 (m, 2H).

Example 65. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0878] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl -3-formylmorpholine-4-carboxylate for *tert*-butyl -3-formylmorpholine-4-carboxylate to provide the product,(*E*)-*N*-(2-chlorophenyl)-7-(3-(4-methylmorpholin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.80 (dd, *J* = 15.2, 8.3 Hz, 1H), 6.55 (d, *J* = 15.0 Hz, 1H), 4.93 (s, 2H), 4.47 (d, *J* = 26.1 Hz, 2H), 4.19 – 3.79 (m, 3H), 3.68 (dt, *J* = 13.5, 6.9 Hz, 2H), 3.42 – 3.28 (m, 1H), 2.89 – 2.70 (m, 2H), 2.32 (td, *J* = 11.5, 3.4 Hz, 1H), 2.24 (s, 3H).

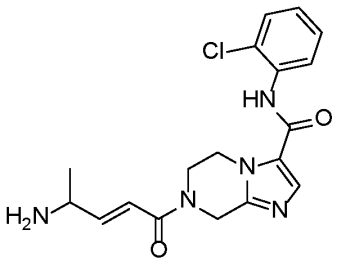
Example 66. Synthesis of *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-1-methyl-4-oxo-but-2-enyl]carbamate.



[0879] The method as described for the synthesis of *tert*-butyl (3*S*)-3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate was applied with substitution of *tert*-butyl (1-oxopropan-2-yl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product *tert*-butyl *N*-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-1-methyl-4-oxo-but-2-enyl]carbamate. LCMS: *m/z* 474.1[M+H]$^+$. ^{1}H NMR (400 MHz,

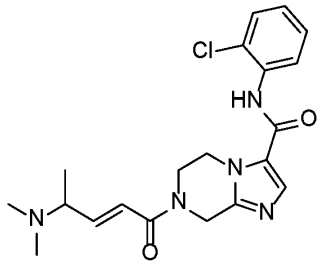
$CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.09 (dd, *J* = 12.3, 4.7 Hz, 1H), 6.86 (s, 1H), 6.38 (d, *J* = 15.2 Hz, 1H), 4.93 (s, 2H), 4.45 (d, *J* = 32.5 Hz, 4H), 4.03 (d, *J* = 44.9 Hz, 2H), 1.46 (s, 9H), 1.30 (d, *J* = 6.9 Hz, 3H).

Example 67. Synthesis of 7-[(*E*)-4-aminopent-2-enoyl]-*N*-(2-chlorophenyl)-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide.



[0880] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (1-oxopropan-2-yl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product 7-[(*E*)-4-aminopent-2-enoyl]-*N*-(2-chlorophenyl)-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 374.1 $[M+H]^+$.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.1 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 15.3 Hz, 1H), 6.45 (s, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.19 – 3.91 (m, 2H), 3.71 (s, 1H), 1.25 (d, *J* = 6.3 Hz, 3H).

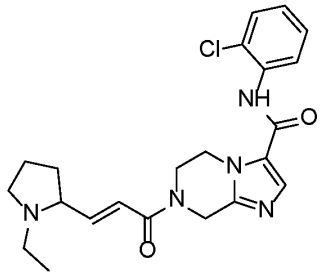
Example 68. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(dimethylamino)pent-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



[0881] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-4-methylmorpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (1-oxopropan-2-yl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-(dimethylamino)pent-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.

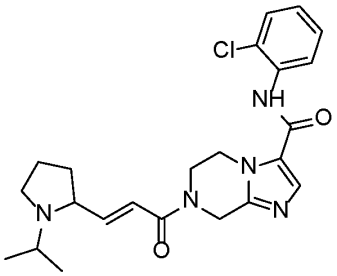
LCMS: *m/z* 402.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.05 (m, 1H), 6.96 (dd, *J* = 15.1, 7.5 Hz, 1H), 6.39 (d, *J* = 15.3 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.28 – 3.96 (m, 2H), 3.24 – 3.03 (m, 1H), 2.35 – 2.21 (m, 6H), 1.21 (d, *J* = 6.7 Hz, 3H).

Example 69. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-ethylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0882] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of acetaldehyde for formaldehyde to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-3-[(2*R*)-1-ethylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.2[M+H]$^+$.^{1}H NMR (400 MHz, MeOD) δ 8.03 (s, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 20.8 Hz, 1H), 6.87 – 6.74 (m, 1H), 5.06 (d, *J* = 26.8 Hz, 2H), 4.54 (d, *J* = 29.7 Hz, 2H), 4.24 – 4.04 (m, 3H), 3.89 – 3.64 (m, 1H), 3.39 (dd, *J* = 12.7, 7.0 Hz, 1H), 3.22 (dd, *J* = 19.6, 8.8 Hz, 1H), 3.09 (dd, *J* = 12.9, 7.2 Hz, 1H), 2.41 (dd, *J* = 12.7, 7.5 Hz, 1H), 2.31 – 2.10 (m, 2H), 2.03 (d, *J* = 5.3 Hz, 1H), 1.36 (t, *J* = 7.3 Hz, 3H).

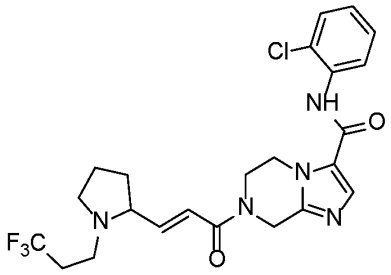
Example 70. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0883] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of acetone for formaldehyde to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-isopropylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-

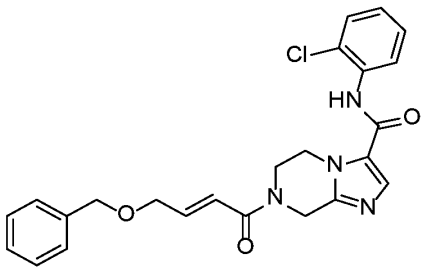
a]pyrazine-3-carboxamide. LCMS: *m/z* 442.2[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.90 (m, 1H), 6.49 (s, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.09 (s, 2H), 3.42 (s, 1H), 2.90 (d, *J* = 48.5 Hz, 2H), 2.60 (s, 1H), 1.87 (d, *J* = 77.3 Hz, 4H), 1.04 (d, *J* = 34.2 Hz, 6H).

Example 71. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0884] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 3,3,3-trifluoropropanal for formaldehyde to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(3-(1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 496.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 6.76 (s, 2H), 4.97 (s, 2H), 4.48 (s, 2H), 4.09 (s, 2H), 3.22 (dd, *J* = 20.9, 11.0 Hz, 2H), 3.02 – 2.91 (m, 1H), 2.53 – 2.29 (m, 4H), 2.09 (dd, *J* = 12.8, 6.9 Hz, 1H), 1.87 (dd, *J* = 15.1, 6.7 Hz, 2H), 1.67 (d, *J* = 7.6 Hz, 1H).

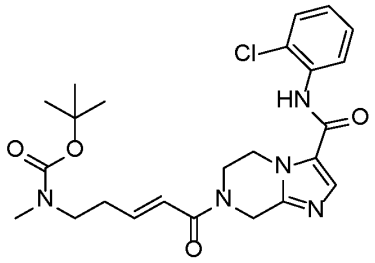
Example 72. Synthesis of (*E*)-7-(4-(benzyloxy)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0885] The method as described for the synthesis of *tert*-butyl 3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate was applied with substitution of 2-(benzyloxy)acetaldehyde

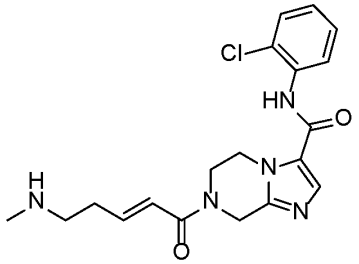
for *tert*-butyl (3*R*)-3-formylmorpholine-4-carboxylate to provide the product (*E*)-7-(4-(benzyloxy)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 451.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.45 – 7.29 (m, 6H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 7.02 (dt, *J* = 15.1, 3.8 Hz, 1H), 6.63 (td, *J* = 14.9, 1.8 Hz, 1H), 4.95 (s, 2H), 4.61 (s, 2H), 4.55 – 4.44(m, 2H), 4.22 (s, 2H), 4.15 – 3.92 (m, 2H).

Example 73. Synthesis of *tert*-butyl (*E*)-(5-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-5-oxopent-3-en-1-yl)(methyl)carbamate.



[0886] The method as described for the synthesis of *tert*-butyl (3*S*)-3-[(*E*)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate was applied with substitution of *tert*-butyl methyl(3-oxopropyl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product *tert*-butyl (*E*)-(5-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-5-oxopent-3-en-1-yl)(methyl)carbamate. LCMS: *m/z* 488.0$[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.12 – 7.06 (m, 1H), 7.02 – 6.90 (m, 1H), 6.47 – 6.25 (m, 1H), 4.97 – 4.81 (m, 2H), 4.55 – 4.42 (m, 2H), 4.11 – 4.02 (m, 1H), 3.93 – 3.73 (m, 2H), 3.42 – 3.32 (m, 1H), 3.29 – 3.22 (m, 1H), 2.92 – 2.76 (m, 3H), 2.54 – 2.44 (m, 1H), 1.45 (s, 9H).

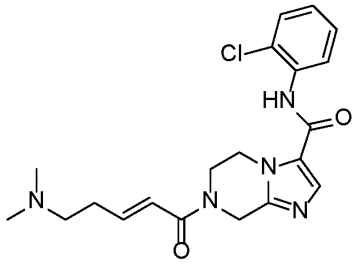
Example 74. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(5-(methylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0887] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was

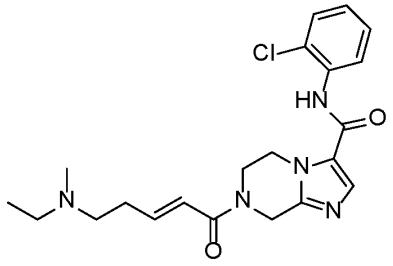
applied with substitution of *tert*-butyl methyl(3-oxopropyl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(5-(methylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 388.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.72 – 7.64 (m, 1H), 7.54 – 7.47 (m, 1H), 7.38 – 7.32 (m, 1H), 7.29 – 7.22 (m, 1H), 6.89 – 6.78 (m, 1H), 6.73 – 6.58 (m, 1H), 5.00 – 4.90 (m, 2H), 4.55 – 4.37 (m, 2H), 4.13 – 3.96 (m, 2H), 3.55 – 3.35 (m, 2H), 2.89 (t, *J* = 7.1 Hz, 1H), 2.60 – 2.46 (m, 4H).

Example 75. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0888] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-3-[(3*S*)-4-methylmorpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl methyl(3-oxopropyl)carbamate for *tert*-butyl (3*S*)-3-formylmorpholine-4-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 402.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.7 Hz, 1H), 8.11 (s, 1H), 7.67 – 7.59 (m, 1H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.09 (td, *J* = 7.9, 1.4 Hz, 1H), 7.02 – 6.92 (m, 1H), 6.35 (d, *J* = 14.8 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.57 – 4.42 (m, 2H), 4.16 – 3.93 (m, 2H), 3.35 – 2.79 (m, 2H), 2.45 (s, 3H), 2.30 – 2.19 (m, 5H).

Example 76. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(5-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

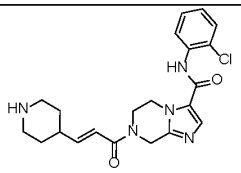


[0889] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(5-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was

applied with substitution of acetaldehyde for formaldehyde to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(5-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 416.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.09 (td, *J* = 7.8, 1.4 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.35 (d, *J* = 15.4 Hz, 1H), 4.98 – 4.88 (m, 2H), 4.54 – 4.45 (m, 2H), 4.12 – 3.98 (m, 2H), 2.62 – 2.34 (m, 6H), 2.26 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

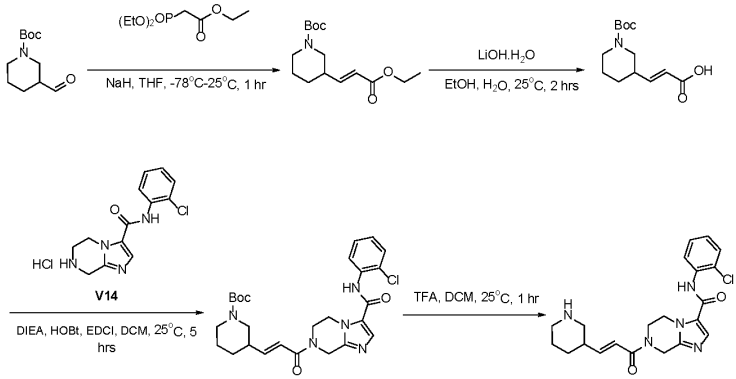
[0890] Compounds in Table B were synthesized following the procedure for (*R*,*E*)-7-(3-(azetidin-2-yl)acryloyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

Table B

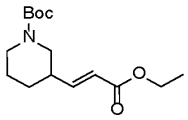
Name	Structure	NMR	LCMS
N-(2-chlorophenyl)-7-[(E)-3-(4-piperidyl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.37-7.27 (m, 2H), 6.70 (dd, *J* = 15.2, 8.4 Hz, 1H), 6.55 (d, *J* = 15.2 Hz, 1H), 4.92-4.70 (m, 2H), 4.30-4.29 (m, 2H), 4.01-3.95 (m, 2H), 2.95-2.67 (m, 2H), 2.56-2.54 (m, 1H), 2.33-2.26 (m, 2H), 1.65 (d, *J* = 12.4 Hz, 2H), 1.29-1.22 (m, 2H).	LCMS: m/z 414.2 [M+H]$^+$

General method F

Example 77. Synthesis of N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide

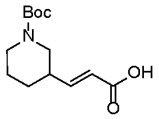


Step 1.1 Synthesis of tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]piperidine-1-carboxylate



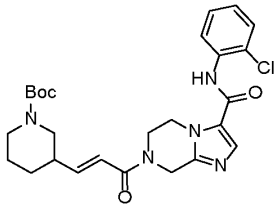
[0891] To a solution of NaH (450.13 mg, 11.25 mmol, 60% purity, 1.2 eq) in THF (20 mL) was added ethyl 2-diethoxyphosphorylacetate (2.52 g, 11.25 mmol, 2.23 mL, 1.2 eq) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl 3-formylpiperidine-1-carboxylate (2 g, 9.38 mmol, 1 eq) in THF (20 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 1 hr. TLC indicated tert-butyl 3-formylpiperidine-1-carboxylate was consumed completely and one new spot formed. The reaction mixture was cooled to 0°C. The reaction mixture was quenched with sat. aq. NH_4Cl (160 mL) at 0°C, and then diluted with EtOAc (80 mL x 3). The combined organic phase was washed with brine (80 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~24% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop- 1-enyl]piperidine-1-carboxylate (2.1 g, 7.41 mmol, 79.03% yield) as yellow oil. LCMS: m/z 228.1 $[M-56+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.82-6.76 (m, 1H), 5.93-5.89 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.70-3.64 (m, 2H), 2.93-2.90 (m, 2H), 2.32 (s, 1H), 1.79-1.77 (m, 2H), 1.38 (s, 9H), 1.36-1.33(m, 2H), 1.16 (t, J = 7.2 Hz, 3H).

Step 1.2 Synthesis of (E)-3-(1-tert-butoxycarbonyl-3-piperidyl)prop-2-enoic acid



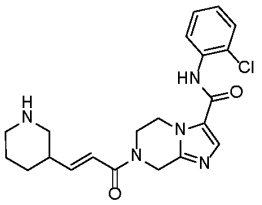
[0892] To a solution of tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]piperidine-1-carboxylate (2.1 g, 7.41 mmol, 1 eq) in EtOH (20 mL) was added dropwise a solution of $LiOH.H_2O$ (932.98 mg, 22.23 mmol, 3 eq) in H_2O (10 mL) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]piperidine-1-carboxylate was consumed completely and one main peak with desired m/z. The reaction mixture was cooled to 0°C, and adjusted pH to 4-5 with HCl (1 M) at 0°C. The reaction mixture was diluted with EtOAc (30 mL x 5). The combined organic phase was washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (E)-3-(1-tert-butoxycarbonyl-3-piperidyl)prop-2-enoic acid (1.8 g, 7.05 mmol, 95.13% yield) as yellow oil. LCMS: m/z 254.1 $[M-H]^-$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.70-6.64 (m, 1H), 5.83-5.79 (m, 1H), 3.77-3.70 (m, 2H), 2.88-2.83 (m, 2H), 2.26-2.25 (m, 1H), 1.77-1.56 (m, 2H), 1.38 (s, 9H), 1.33-1.30 (m, 2H).

Step 1.3 Synthesis of tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]piperidine-1-carboxylate



[0893] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (200 mg, 638.61 μmol, 1 eq, HCl) in DCM (3 mL) were added (E)-3-(1-tert-butoxycarbonyl-3-piperidyl)prop-2-enoic acid (195.65 mg, 766.33 μmol, 1.2 eq), DIEA (247.60 mg, 1.92 mmol, 333.69 μL, 3 eq), HOBt (172.58 mg, 1.28 mmol, 2 eq) and EDCI (183.63 mg, 957.91 μmol, 1.5 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 5 hrs. LCMS showed N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide was consumed completely and desired mass was detected. The reaction mixture was poured into water (6 mL) and stirred for 2 min at 25°C. The mixture was extracted with ethyl acetate (3 mL x 5). The combined organic phase was washed with brine (3 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 45 mL/min) to give tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]piperidine-1-carboxylate (300 mg, 583.64 μmol, 91.39% yield) as yellow oil. LCMS: m/z 514.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.86 (s, 1H), 7.55-7.53 (m, 2H), 7.52-7.51 (m, 1H), 7.37-7.35 (m, 1H), 6.66 (s, 2H), 4.93-4.74 (m, 2H), 4.31-4.30 (m, 2H), 4.01-3.77 (m, 2H), 3.75-3.72 (m, 1H), 2.88-2.84 (m, 2H), 2.33-2.32 (m, 2H), 1.98-1.80 (m, 2H), 1.39 (s, 9H), 1.36-1.34 (m, 2H).

Step 1.4 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide

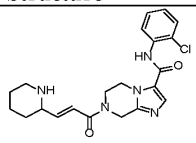


[0894] To a solution of tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]piperidine-1-carboxylate (280 mg, 544.73

μmol, 1 eq) in DCM (2 mL) was added dropwise TFA (1.54 g, 13.46 mmol, 1 mL, 24.71 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hr. LCMS showed tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]piperidine-1-carboxylate was consumed completely and one main peak with desired m/z. The reaction mixture was cooled to 0°C. The reaction mixture was adjusted pH to 7 with sat. aq. $NaHCO_3$ at 0°C, then concentrated under educed pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (126.4 mg, 303.04 μmol, 55.63% yield, 99.23% purity) as a white solid. LCMS: m/z 414.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.31 (td, J = 8 Hz, 2 Hz, 1H), 6.70-6.66 (m, 1H), 6.61 (m, 1H), 4.92-4.73 (m, 2H), 4.30-4.27 (m, 2H), 4.01-3.93 (m, 2H), 2.93-2.85 (m, 2H), 2.40-2.33 (m, 2H), 2.32-2.27 (m, 1H), 1.80-1.78(m, 1H), 1.54-1.52 (m, 1H), 1.35-1.29 (m, 2H).

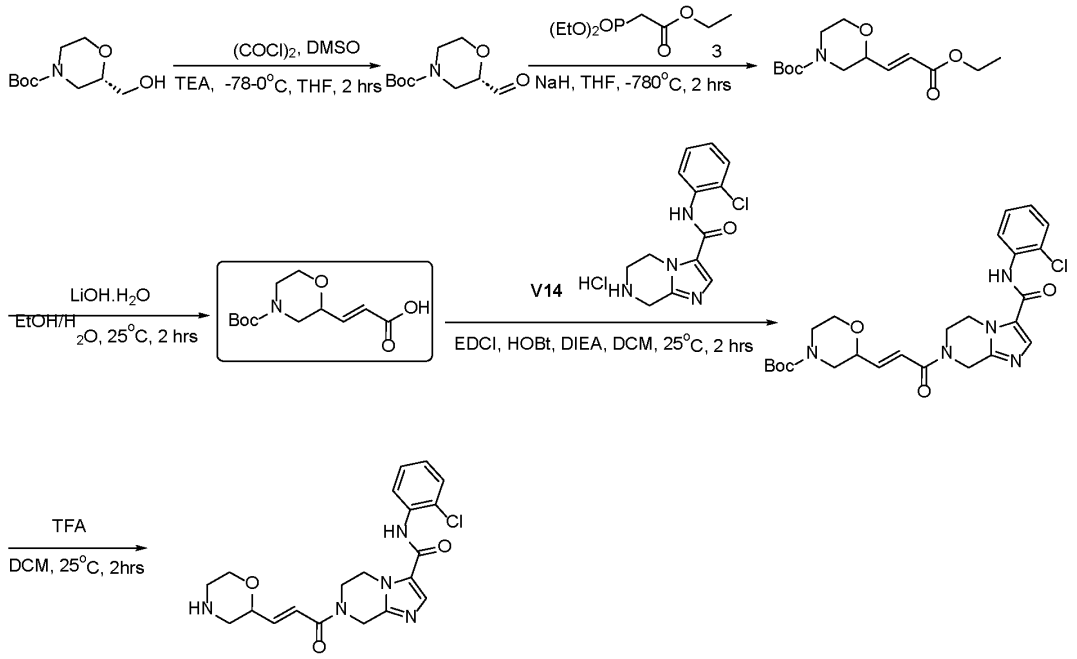
[0895] Compounds in Table C were synthesized following the procedure for N-(2-chlorophenyl)-7-[(E)-3-(3-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table C

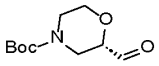
Name	Structure	NMR	LCMS
N-(2-chlorophenyl)-7-[(E)-3-(2-piperidyl)prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.6 Hz, 2H), 7.36 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8 Hz, 1.6 Hz, 1H), 6.72-6.69 (m, 1H), 6.68-6.67 (m, 1H), 4.92-4.74 (m, 2H), 4.30-4.27 (m, 2H), 4.01-4.00 (m, 2H), 3.18-3.17 (m, 1H), 2.97-2.94 (m, 1H), 2.53-2.52 (m, 1H), 1.75-1.72 (m, 2H), 1.69-1.66 (m, 1H), 1.33-1.30 (m, 2H), 1.11-1.07 (m, 1H).	LCMS: m/z 414.2 $[M+H]^+$

General method G

Example 78. Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2R)-morpholin-2-yl]prop-2 -enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

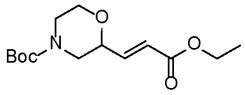


Step 1.1 Synthesis of tert-butyl rac-(2S)-2-formylmorpholine-4-carboxylate



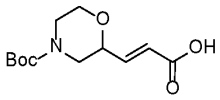
[0896] To a solution of oxalyl dichloride (876.31 mg, 6.90 mmol, 604.35 μL, 1.5 eq) in DCM (10 mL) was added dropwise DMSO (647.33 mg, 8.28 mmol, 647.33 μL, 1.8 eq) at -78°C, the reaction mixture was stirred at -78°C for 0.5 hr under N_2 atmosphere, then the solution of tert-butyl rac-(2S)-2-(hydroxymethyl)morpholine-4-carboxylate (1.00 g, 4.60 mmol, 1 eq) in DCM (10 mL) was added dropwise into the reaction mixture at -78°C, the reaction mixture was stirred at 25°C for 1 hr, then the TEA (2.33 g, 23.01 mmol, 3.20 mL, 5 eq) was added into the mixture at -78°C. The mixture was slowly warmed to 25°C and stirred at 25°C for 0.5hr. TLC indicated tert-butyl rac-(2S)-2-(hydroxymethyl)morpholine-4-carboxylate was consumed completely and one new spot formed. The reaction mixture was quenched by addition H_2O (5mL) at 25 °C, and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 50 mL/min). Compound tert-butyl rac-(2S)-2-formylmorpholine-4-carboxylate (0.4 g, 1.86 mmol, 40.37% yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.65 (s, 1H), 4.04-3.78 (m, 4H), 3.67-3.61 (m, 1H), 3.08-2.90 (m, 2H), 1.48 (s, 1H).

Step 1.2 Synthesis of tert-butyl rac-(2R)-2-[rac-(E)-3-ethoxy-3-oxo-prop-1-enyl]morpholine-4- carboxylate



[0897] To a solution of NaH (80.28 mg, 2.01 mmol, 60% purity, 1.2 eq) in THF (4 mL) was added dropwise ethyl 2-diethoxyphosphorylacetate (449.95 mg, 2.01 mmol, 398.19 µL, 1.2 eq) at -78°C under N_2 atmosphere. The reaction mixture was stirred at -78 °C for 10 min. Then a solution of tert-butyl rac-(2S)-2-formylmorpholine-4-carboxylate (360.00 mg, 1.67 mmol, 1 eq) in THF (4 mL) was added dropwise into the reaction mixture at -78°C, then the reaction mixture was warmed to 25°C, then the reaction mixture was stirred at 25°C for 2 hrs. TLC indicated tert-butyl rac-(2S)-2-formylmorpholine-4-carboxylate was consumed completely and one new spot formed. The reaction mixture was quenched by addition H_2O (10 mL) at 25°C, and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 36 mL/min). Compound tert-butyl rac-(2R)-2-[rac-(E)-3-ethoxy-3-oxo-prop-1-enyl] morpholine-4-carboxylate (0.24 g, 841.12 µmol, 50.29% yield) was obtained as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.83 (dd, *J* = 15.6 Hz, 4.0 Hz, 1H), 6.13 (dd, *J* = 15.6 Hz, 1.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.09-4.04 (m, 1H), 3.96-3.92 (m, 1H), 3.89-3.85 (m, 1H), 3.58 (td, *J* =11.6 Hz, 2.4 Hz, 1H), 3.00-2.94 (m, 1H), 2.68-2.67 (m, 1H), 1.48 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H).

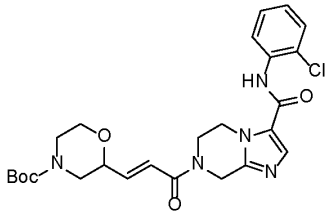
Step 1.3 Synthesis of (E)-3-[(2R)-4-tert-butoxycarbonylmorpholin-2-yl]prop-2-enoic acid



[0898] To a solution of tert-butyl (2R)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]morpholine-4-carboxylate (0.24 g, 841.12 µmol, 1 eq) in EtOH (2 mL) and H_2O(1 mL) was added $LiOH.H_2O$ (70.59 mg, 1.68 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove the EtOH, and adjusted pH = 3 by 1 N HCl, and extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (15 mL * 1), dried over [Na_2SO_4], filtered and concentrated to give (E)-3-[(2R)-4-tert-butoxycarbonylmorpholin-2-yl]prop-2-enoic acid (0.15 g, 583.02 µmol, 69.31% yield) as a

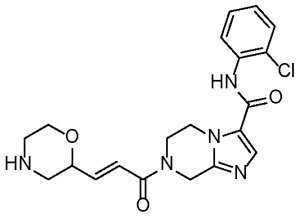
yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.83 (dd, *J* = 16.0 Hz, 4.0 Hz, 1H), 6.15 (dd, *J* = 15.6 Hz, 1.6 Hz, 1H), 4.11-4.03 (m, 2H), 3.97-3.94 (m, 1H), 3.92-3.87 (m, 2H), 3.59 (td, *J* = 12.0 Hz, 2.4 Hz, 1H), 3.00-2.94 (m, 1H), 1.48 (s, 9H).

Step 1.4 Synthesis of tert-butyl (2R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H- imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate



[0899] To a reaction mixture of (E)-3-[(2R)-4-tert-butoxycarbonylmorpholin-2-yl]prop-2-enoic acid (0.15 g, 583.02 µmol, 1.2 eq), N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (134.44 mg, 429.29 µmol, 1 eq, HCl) in DCM (2 mL) were added EDCI (186.28 mg, 971.70 µmol, 2 eq), HOBt (98.47 mg, 728.77 µmol, 1.5 eq) and DIEA (188.38 mg, 1.46 mmol, 253.88 µL, 3 eq) at 25°C and then the reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4g Sepa Flash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 36 mL/min). Compound tert-butyl (2R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (0.3 g, crude) was obtained as a yellow solid. LCMS: m/z 516.3 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.79-6.64 (m, 2H), 4.93-4.71 (m, 2H), 4.36-4.29 (m, 2H), 4.09-3.84 (m, 6H), 3.73-3.70 (m, 1H), 3.50-3.43 (m, 2H), 1.41 (s, 9H).

Step 1.5 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2R)-morpholin-2-yl]prop-2 -enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

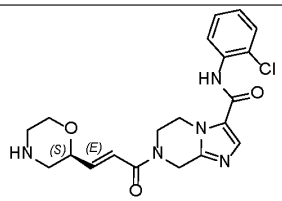


[0900] To a solution of tert-butyl (2R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (0.3 g, 581.41

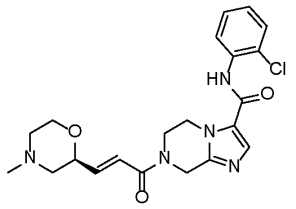
μmol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 23.15 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The 0.1 g crude was purified by prep-HPLC (column: Waters Xbridge Prep OBD C_{18} 150*40mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 5%-45% B over 8.0 min). Compound N-(2-chlorophenyl)-7-[(E)-3-[(2R)-morpholin-2-yl]prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (26 mg, 62.52 μmol, 10.75% yield) was obtained as a white solid. LCMS: m/z 416.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (m, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.70-6.62 (m, 2H), 4.87-4.74 (m, 2H), 4.32-4.28 (m, 2H), 4.06-3.98 (m, 3H), 3.80 (d, J = 10.8 Hz, 1H), 3.50 (td, J = 10.8 Hz, 3.2 Hz, 1H), 3.90 (d, J = 12.4 Hz, 1H), 2.70-2.59 (m, 2H), 2.36 (t, J = 10.0 Hz, 1H).

[0901] Compounds in Table D were synthesized following the procedure for N-(2-chlorophenyl)-7-[(E)-3-[(2R)-morpholin-2-yl]prop-2 -enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table D

Name	Structure	NMR	LCMS
N-(2-chlorophenyl)-7-[(E)-3-[(2S)-morpholin-2-yl]prop-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.86 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz,2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.65-6.64 (m, 2H), 4.89-4.74 (m, 2H), 4.32-4.28 (m, 2H), 4.06-4.03(m, 1H), 3.98-3.95 (m, 2H), 3.81-3.78 (m, 1H), 3.49 (td, J = 12 Hz, 3.2 Hz, 1H), 2.92-2.89 (m, 1H), 2.66-2.62 (m, 2H), 2.39-2.35 (m, 1H).	LCMS: m/z 416.2 $[M+H]^+$

Example 79. Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2S)-4-methylmorpholin-2-yl]prop -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

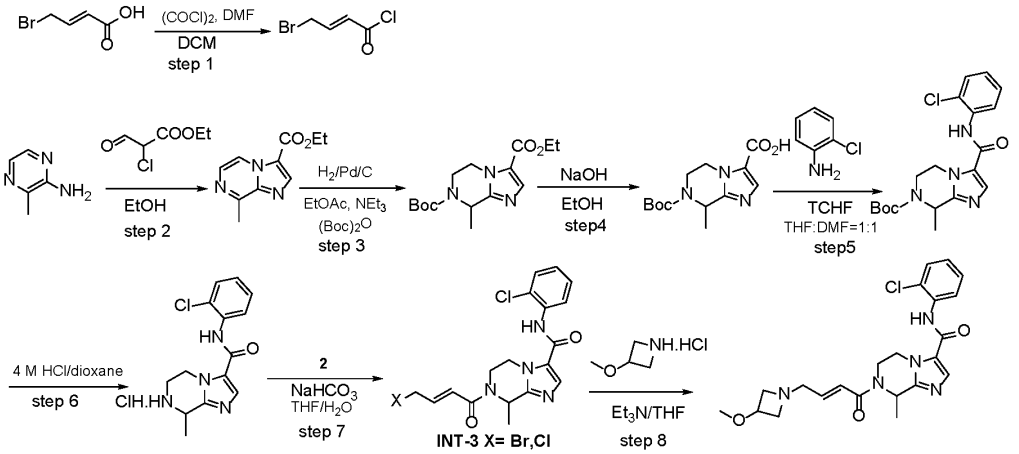


[0902] To a solution of N-(2-chlorophenyl)-7-[(E)-3-[(2S)-morpholin-2-yl]prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide (180 mg, 432.82 μmol, 1 eq) in DCE (2 mL) was added paraformaldehyde (300 mg) in one portion at 25°C. The reaction mixture

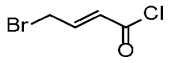
was stirred at 25°C for 15 min. Then $NaBH(OAc)_3$ (183.47 mg, 865.65 μmol, 2 eq) was added to the reaction mixture in one portion at 25°C. The reaction mixture was stirred at 25°C for 1 hr. LCMS showed N-(2-chlorophenyl)-7-[(E)-3-[(2S)-morpholin-2-yl]prop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide was consumed completely and one main peak with desired m/z. The reaction mixture was cooled to 0°C. The reaction mixture was poured into ice-water (3 mL) and stirred for 2 min, and concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-65% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-[(2S)-4-methylmorpholin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (51.5 mg, 119.80 μmol, 27.68% yield, 96.30% purity) as a white solid. LCMS: m/z 430.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.86 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz,2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz,1H), 7.28 (td, J = 8 Hz, 1.6 Hz,1H), 6.70-6.67 (m, 2H), 4.89-4.74 (m, 2H), 4.32-4.27 (m, 2H), 4.16-4.14 (dt, J = 6 Hz, 2.4 Hz,1H), 3.98-3.94 (m, 2H), 3.86-3.83 (m, 1H), 3.57 (td, J = 11.2 Hz, 2.4 Hz, 1H), 2.82 (d, J = 11.6 Hz, 1H), 2.60 (d, J = 11.2 Hz, 1H), 2.18 (s, 3H), 1.99 (td, J = 11.2 Hz, 3.2 Hz, 1H), 1.72 (t, J = 10.4 Hz, 1H).

General method H

Example 80. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide

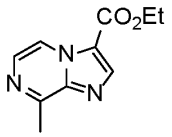


Step 1. Synthesis of (E)-4-bromobut-2-enoyl chloride



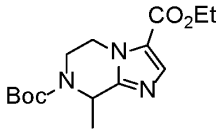
[0903] To a solution of (*E*)-4-bromobut-2-enoic acid (0.3 g, 1.82 mmol) and DMF (1 drop) in dichloromethane (8 mL) at 0 °C was added dropwise Oxalyl chloride (461.59 mg, 3.64 mmol, 317.25 μL) and the mixture was stirred at 0°C under N_2 for 1 hour. The reaction solution was concentrated, the residue was used directly for the next step.

Step 2. Synthesis of ethyl 8-methylimidazo[1,2-a]pyrazine-3-carboxylate



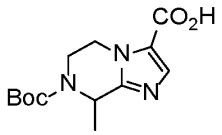
[0904] To a solution of 3-methylpyrazin-2-amine (4 g, 36.65 mmol) in ethanol (40 mL) was added ethyl 2-chloro-3-oxo-propanoate (9.93 g, 65.98 mmol). The mixture was stirred at 80°C under N_2 overnight and concentrated. The residue was purified by flash chromatography (eluting with dichloromethane: methanol=0-8%) to give ethyl 8-methylimidazo[1,2-*a*]pyrazine-3-carboxylate (7.0 g, 33.43 mmol, 91.20% yield, 98% purity) as brown solid. LCMS: *m/z* 206.1 $[M+H]^+$.

Step 3. Synthesis of 7-(tert-butyl) 3-ethyl 8-methyl-5,6-dihydroimidazo[1,2-a]pyrazine-3,7(8H)-dicarboxylate



[0905] To a solution of ethyl 8-methylimidazo[1,2-*a*]pyrazine-3-carboxylate (3.0 g, 14.62 mmol) in ethyl acetate (80 mL) was added triethylamine (2.95 g, 29.24 mmol), $(Boc)_2O$ (4.78 g, 21.93 mmol) and 10% Palladium on carbon wet (1.4 g). The mixture was stirred at room temperature under H_2 overnight, filtered and concentrated. The residue was purified by flash chromatography (eluting with dichloromethane: methanol=0-5%) to give 7-(*tert-butyl*) 3-ethyl 8-methyl-5,6-dihydroimidazo[1,2-*a*]pyrazine-3,7(8*H*)-dicarboxylate (2.5 g, 7.90 mmol, 54.06% yield, 97.8% purity) as yellow solid. LCMS: *m/z* 310.0 $[M+H]^+$.

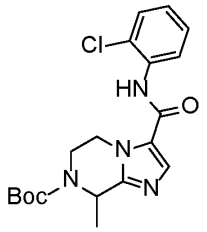
Step 4. Synthesis of 7-(tert-butoxycarbonyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid



[0906] To a solution of 7-(*tert-butyl*) 3-ethyl 8-methyl-5,6-dihydroimidazo[1,2-*a*]pyrazine-3,7(8*H*)-dicarboxylate (6.88 g, 22.24 mmol) in ethanol/water(50 mL/ 50 mL) was added

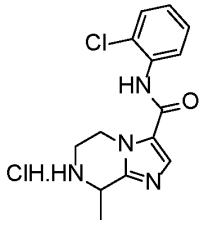
NaOH (2.67 g, 66.72 mmol, 1.25 mL). The mixture was stirred at room temperature overnight. The reaction solution was concentrated and adjusted pH to 6 with 1M HCl. The water phase was purified by flash chromatography (eluting with 10 mmol NH_4HCO_3: CH_3CN= 0-10%) to give 7-*tert*-butoxycarbonyl-8-methyl-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxylic acid (8.5 g, crude) as yellow solid, which was used directly for the next step. LCMS: *m/z* 282.1 $[M+H]^+$.

Step 5. Synthesis of tert-butyl 3-((2-chlorophenyl)carbamoyl)-8-methyl-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate



[0907] To a solution of 7-*tert*-butoxycarbonyl-8-methyl-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxylic acid (3 g, 10.66 mmol) in mixture solvents THF/DMF (20 mL/ 20 mL) was added 2-chloroaniline (2.72 g, 21.33 mmol), N,N,N',N'-Tetramethylchloroformamidinium hexafluorophosphate (8.98 g, 31.99 mmol) and 4-Methylimidazole (2.63 g, 31.99 mmol, 2.58 mL). The mixture was stirred at room temperature under N_2 overnight and concentrated. The residue was purified by flash chromatography (eluting with 10 mmol NH_4HCO_3: CH_3CN=0- 50%) to give *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-8-methyl-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-7-carboxylate (2.8 g, 7.04 mmol, 66.03% yield, 98.3% purity) as yellow oil. LCMS: *m/z* 391.1 $[M+H]^+$.

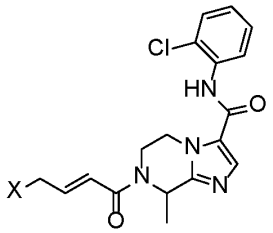
Step 6. Synthesis of N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride



[0908] To a solution of *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-8-methyl-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-7-carboxylate (2.8 g, 7.16 mmol) in dichloromethane (30 mL) was added HCl in dioxane (4M, 4 mL) and the mixture was stirred at room temperature overnight and concentrated. The residue was washed by petrol ether (15 mL) and dichloromethane (5 mL) to give *N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo

[1,2-*a*]pyrazine-3-carboxamide hydrochloride (2.8 g, crude, Cl) as white solid. LCMS: *m/z* 291.1 $[M+H]^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.32 (s, 1H), 7.67 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 (td, *J* = 7.7, 1.5 Hz, 1H), 7.31 (td, *J* = 7.7, 1.6 Hz, 1H), 5.11 (q, *J* = 6.9 Hz, 1H), 4.99 – 4.92 (m, 1H), 4.80 – 4.69 (m, 1H), 4.03 – 3.95 (m, 1H), 3.84 – 3.73 (m, 1H), 1.90 (d, *J* = 6.9 Hz, 3H).

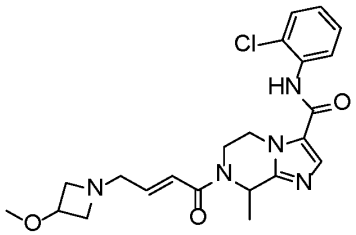
Step 7. Synthesis of (E)-7-(4-bromobut-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



INT-3 X= Br,Cl

[0909] To a solution of *N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride (0.4 g, 1.38 mmol) in THF (6 mL) was added *aq. sat.* $NaHCO_3$ (3 mL) and the mixture was stirred at room temperature for 10 min. (*E*)-4-bromobut-2-enoyl chloride (378.54 mg, 2.06 mmol) in dichloromethane (2 mL) was added dropwise at 0 °C and the mixture was stirred at room temperature for 1 hour. The organic phase was separated and used in the next step directly. LCMS: *m/z* 437.0$[M+H]^+$.

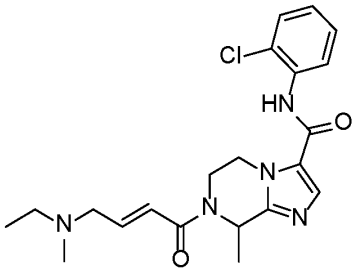
Step 8. Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[0910] To a solution of (*E*)-7-(4-bromobut-2-enoyl)-*N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (**8**) (0.45 g, 1.03 mmol) in THF (10 mL) was added 3-methoxyazetidine (254.10 mg, 2.06 mmol, CL) and DIPEA (531.48 mg, 4.11 mmol, 716.28 μL). The mixture was stirred at room temperature under N_2 overnight and concentrated. The residue was purified by flash chromatography (eluting with 10mmol NH_4HCO_3: CH_3CN=0 - 30%) and Prep-HPLC under basic condition to give (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-

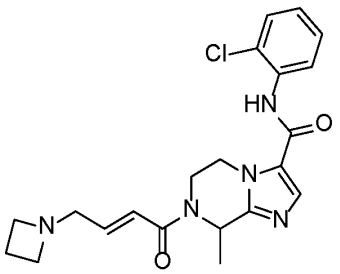
tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (0.046 g, 103.10 μmol, 10.03% yield, 99.5% purity) as white solid. LCMS: *m/z* 444.3 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.21 (m, 1H), 6.86 – 6.61 (m, 2H), 5.59 (d, *J* = 101.0 Hz, 1H), 4.74 (d, *J* = 11.4 Hz, 1H), 4.45 – 3.65 (m, 6H), 3.43 – 3.36 (m, 2H), 3.28 – 3.24 (m, 3H), 3.19 – 3.07 (m, 2H), 1.62 (d, *J* = 34.3 Hz, 3H).

Example 81. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0911] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-methylethanamine for 3-methoxyazetidine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 416.2$[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.28 – 7.22 (m, 1H), 6.96 – 6.73 (m, 2H), 5.80 – 5.36 (m, 1H), 4.74 (dd, *J* = 13.8, 2.7 Hz, 1H), 4.52 – 3.64 (m, 2H), 3.48 – 3.31 (m, 3H), 2.67 – 2.56 (m, 2H), 2.39 – 2.32 (m, 3H), 1.63 (d, *J* = 29.3 Hz, 3H), 1.18 – 1.12 (m, 3H).

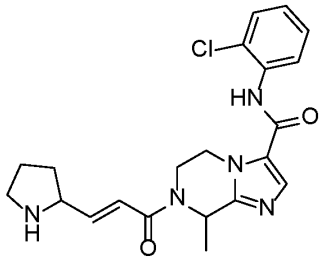
Example 82. Synthesis of (*E*)-7-(4-(azetidin-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0912] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of azetidine for 3-methoxyazetidine to provide the

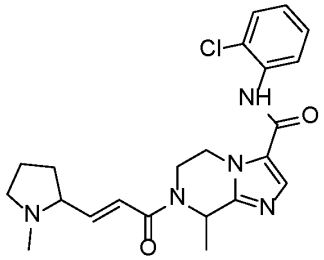
product (*E*)-7-(4-(azetidin-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.81 – 6.60 (m, 2H), 5.58 (d, *J* = 113.1 Hz, 1H), 4.74 (dd, *J* = 13.5, 2.4 Hz, 1H), 4.52 – 3.58 (m, 3H), 3.50 – 3.37 (m, 6H), 2.28 – 2.13 (m, 2H), 1.62 (d, *J* = 31.3 Hz, 3H).

Example 83. Synthesis of *N*-(2-chlorophenyl)-8-methyl-7-((*E*)-3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



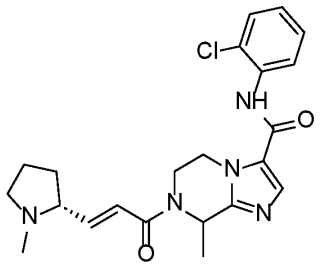
[0913] The method as described for the synthesis of (*S*,*E*)-*N*-(2-chlorophenyl)-7-(3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride for *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride to provide the product *N*-(2-chlorophenyl)-8-methyl-7-((*E*)-3-(pyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 [M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.5 Hz, 1H), 8.10 (s, 1H), 7.63 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.08 (td, *J* = 7.9, 1.5 Hz, 1H), 7.03 – 6.93 (m, 1H), 6.48 (d, *J* = 14.9 Hz, 1H), 6.01 – 4.87 (m, 1H), 4.81 – 4.71 (m, 1H), 4.40 – 3.10 (m, 3H), 3.11 – 2.90 (m, 2H), 2.10 – 1.95 (m, 1H), 1.90 – 1.72 (m, 2H), 1.63 (s, 3H), 1.57 – 1.45 (m, 2H).

Example 84. Synthesis of *N*-(2-chlorophenyl)-8-methyl-7-((*E*)-3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



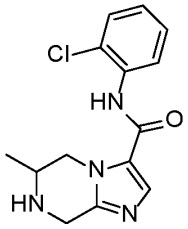
[0914] The method as described for the synthesis of (*S*,*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride for *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride to provide the product *N*-(2-chlorophenyl)-8-methyl-7-((*E*)-3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.10 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.08 (td, *J* = 7.9, 1.5 Hz, 1H), 6.90 (dd, *J* = 14.9, 7.3 Hz, 1H), 6.69 (s, 1H), 5.98 – 4.93 (m, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.55 – 2.78 (m, 4H), 2.38 (s, 4H), 2.18 – 1.69 (m, 7H).

Example 85. Synthesis of *N*-(2-chlorophenyl)-8-methyl-7-[(*E*)-3-[(2*R*)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



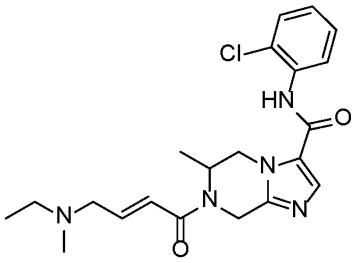
[0915] The method as described for the synthesis of (*R*,*E*)-*N*-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride for *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride to provide the product *N*-(2-chlorophenyl)-8-methyl-7-[(*E*)-3-[(2*R*)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.4 Hz, 1H), 8.10 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.08 (td, *J* = 7.9, 1.5 Hz, 1H), 6.89 (dd, *J* = 15.0, 7.5 Hz, 1H), 6.44 (d, *J* = 15.0 Hz, 1H), 5.21 (d, *J* = 149.0 Hz, 1H), 4.78 (dd, *J* = 13.8, 2.8 Hz, 1H), 4.33 – 4.02 (m, 1H), 3.83 – 3.03 (m, 2H), 2.79 (d, *J* = 7.7 Hz, 1H), 2.33 – 2.27 (m, 3H), 2.09 – 1.98 (m, 1H), 1.82 (dt, *J* = 12.4, 11.9 Hz, 2H), 1.66 (s, 6H).

Example 86. Synthesis of *N*-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



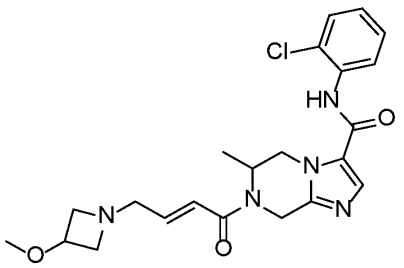
[0916] The method as described for the synthesis of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride was applied with substitution of 5-methylpyrazin-2-amine for pyrazin-2-amine to provide the product *N*-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 291.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.12 (s, 1H), 7.60 (s, 1H), 7.41 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.11 – 7.03 (m, 1H), 4.62 (dd, *J* = 13.1, 4.3 Hz, 1H), 4.29 (d, *J* = 16.6 Hz, 1H), 4.15 (d, *J* = 16.6 Hz, 1H), 3.76 (dd, *J* = 13.3, 10.6 Hz, 1H), 3.27 – 3.16 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H).

Example 87. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



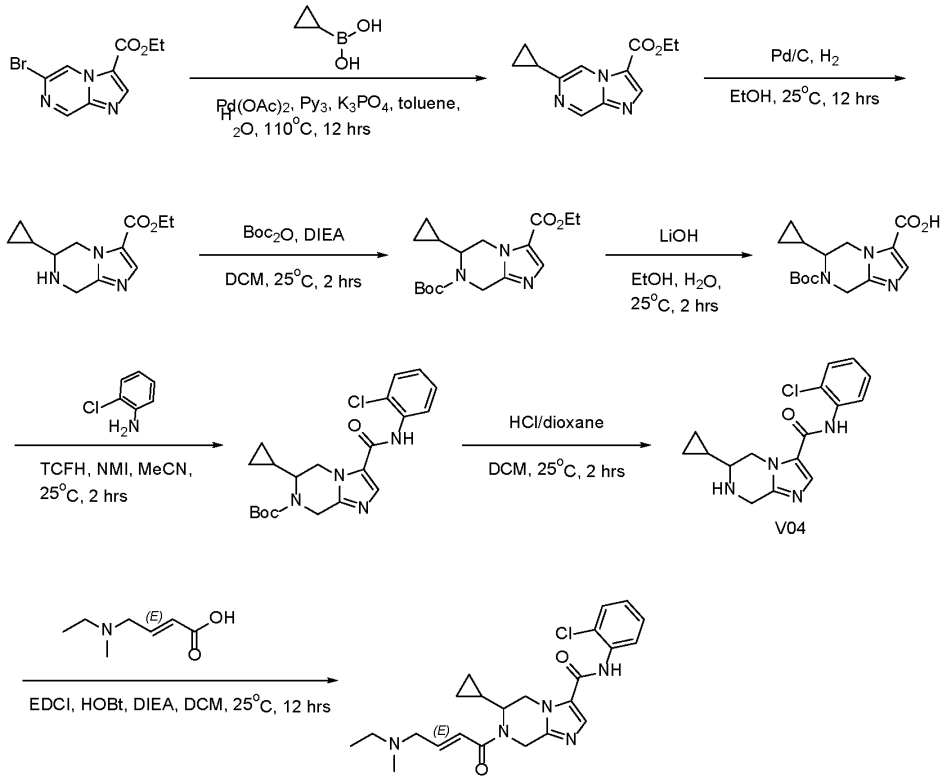
[0917] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide for *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 416.0[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.13 (s, 1H), 7.68 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.9 Hz, 1H), 6.48 (d, *J* = 14.8 Hz, 1H), 5.31 – 4.65 (m, 4H), 4.23 (dd, *J* = 13.7, 4.4 Hz, 1H), 3.20 (d, *J* = 5.2 Hz, 2H), 2.47 (q, *J* = 7.1 Hz, 2H), 2.26 (s, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H).

Example 88. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



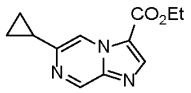
[0918] The method as described for the synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *N*-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide for *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride and 3-methoxyazetidine for *N*-methylethanamine to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxyazetidin-1-yl)but-2-enoyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 444.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.3, 1.2 Hz, 1H), 8.13 (s, 1H), 7.68 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.89 (dt, *J* = 15.1, 4.9 Hz, 1H), 6.43 (d, *J* = 15.3 Hz, 1H), 5.49 – 5.07 (m, 2H), 4.83 – 4.59 (m, 2H), 4.22 (dd, *J* = 13.5, 4.2 Hz, 1H), 4.08 (p, *J* = 5.8 Hz, 1H), 3.74 – 3.63 (m, 2H), 3.38 – 3.16 (m, 5H), 2.98 (t, *J* = 6.7 Hz, 2H), 1.25 (d, *J* = 6.8 Hz, 3H).

General method I



Example 89. Synthesis of N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

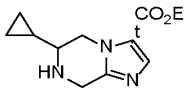
Step 1.1 Synthesis of ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate



[0919] To a reaction mixture of ethyl 6-bromoimidazo[1,2-a]pyrazine-3-carboxylate (3 g, 11.11 mmol, 1 eq), cyclopropylboronic acid (1.43 g, 16.66 mmol, 1.5 eq) in toluene (60 mL) and H_2O (3 mL) were added $Pd(OAc)_2$ (249.38 mg, 1.11 mmol, 0.1 eq), K_3PO_4 (8.25 g, 38.88 mmol, 3.5 eq), PCy_3 (622.98 mg, 2.22 mmol, 720.21 µL, 0.2 eq) at 25°C, and then the reaction mixture was heated to 110°C and stirred at 110°C for 12 hrs under N_2 atmosphere. LC-MS showed the reaction was completed. The reaction mixture was quenched by addition H_2O (5 mL) at 25°C, and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl

acetate/Petroleum ether gradient @ 50 mL/min) to give ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (1 g, 4.32 mmol, 38.93% yield) was obtained as a white solid. LCMS: m/z 231.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.17 (d, J = 1.2 Hz, 1H), 9.06 (d, J = 1.6 Hz, 1H), 8.37 (s, 1H), 4.41 (q, J = 7.2 Hz, 2H), 2.33-2.29 (m, 1H), 1.37 (t, J = 6.8 Hz, 1H), 0.99-0.93 (m, 4H).

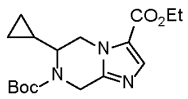
Step 1.2 Synthesis of ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate



[0920] The PtO_2 (0.2 g, 880.76 µmol, 0.2 eq) was added into flask stand-up bottom under Ar atmosphere at 25°C, then EtOH (20 mL) was added into flask stand-up bottom, then reaction mixture was added ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (0.96 g, 4.15 mmol, 1 eq) and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 25°C for 12 hrs under H_2 atmosphere. LC-MS showed the reaction was completed. The reaction solution was filtered and the filtration was concentrated to give ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxylate (0.7 g, 2.98 mmol, 71.67% yield) as a black oil. LCMS: m/z 236.1 $[M+H]^+$

^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (s, 1H), 4.39-4.36 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.00-3.96 (m, 1H), 3.83-3.73 (m, 2H), 2.31-2.25 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.88-0.83 (m, 1H), 0.48-0.46 (m, 2H), 0.34-0.31 (m, 2H).

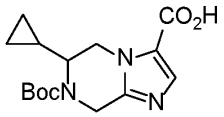
Step 1.3 Synthesis of O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate



[0921] To a solution of ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (0.7 g, 2.98 mmol, 1 eq) in DCM (7 mL) were added Boc_2O (779.18 mg, 3.57 mmol, 820.19 µL, 1.2 eq) and DIEA (576.78 mg, 4.46 mmol, 777.33 µL, 1.5 eq). The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed reaction was completed. The reaction mixture was quenched by addition H_2O (5 mL) at 25 °C, and adjusted the reaction mixture pH = 5 by sat. aq. citric acid and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3,7-dicarboxylate (1 g, crude) as a white solid. LCMS:

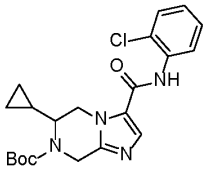
m/z 336.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (s, 1H), 4.87 (d, J = 18 Hz, 1H), 4.63 (d, J = 14 Hz, 1H), 4.45-4.40 (m, 1H), 4.26 (q, J = 6.8 Hz, 2H), 4.13 (dd, J = 4.8 Hz, 14 Hz, 1H), 3.87-3.86 (m, 1H), 1.44 (s, 9H), 0.90-0.85 (m, 1H), 0.47-0.34 (m, 4H).

Step 1.4 Synthesis of 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



[0922] To a solution of O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate (1 g, 2.98 mmol, 1 eq) in EtOH (8 mL) and H_2O (2 mL) was added LiOH.H_2O (375.35 mg, 8.94 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to remove EtOH, then the reaction mixture was added H_2O (5 mL) then the reaction mixture was adjusted pH = 3-4 by 1 N HCl and extracted with DCM: isopropanol =3:1 (10 mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (1 g, crude) as a yellow oil. LCMS: m/z 308.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.76 (s, 1H), 7.62 (s, 1H), 4.84 (d, J = 17.6 Hz, 1H), 4.64 (d, J = 13.6 Hz, 1H), 4.20 (d, J = 17.6 Hz, 1H), 4.08 (dd, J = 13.6 Hz, 4.4 Hz, 1H), 3.84-3.85 (m, 1H), 1.44 (s, 9H), 0.83-0.80 (m, 1H), 0.48-0.35 (m, 4H).

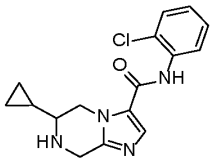
Step 1.5 Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro-5H -imidazo[1,2-a]pyrazine-7-carboxylate



[0923] To a solution of 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (1 g, 3.25 mmol, 1 eq) in MeCN (10 mL) and DMF(10 mL) were added 2-chloroaniline (830.15 mg, 6.51 mmol, 686.08 µL, 2 eq), TCFH (2.74 g, 9.76 mmol, 3 eq) and NMI (801.38 mg, 9.76 mmol, 778.04 µL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was completed. The reaction mixture was quenched by addition H_2O (10 mL) at 25 °C, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over

Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate (0.8 g, 1.92 mmol, 58.98% yield) was obtained as a yellow oil. LCMS: m/z 317.2 $[M-100]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.04 (s, 1H), 8.08 (s, 1H), 7.58-7.54 (m, 2H), 7.39 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.31 (td, J = 8.0 Hz, 1.6 Hz, 1H), 4.98 (d, J = 17.6 Hz, 1H), 4.78 (d, J = 13.6 Hz, 1H), 4.53-4.49 (m, 1H), 4.16 (dd, J = 4.8 Hz, 14.0 Hz, 1H), 3.86-3.85 (m, 1H), 1.44 (s, 9H), 0.99-0.97 (m, 1H), 0.48-0.36 (m, 4H).

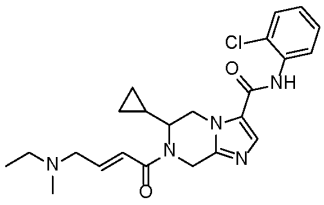
Step 1.6 Synthesis of N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V04)



V04

[0924] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro-5H -imidazo[1,2-a]pyrazine-7-carboxylate (0.8 g, 1.92 mmol, 1 eq) in DCM (4 mL) was added HCl/dioxane (4 M, 4 mL, 8.34 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. TLC indicated the reaction was completed and one new spot formed. The reaction mixture was concentrated under reduced pressure to give N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V04) (0.6 g, 1.89 mmol, 98.70% yield) as a white solid.

Step 1.7 Synthesis of N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

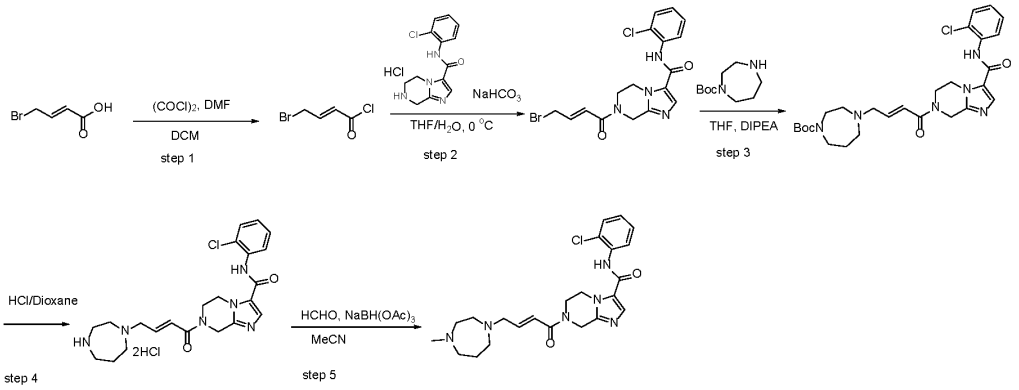


[0925] To a reaction mixture of N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (600 mg, 1.70 mmol, 1 eq, HCl), (E)-4-[ethyl(methyl)amino] but-2-enoic acid (486.40 mg, 3.40 mmol, 2 eq) in DCM (10 mL) were added EDCI (716.34 mg, 3.74 mmol, 2.2 eq), HOBt (504.91 mg, 3.74 mmol, 2.2 eq) and DIEA (658.56 mg, 5.10 mmol, 887.54 μL, 3 eq) at 25°C, and then the reaction mixture was stirred at 25°C for 12 hrs.

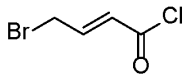
LC-MS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40mm*10um;mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%-50% B over 8.0 min) to give 55 mg (90% purity), then the crude was purified by prep-TLC (SiO_2, DCM: MeOH = 6:1). Compound N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (21 mg, 47.52 μmol, 2.80% yield) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.93 (s, 1H), 7.66-7.39 (m, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.70-6.69 (m, 2H), 5.20 (d, J = 18.0 Hz, 2H), 4.77 (d, J = 13.6 Hz, 2H), 4.40-4.37 (m, 1H), 4.19-4.03 (m, 2H), 3.13 (s, 2H), 2.37 (q, J = 6.8 Hz, 2H), 1.01-0.97 (m, 4H), 0.46-0.19 (m, 4H).

General method J

Example 90. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

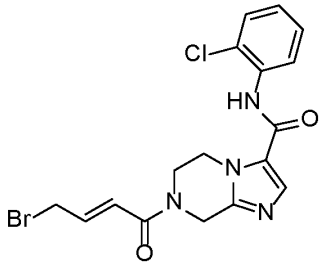


Step 1. Synthesis of (E)-4-bromobut-2-enoyl chloride



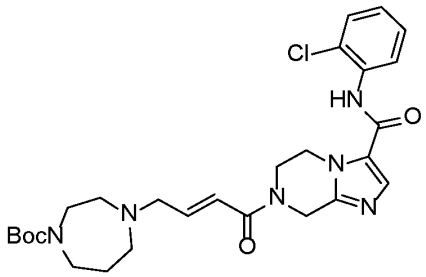
[0926] To a solution of (*E*)-4-bromobut-2-enoic acid (1.24 g, 7.5 mmol) in DCM (15 mL) were added oxalyl dichloride (1.43 g, 11.25 mmol, 981.39 μL) and DMF (10.96 mg, 150.00 μmol, 11.61 μL). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated to give (*E*)-4-bromobut-2-enoyl chloride (1.38 g, crude) as light-yellow oil. The oil was used for subsequent step without further purification.

Step 2. Synthesis of (E)-7-(4-bromobut-2-enoyl)-N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



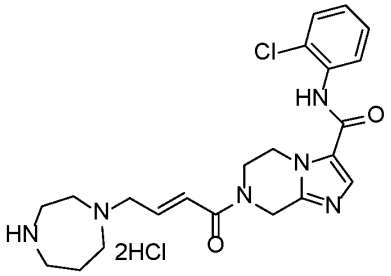
[0927] To a solution of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1.57 g, 5 mmol, CL) in THF (20 mL) was added sat. Sodium bicarbonate (10 mL) and the mixture was stirred at room temperature for 5min. Then (*E*)-4-bromobut-2-enoyl chloride (1.38 g, 7.50 mmol) in THF (5 mL) was added dropwise at 0°C, then warmed to room temperature and stirred for 2h. The organic phase (in 40 mL THF) was seperated and used in the next step directly. LCMS: *m/z* 425.0 $[M+H]^+$.

Step 3. Synthesis of tert-butyl 4-[(E)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate



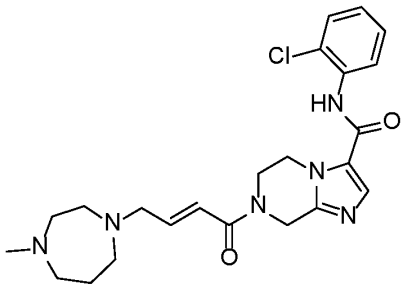
[0928] To a solution of 7-[(*E*)-4-bromobut-2-enoyl]-N-(2-chlorophenyl)-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (0.2 M, 15.00 mL) in THF (10 mL) was added *tert*-butyl 1,4-diazepane-1-carboxylate (1.20 g, 6.00 mmol, 1.18 mL) and DIPEA (1.94 g, 15.00 mmol, 2.61 mL). The resulting mixture was stirred at room temperature for 2h. The reaction mixture was concentrated and the residue was purified by Prep-HPLC under basic condition to give *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (0.5 g, 920.72 μmol, 30.69% yield) as a white solid. LCMS: *m/z* 543.1 $[M+H]^+$. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.37 – 7.28 (m, 1H), 7.14 – 7.05 (m, 1H), 6.97 (dt, *J* = 15.2, 5.7 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.17 – 3.91 (m, 2H), 3.57 – 3.40 (m, 4H), 3.30 (d, *J* = 5.4 Hz, 2H), 2.72 – 2.56 (m, 4H), 1.92 – 1.76 (m, 2H), 1.47 (s, 9H).

Step 4. Synthesis of N-(2-chlorophenyl)-7-[(E)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[0929] *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (0.5 g, 920.72 µmol) was dissolved in DCM (3 mL) and HCl/Dioxane (4 M, 3 mL). The resulting mixture was stirred at room temperature for 2 h and concentrated to give *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide (420 mg, 876.09 µmol, 95.15% yield, CL) as a light-yellow solid. LCMS: *m/z* 443.1[M+H]$^+$.^{1}H NMR (400 MHz, Methanol-d_4) δ 8.34 (s, 1H), 7.67 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 (td, *J* = 7.7, 1.5 Hz, 1H), 7.31 (td, *J* = 7.8, 1.6 Hz, 1H), 7.19 (d, *J* = 15.3 Hz, 1H), 6.96 – 6.82 (m, 1H), 5.42 – 5.12 (m, 2H), 4.76 – 4.53 (m, 2H), 4.34 – 4.09 (m, 4H), 3.90 – 3.41 (m, 8H), 2.44 – 2.31 (m, 2H).

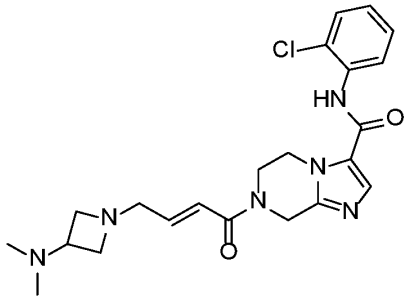
Step 5. Synthesis of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide hydrochloride



[0930] To a solution of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (200 mg, 451.53 µmol) in Acetonitrile (5 mL) was added 37% aqueous Formaldehyde (2 mL, 26.8 mmol) , Sodium triacetoxyborohydride (287.09 mg, 1.35 mmol) and 1 drop of Acetic acid. The resulting mixture was stirred at room temperature for 3h. The mixture was concentrated and the residue was purified by Prep-HPLC under basic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (91.1 mg, 199.36 µmol, 44.15% yield) as a white solid. LCMS: *m/z* 457.0[M+H]$^+$.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.2 Hz, 1H), 8.12 (s, 1H), 7.64 (s,

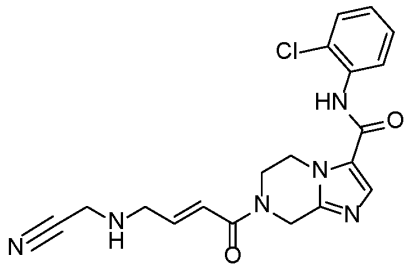
1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.98 (dt, *J* = 15.1, 5.7 Hz, 1H), 6.48 (d, *J* = 15.2 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.04 (d, *J* = 34.5 Hz, 2H), 3.32 (dd, *J* = 5.7, 1.3 Hz, 2H), 2.81 – 2.55 (m, 8H), 1.84 (dd, *J* = 11.8, 6.0 Hz, 2H), 1.72 (s, 3H).

Example 91. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-(dimethylamino)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0931] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *N*,*N*-dimethylazetidin-3-amine dihydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-(dimethylamino)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 443.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.7 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.09 (dd, *J* = 11.5, 4.0 Hz, 1H), 6.89 (dt, *J* = 15.1, 4.9 Hz, 1H), 6.44 (d, *J* = 15.1 Hz, 1H), 4.94 (s, 2H), 4.49 (s, 2H), 4.09 (s, 2H), 3.59 (s, 2H), 3.29 (d, *J* = 3.5 Hz, 2H), 2.90 (s, 2H), 2.12 (s, 6H).

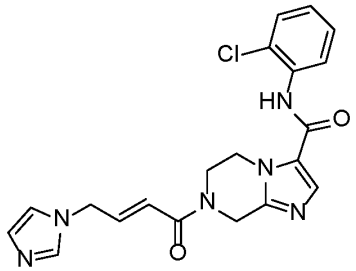
Example 92. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyanomethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide TFA.



[0932] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2-aminoacetonitrile

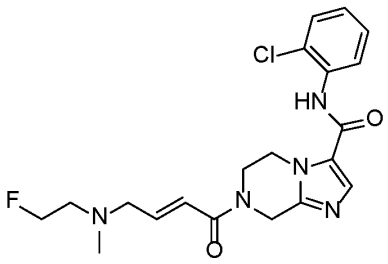
hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyanomethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide TFA. LCMS: *m/z* 399.0 $[M+H]^+$. ^{1}HNMR(400MHz, MeOH-d4) δ 8.12 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.38 (td, *J* = 7.8, 1.3 Hz, 1H), 7.32-7.28 (m, 1H), 7.01-6.94 (m, 1H), 6.87 – 6.78 (m, 1H), 5.12-5.07 (m, 2H), 4.60-4.52(m, 2H), 4.18-4.14 (m, 4H), 3.90 (d, *J* = 5.9 Hz, 2H).

Example 93. Synthesis of (*E*)-7-(4-(1*H*-imidazol-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0933] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 1*H*-imidazole for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(1*H*-imidazol-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 411.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.69 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, *J* = 8.0, 1.6 Hz, 1H), 7.29 (td, *J* = 7.6, 1.6 Hz, 1H), 7.20 (s, 1H), 6.95 (s, 1H), 6.70-6.58 (m, 2H), 4.86-4.75 (m, 4H), 4.30 (d, *J* = 24.8 Hz, 2H), 3.96 (s, 2H).

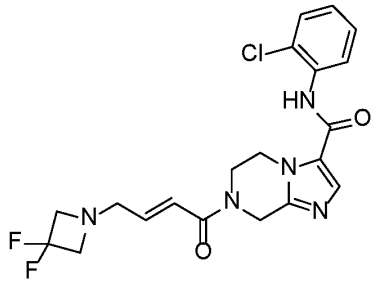
Example 94. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-fluoroethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0934] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2-fluoro-*N*-methylethan-1-

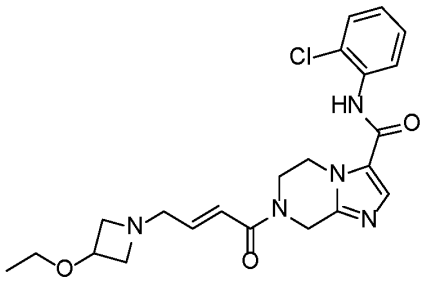
amine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-fluoroethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 420.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.87 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, *J* = 7.6, 1.6 Hz, 1H), 7.28 (td, *J* = 7.6, 1.6 Hz, 1H), 6.77-6.65 (m, 2H), 4.92-4.75 (m, 2H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.46 (t, *J* = 5.2 Hz, 1H), 4.32-4.27 (m, 2H), 4.00-3.95 (m, 2H), 3.22 (d, *J* = 5.2 Hz, 2H), 2.65 (dt, *J* = 28.0, 4.8 Hz, 2H), 2.23 (s, 3H).

Example 95. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3,3-difluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



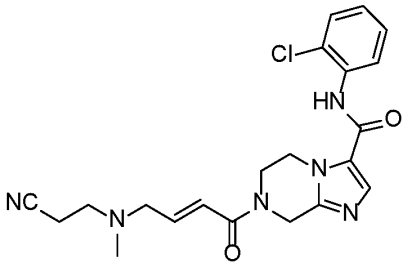
[0935] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3,3-difluoroazetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3,3-difluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 436.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, 7.6, 1.6 Hz, 1H), 7.28 (td, *J* = 7.6, 1.6 Hz, 1H),6.70- 6.59 (m, 2H), 4.93-4.74(m, 2H), 4.30 (d, *J* = 22.4 Hz, 2H), 3.98 (d, *J* = 26.8 Hz, 2H), 3.64 (t, *J* = 12.6 Hz, 4H), 3.36 (d, *J* = 4.4 Hz, 2H).

Example 96. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-ethoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



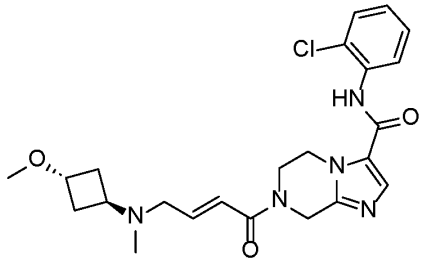
[0936] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-ethoxyazetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-ethoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 444.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, *J* = 8.0, 1.2 Hz, 1H), 7.28 (td, *J* = 7.6, 1.2 Hz, 1H), 6.66-6.55 (m, 2H), 4.90-4.74 (m, 2H), 4.31-4.26 (m, 2H), 4.06-3.93 (m, 3H), 3.56-3.52 (m, 2H), 3.31 (s, 2H), 3.20 (d, *J* = 4.0 Hz, 2H), 2.83-2.79 (m, 2H), 1.08 (t, *J* = 7.2 Hz , 3H).

Example 97. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-cyanoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



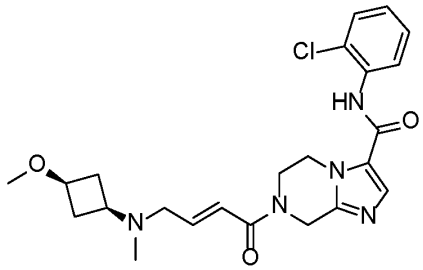
[0937] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-(methylamino)propanenitrile hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-cyanoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 427.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 8.0, 1.6 Hz, 2H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.28 (td, *J* = 8.0, 1.6 Hz, 1H), 6.81- 6.66 (m, 2H), 4.92-4.75 (m, 2H), 4.32-4.24 (m, 2H), 4.02-3.95 (m, 2H), 3.21 (d, *J* = 5.6 Hz, 2H), 2.70-2.57 (m, 4H), 2.22 (s, 3H).

Example 98. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-4-(((1*r*,3*r*)-3-methoxycyclobutyl)(methyl) amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0938] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (1*r*,3*r*)-3-methoxy-*N*-methylcyclobutan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *N*-(2-chlorophenyl)-7-((*E*)-4-(((1*r*,3*r*)-3-methoxycyclobutyl)(methyl) amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide as a white solid. LCMS: *m/z* 458.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 8.0, 1.2 Hz, 2H), 7.37 (td, *J* = 8.0, 1.2 Hz, 1H), 7.28 (td, *J* = 8.0, 1.6 Hz, 1H), 6.75-6.64 (m, 2H), 4.83 (d, *J* = 67.2 Hz, 2H), 4.35-4.26 (m, 2H), 3.98 (d, *J* = 22.8 Hz, 2H), 3.86-3.81 (m, 1H), 3.12 (s, 3H), 3.04 (d, *J* = 4.8 Hz, 2H), 2.99-2.92 (m, 1H), 2.08 -1.93 (m, 7H).

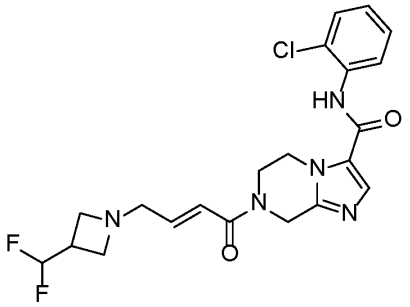
Example 99. Synthesis of N-(2-chlorophenyl)-7-((E)-4-(((1s,3s)-3-methoxycyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



[0939] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (1*s*,3*s*)-3-methoxy-*N*-methylcyclobutan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *N*-(2-chlorophenyl)-7-((*E*)-4-(((1*s*,3*s*)-3-methoxycyclobutyl)(methyl) amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 458.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.53 (td, *J* = 8.0, 1.2 Hz, 2H),), 7.37 (td, *J* = 8.0, 1.2 Hz, 1H), 7.28 (td, *J* = 8.0, 1.6 Hz, 1H), 6.74- 6.64 (m, 2H), 4.83 (d, *J* = 66.8

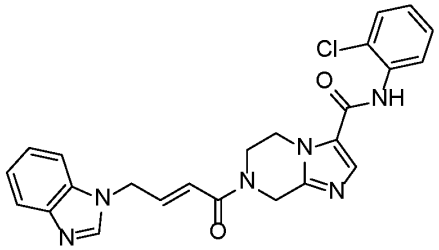
Hz, 2H), 4.32-4.26 (m, 2H), 3.97 (d, *J* = 27.2 Hz, 2H), 3.56-3.49 (m, 1H), 3.10 (s, 3H), 3.04 (d, *J* = 4.4 Hz, 2H), 2.40-2.32 (m, 3H), 2.03 (s, 3H), 1.63-1.56 (m, 2H).

Example 100. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-(difluoromethyl)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0940] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-(difluoromethyl)azetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-(difluoromethyl)azetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 450.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.13 (s, 1H), 7.66 (s, 1H), 7.43 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35-7.30 (m, 1H), 7.10 (td, *J* = 8.0, 1.2 Hz, 1H), 6.90-6.83 (m, 1H), 6.44 (d, *J* = 14.8 Hz, 1H), 6.00 (td, *J* = 56.8, 5.2 Hz, 1H), 4.95 (s, 2H), 4.51 (s, 2H), 4.13-3.96 (m, 2H), 3.42 (t, *J* = 7.6 Hz, 2H), 3.28-3.23 (m, 4H), 2.97-2.85 (m, 1H).

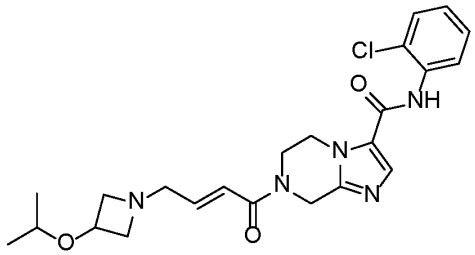
Example 101. Synthesis of (*E*)-7-(4-(1*H*-benzo[d]imidazol-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0941] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 1*H*-benzo[d]imidazole for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(1*H*-benzo[d]imidazol-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-

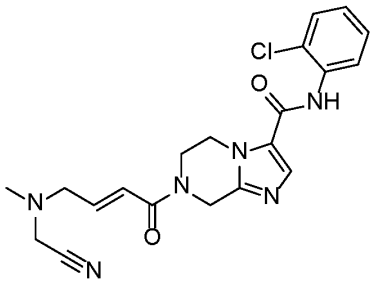
carboxamide. LCMS: *m/z* 461.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.8 Hz, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.89-7.84 (m, 1H), 7.61 (s, 1H), 7.41 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 (dd, *J* = 16.1, 5.6 Hz, 4H), 7.18-7.05 (m, 2H), 6.25-5.76 (m, 1H), 5.02 (s, 2H), 4.96-4.85 (m, 1H), 4.72-4.61 (m, 1H), 4.50-4.30 (m, 2H), 4.15-3.98 (m, 1H), 3.74-3.54 (m, 1H).

Example 102. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-isopropoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0942] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-isopropoxyazetidine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-isopropoxyazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 458.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.5 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.88 (dt, *J* = 15.1, 4.9 Hz, 1H), 6.44 (d, *J* = 14.7 Hz, 1H), 4.94 (s, 2H), 4.49 (s, 2H), 4.20 (p, *J* = 6.1 Hz, 1H), 4.14-3.94 (m, 2H), 3.81-3.69 (m, 2H), 3.67-3.53 (m, 1H), 3.30 (d, *J* = 3.4 Hz, 2H), 2.93 (t, *J* = 5.5 Hz, 2H), 1.14 (d, *J* = 6.1 Hz, 6H).

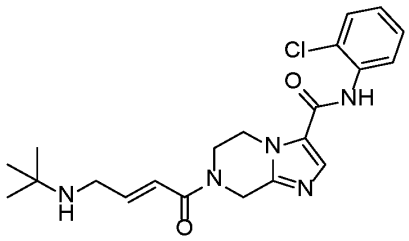
Example 103. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyanomethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0943] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-

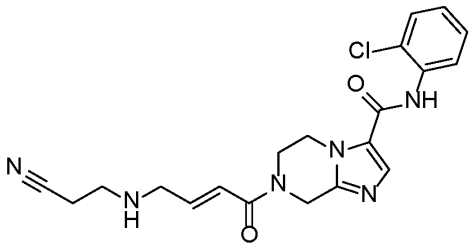
1,4-diazepane-1-carboxylate was applied with substitution of 2-(methylamino)acetonitrile for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyanomethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 413.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.80 (s, 2H), 5.01-4.91 (m, 2H), 4.52-4.39 (m, 2H), 4.13-4.05 (m, 2H), 3.69 (s, 2H), 3.38-3.32 (m, 2H), 2.40 (s, 3H).

Example 104. Synthesis of (*E*)-7-(4-(tert-butylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0944] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2-methylpropan-2-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(tert-butylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide. LCMS: *m/z* 416.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.31-7.21 (m, 1H), 6.86 (s, 2H), 5.03-4.92 (m, 2H), 4.56-4.39 (m, 2H), 4.11 (s, 2H), 3.65 (s, 2H), 1.29 (s, 9H).

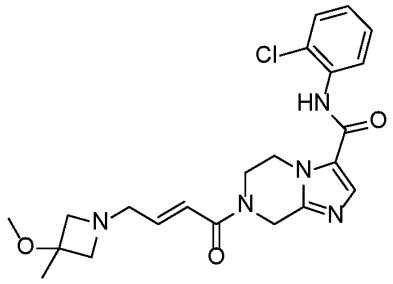
Example 105. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-cyanoethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0945] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-aminopropanenitrile for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-

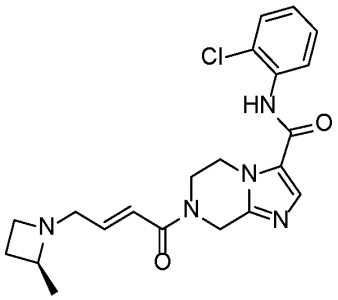
cyanoethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 413.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.7, 1.5 Hz, 1H), 6.90 (dt, *J* = 15.3, 5.3 Hz, 1H), 6.82-6.67 (m, 1H), 5.02-4.91 (m, 2H), 4.45 (dt, *J* = 16.0, 6.8 Hz, 2H), 4.15-4.04 (m, 2H), 3.48 (dd, *J* = 5.3, 1.5 Hz, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 2.62 (t, *J* = 6.7 Hz, 2H).

Example 106. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxy-3-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



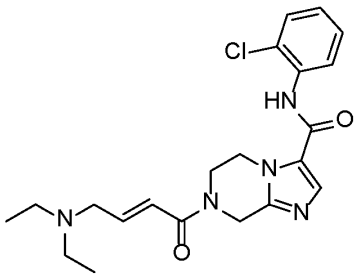
[0946] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-methoxy-3-methylazetidine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-methoxy-3-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 444.0 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.69 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.76 (dt, *J* = 15.5, 5.5 Hz, 1H), 6.71-6.58 (m, 1H), 4.53-4.39 (m, 2H), 4.13-4.05 (m, 2H), 3.40-3.32 (m, 6H), 3.23 (d, *J* = 8.6 Hz, 2H), 3.20 (s, 3H), 1.46 (s, 3H).

Example 107. Synthesis of (*S*,*E*)-*N*-(2-chlorophenyl)-7-(4-(2-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



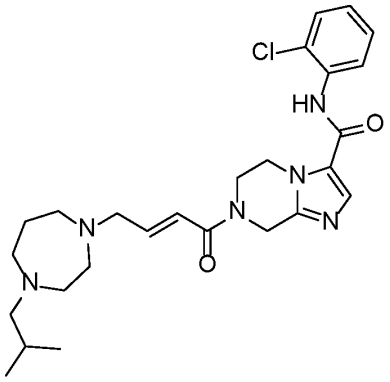
[0947] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (*S*)-2-methylazetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*S*,*E*)-*N*-(2-chlorophenyl)-7-(4-(2-methylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 7.89 (s, 1H), 7.54 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 2H), 7.33 (dtd, *J* = 34.9, 7.6, 1.4 Hz, 2H), 7.02-6.79 (m, 1H), 6.70-6.48 (m, 1H), 4.94 (s, 1H), 4.77 (s, 1H), 4.31 (d, *J* = 23.6 Hz, 2H), 4.00 (d, *J* = 31.5 Hz, 2H), 3.88-3.53 (m, 3H), 2.30-1.80 (m, 3H), 1.56-1.15 (m, 4H).

Example 108. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(diethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



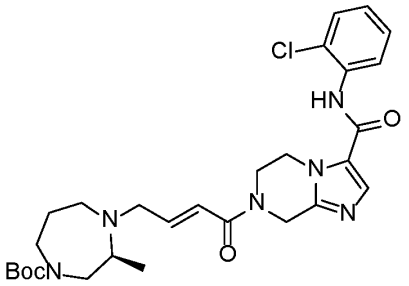
[0948] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of diethylamine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(diethylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 416.3$[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.95 – 6.74 (m, 2H), 4.94 (d, *J* = 24.4 Hz, 2H), 4.46 (d, *J* = 17.2 Hz, 2H), 4.09 (t, *J* = 5.3 Hz, 2H), 3.48 (s, 2H), 2.71 (dd, *J* = 13.3, 6.6 Hz, 4H), 1.13 (t, *J* = 5.6 Hz, 6H).

Example 109. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(4-isobutyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0949] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 1-isobutyl-1,4-diazepane for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(4-isobutyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 499.2 $[M+H]^+$. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.95 – 6.65 (m, 2H), 5.02 – 4.90 (m, 3H), 4.52 – 4.39 (m, 2H), 4.12 – 4.04 (m, 2H), 3.42 (d, *J* = 6.1 Hz, 2H), 3.15 – 3.03 (m, 4H), 2.89 – 2.78 (m, 4H), 2.71 – 2.58 (m, 2H), 2.02 – 1.86 (m, 3H), 0.98 (d, *J* = 6.6 Hz, 6H).

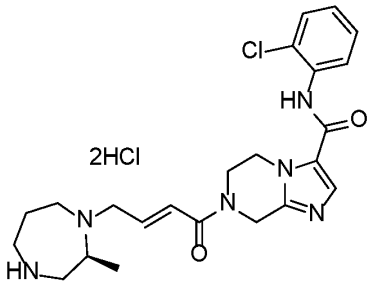
Example 110. Synthesis of *tert*-butyl (*S,E*)-4-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-3-methyl-1,4-diazepane-1-carboxylate.



[0950] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *tert*-butyl (*S*)-3-methyl-1,4-diazepane-1-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *tert*-butyl (*S,E*)-4-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-3-methyl-1,4-diazepane-1-carboxylate. LCMS: *m/z* 557.3

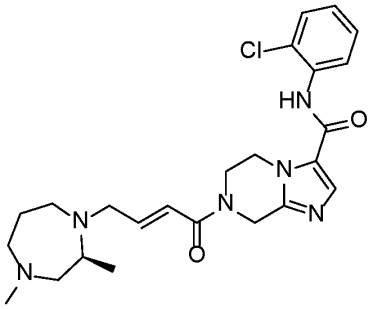
$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.36-7.28 (m, 1H), 7.09 (td, *J* = 7.8, 1.5 Hz, 1H), 7.00-6.90 (m, 1H), 6.50 (d, *J* = 15.2 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.09 (s, 2H), 3.49 (s, 2H), 3.31 (d, *J* = 23.3 Hz, 4H), 3.04 (d, *J* = 32.7 Hz, 1H), 2.85 (d, *J* = 12.8 Hz, 1H), 2.66 (d, *J* = 8.4 Hz, 1H), 1.79 (d, *J* = 43.1 Hz, 2H), 1.45 (s, 9H), 1.00 (dd, *J* = 6.4, 3.5 Hz, 3H).

Example 111. Synthesis of (*S,E*)-*N*-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0951] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (*S*)-3-methyl-1,4-diazepane-1-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*S,E*)-*N*-(2-chlorophenyl)-7-(4-(2-methyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (HCl salt). LCMS: *m/z* 457.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.67 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.31 (td, *J* = 7.8, 1.6 Hz, 1H), 7.23 (d, *J* = 14.9 Hz, 1H), 6.92 (s, 1H), 5.26 (d, *J* = 70.3 Hz, 2H), 4.70 (s, 2H), 4.34 – 4.07 (m, 5H), 3.66 (t, *J* = 27.8 Hz, 5H), 3.43 (d, *J* = 54.2 Hz, 2H), 2.35 (s, 2H), 1.60 (d, *J* = 6.4 Hz, 3H).

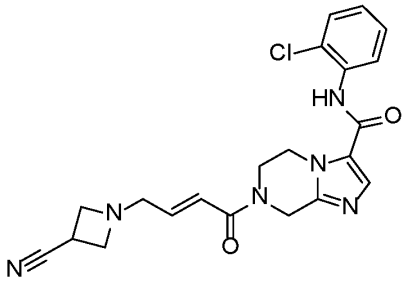
Example 112. Synthesis of (*S,E*)-*N*-(2-chlorophenyl)-7-(4-(2,4-dimethyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0952] The method as described for the synthesis of *N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride was applied with

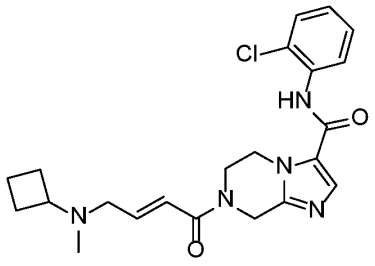
substitution of *tert*-butyl (*S*)-3-methyl-1,4-diazepane-1-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the (*S,E*)-*N*-(2-chlorophenyl)-7-(4-(2,4-dimethyl-1,4-diazepan-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 470.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.4 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34-7.29 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.99 (dt, *J* = 15.0, 5.4 Hz, 1H), 6.53 (d, *J* = 14.7 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.08 (s, 2H), 3.40 (d, *J* = 5.4 Hz, 2H), 3.00-2.82 (m, 2H), 2.76-2.55 (m, 3H), 2.47-2.34 (m, 5H), 1.85-1.75 (m, 1H), 1.25 (s, 1H), 1.03 (d, *J* = 6.4 Hz, 3H).

Example 113. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



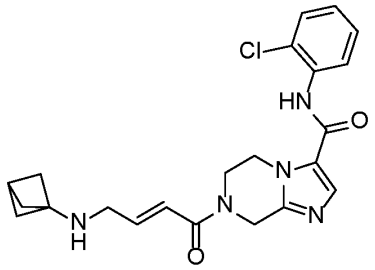
[0953] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of azetidine-3-carbonitrile for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-cyanoazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 425.1$[M+H]^+$. ^{1}H NMR (400 MHz, d^6-DMSO)δ 9.85 (s, 1H), 7.87 (s, 1H), 7.58 – 7.50 (m, 2H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.29 (td, *J* = 7.8, 1.6 Hz, 1H), 6.66 d, *J* = 15.2 Hz, 1H), 6.56 (dt, *J* = 15.2, 5.3 Hz, 1H), 4.92 (s, 1H), 4.74 (s, 1H), 4.33 (s, 1H), 3.98 (d, *J* = 22.3 Hz, 2H), 3.49 (d, *J* = 2.7 Hz, 3H), 3.30 (t, *J* = 4.0 Hz, 2H), 3.21 (d, *J* = 4.6 Hz, 2H)

Example 114. Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(cyclobutyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



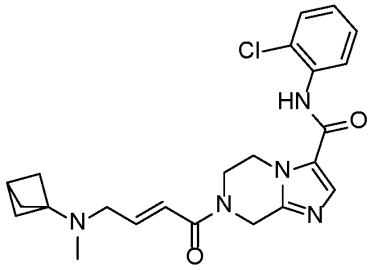
[0954] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *N*-methylcyclobutanamine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-ethynylazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.7, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.88 (dt, *J* = 14.9, 6.6 Hz, 1H), 6.75 (d, *J* = 15.4 Hz, 1H), 4.94 (d, *J* = 27.0 Hz, 2H), 4.48 (s, 2H), 4.09 (t, *J* = 5.2 Hz, 2H), 3.17 (d, *J* = 6.4 Hz, 2H), 2.95 (ddd, *J* = 16.0, 8.4, 7.5 Hz, 1H), 2.15 (s, 3H), 2.09 (dtd, *J* = 9.7, 7.2, 2.8 Hz, 2H), 1.99 – 1.84 (m, 2H), 1.76 – 1.63 (m, 2H).

Example 115. Synthesis of (*E*)-7-(4-(bicyclo[1.1.1]pentan-1-ylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



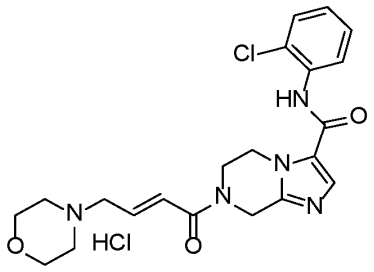
[0955] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of bicyclo[1.1.1]pentan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(bicyclo[1.1.1]pentan-1-ylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 426.2[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.97 – 6.87 (m, 1H), 6.71 (d, *J* = 10.9 Hz, 1H), 4.94 (d, *J* = 25.7 Hz, 3H), 4.48 (s, 2H), 4.10 (s, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 2.43 (s, 1H), 1.86 (s, 5H).

Example 116. Synthesis of (*E*)-7-(4-(bicyclo[1.1.1]pentan-1-yl(methyl)amino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



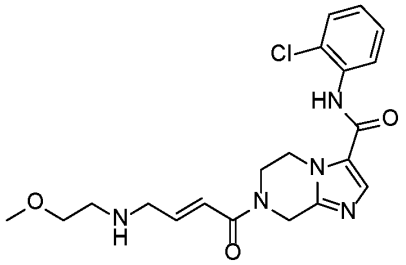
[0956] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of bicyclo[1.1.1]pentan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(bicyclo[1.1.1]pentan-1-yl(methyl)amino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 440.1[M+H]$^+$.^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.88 (dt, *J* = 15.1, 6.2 Hz, 1H), 6.76 (d, *J* = 15.6 Hz, 1H), 4.91 (s, 2H), 4.47 (s, 2H), 4.15 – 4.05 (m, 2H), 3.30 (s, 4H), 2.46 (s, 1H), 2.25 (s, 2H), 1.85 (s, 5H).

Example 117. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-morpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride.



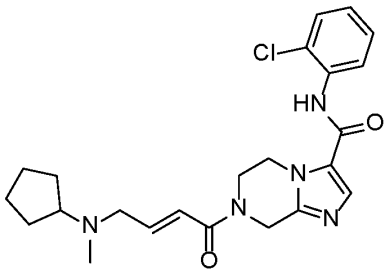
[0957] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of morpholine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-morpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide hydrochloride. LCMS: *m/z* 430.0 [M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.80 – 6.67 (m, 1H), 5.01 – 4.89 (m, 2H), 4.55 – 4.38 (m, 2H), 4.08 (t, *J* = 5.4 Hz, 2H), 3.74 – 3.67 (m, 4H), 3.23 (d, *J* = 6.2 Hz, 2H), 2.56 – 2.44 (m, 4H).

Example 118. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-methoxyethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



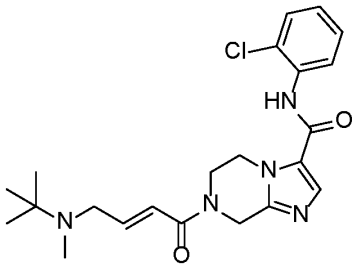
[0958] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2-methoxyethan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-methoxyethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 418.0 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.72 – 7.64 (m, 1H), 7.50 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.90 (dt, *J* = 15.2, 5.6 Hz, 1H), 6.73 (d, *J* = 15.0 Hz, 1H), 5.02 – 4.90 (m, 2H), 4.48 (s, 2H), 4.10 (s, 2H), 3.55 – 3.50 (m, 2H), 3.50 – 3.46 (m, 2H), 3.36 (s, 3H), 2.81 (t, *J* = 5.3 Hz, 2H).

Example 119. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopentyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



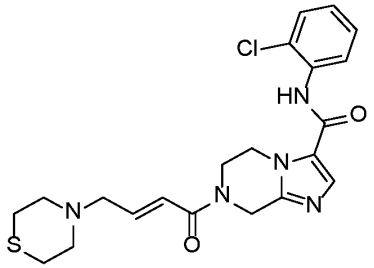
[0959] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *N*-methylcyclopentanamine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclopentyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 442.2 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.98 – 6.87 (m, 1H), 6.77 (d, *J* = 15.5 Hz, 1H), 5.01 – 4.90 (m, 2H), 4.52 – 4.41 (m, 2H), 4.09 (t, *J* = 5.0 Hz, 2H), 3.36 (d, *J* = 6.6 Hz, 2H), 2.89 – 2.75 (m, 1H), 2.30 (s, 3H), 2.01 – 1.86 (m, 2H), 1.79 – 1.67 (m, 2H), 1.65 – 1.52 (m, 2H), 1.53 – 1.39 (m, 2H).

Example 120. Synthesis of (*E*)-7-(4-(tert-butyl(methyl)amino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0960] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *N*,2-dimethylpropan-2-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(tert-butyl(methyl)amino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.2[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35 (td, *J* = 7.8, 1.3 Hz, 1H), 7.25 (td, *J* = 7.8, 1.5 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.81 – 6.72 (m, 1H), 5.04 – 4.94 (m, 2H), 4.62 – 4.42 (m, 2H), 4.09 (t, *J* = 5.3 Hz, 2H), 3.44 (d, *J* = 30.6 Hz, 2H), 2.30 (s, 3H), 1.17 (s, 9H).

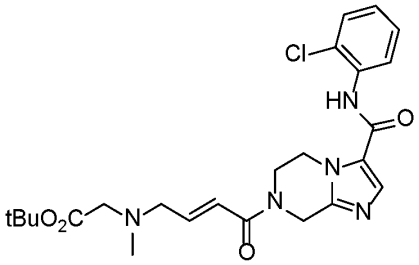
Example 121. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-thiomorpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0961] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of thiomorpholine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-thiomorpholinobut-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 446.1 [M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 6.9 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz,

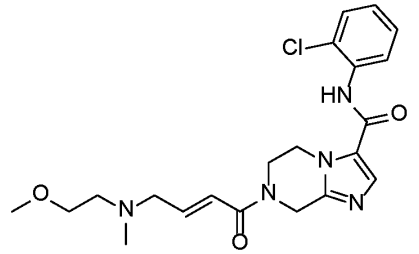
1H), 6.91 – 6.66 (m, 2H), 4.99 – 4.89 (m, 2H), 4.54 – 4.37 (m, 2H), 4.12 – 4.02 (m, 2H), 3.28 – 3.22 (m, 2H), 2.81 – 2.73 (m, 4H), 2.72 – 2.65 (m, 4H).

Example 122. Synthesis of *tert*-butyl (*E*)-*N*-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-*N*-methylglycinate.



[0962] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *tert*-butyl methylglycinate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *tert*-butyl (*E*)-*N*-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-*N*-methylglycinate. LCMS: *m/z* 488.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.68 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.91 – 6.66 (m, 2H), 5.02 – 4.91 (m, 2H), 4.53 – 4.37 (m, 2H), 4.13 – 4.03 (m, 2H), 3.36 (d, *J* = 5.5 Hz, 2H), 3.20 (s, 2H), 2.37 (s, 3H), 1.47 (s, 9H).

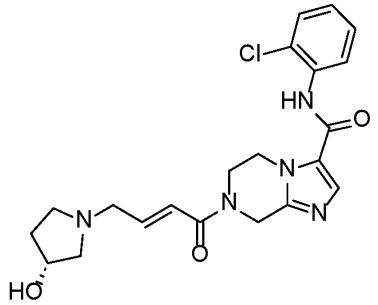
Example 123. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-methoxyethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0963] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2-methoxy-*N*-methylethan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-methoxyethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 432.2$[M+H]^+$. ^{1}H NMR (400

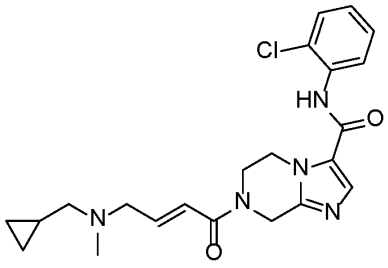
MHz, MeOD) δ 7.82 (s, 1H), 7.69 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.4 Hz, 1H), 7.24 (td, *J* = 7.8, 1.6 Hz, 1H), 6.92 – 6.71 (m, 2H), 4.94 (d, *J* = 28.9 Hz, 2H), 4.51 – 4.39 (m, 2H), 4.13 – 4.04 (m, 2H), 3.53 (t, *J* = 5.4 Hz, 2H), 3.36 – 3.31 (m, 5H), 2.65 (t, *J* = 5.4 Hz, 2H), 2.34 (s, 3H).

Example 124. Synthesis of (*R*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0964] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (*R*)-pyrrolidin-3-ol for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*R*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 430.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.88 (dt, *J* = 15.0, 6.1 Hz, 1H), 6.78 (d, *J* = 15.8 Hz, 1H), 5.00 – 4.90 (m, 2H), 4.52 – 4.42 (m, 2H), 4.40 – 4.33 (m, 1H), 4.15 – 4.05 (m, 2H), 3.46 – 3.35 (m, 2H), 2.91 – 2.82 (m, 2H), 2.69 – 2.59 (m, 2H), 2.21 – 2.09 (m, 2H), 1.82 – 1.72 (m, 1H).

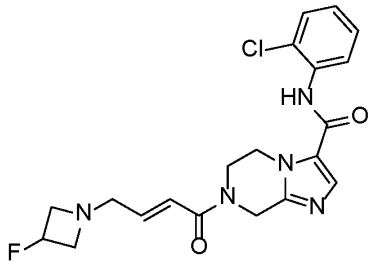
Example 125. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyclopropylmethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0965] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-

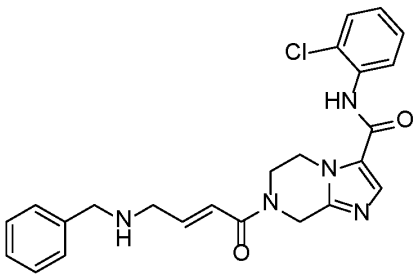
1,4-diazepane-1-carboxylate was applied with substitution of 1-cyclopropyl-*N*-methylmethanamine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((cyclopropylmethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.0[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.69 (d, *J* = 6.8 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.96 – 6.84 (m, 1H), 6.82 – 6.66 (m, 1H), 4.94 (d, *J* = 25.3 Hz, 2H), 4.52 – 4.40 (m, 2H), 4.09 (t, *J* = 5.3 Hz, 2H), 3.37 (d, *J* = 6.4 Hz, 2H), 2.40 – 2.35 (m, 5H), 0.97 – 0.87 (m, 1H), 0.60 – 0.54 (m, 2H), 0.20 – 0.15 (m, 2H).

Example 126. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-fluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



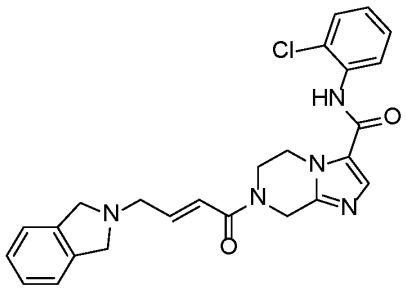
[0966] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-fluoroazetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(3-fluoroazetidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 418.1 [M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.69 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.79 – 6.61 (m, 2H), 5.28 – 5.06 (m, 1H), 4.93 (d, *J* = 28.8 Hz, 2H), 4.48 (s, 2H), 4.09 (d, *J* = 5.4 Hz, 2H), 3.79 – 3.67 (m, 2H), 3.38 (dd, *J* = 21.2, 4.5 Hz, 4H).

Example 127. Synthesis of (*E*)-7-(4-(benzylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



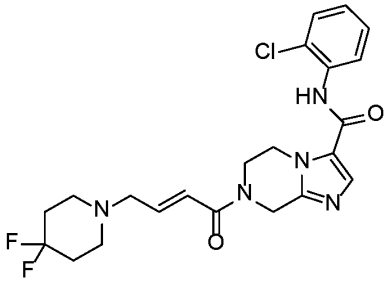
[0967] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of phenylmethanamine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(benzylamino)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 450.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 – 7.27 (m, 6H), 7.13 – 6.99 (m, 2H), 6.53 (d, *J* = 15.1 Hz, 1H), 4.94 (s, 2H), 4.49 (t, *J* = 5.3 Hz, 2H), 4.20 – 3.88 (m, 2H), 3.84 (s, 2H), 3.48 (d, *J* = 3.6 Hz, 2H).

Example 128. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(isoindolin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



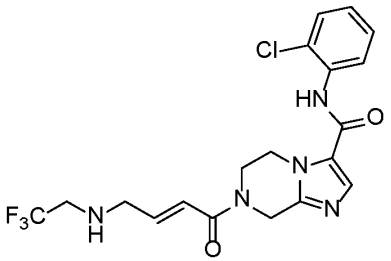
[0968] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of isoindoline for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(isoindolin-2-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 462.1$[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.69 (d, *J* = 7.1 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.27 – 7.20 (m, 5H), 7.00 – 6.90 (m, 1H), 6.83 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 31.2 Hz, 2H), 4.53 – 4.42 (m, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 4.03 (s, 4H), 3.64 (d, *J* = 6.0 Hz, 2H).

Example 129. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(4,4-difluoropiperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



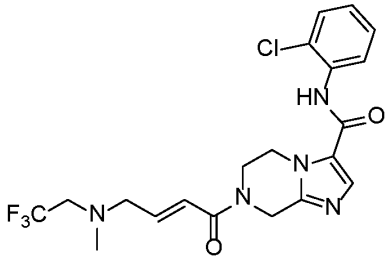
[0969] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 4,4-difluoropiperidine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(4,4-difluoropiperidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 464.1 $[M+H]^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 6.8 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.92 – 6.70 (m, 2H), 5.02 – 4.89 (m, 2H), 4.54 – 4.37 (m, 2H), 4.15 – 4.03 (m, 2H), 3.30 (m, 2H), 2.72 – 2.56 (m, 4H), 2.11 – 1.91 (m, 4H).

Example 130. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



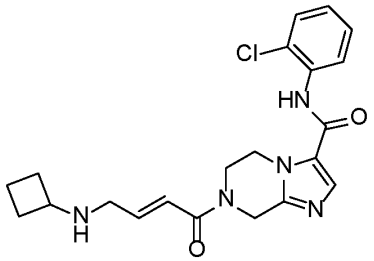
[0970] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2,2,2-trifluoroethan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 442.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.8, 1.5 Hz, 1H), 6.97 (dt, *J* = 15.1, 4.9 Hz, 1H), 6.57 (d, *J* = 13.9 Hz, 1H), 4.95 (s, 2H), 4.50 (s, 2H), 4.05 (d, *J* = 42.9 Hz, 2H), 3.59 (d, *J* = 4.4 Hz, 2H), 3.23 (q, *J* = 9.3 Hz, 2H).

Example 131. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(methyl(2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0971] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 2,2,2-trifluoro-*N*-methylethan-1-amine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(methyl(2,2,2-trifluoroethyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 456.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 6.94 (dt, *J* = 15.1, 5.4 Hz, 1H), 6.66 – 6.49 (m, 1H), 4.94 (s, 2H), 4.51 (s, 2H), 4.20 – 3.89 (m, 2H), 3.41 (d, *J* = 4.6 Hz, 2H), 3.05 (q, *J* = 9.4 Hz, 2H), 2.49 (s, 3H).

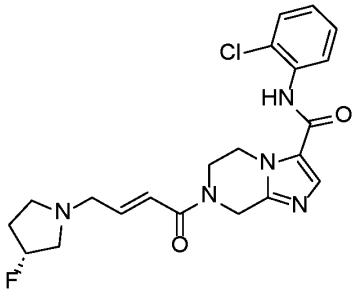
Example 132. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclobutylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0972] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3-fluoroazetidine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclobutylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.14 – 6.96 (m, 2H),

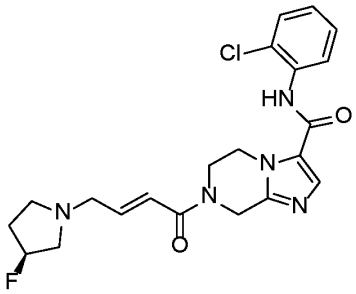
6.50 (d, *J* = 14.5 Hz, 1H), 4.95 (s, 2H), 4.49 (s, 2H), 4.04 (d, *J* = 37.6 Hz, 2H), 3.39 (dd, *J* = 5.0, 1.3 Hz, 2H), 3.34 – 3.23 (m, 1H), 2.30 – 2.18 (m, 2H), 1.79 – 1.66 (m, 4H).

Example 133. Synthesis of (*R*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-fluoropyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0973] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (*R*)-3-fluoropyrrolidine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*R*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-fluoropyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 432.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8f.35 (d, *J* = 8.1 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.6 Hz, 1H), 6.52 (d, *J* = 14.7 Hz, 1H), 5.19 (dt, *J* = 55.3, 5.5 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.21 – 3.88 (m, 2H), 3.35 (d, *J* = 4.6 Hz, 2H), 3.03 – 2.67 (m, 3H), 2.59 – 2.46 (m, 1H), 2.28 – 1.96 (m, 2H).

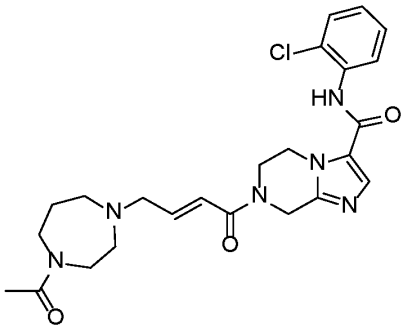
Example 134. Synthesis of (*S*,*E*)-*N*-(2-chlorophenyl)-7-(4-(3-fluoropyrrolidin-1-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0974] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of (*S*)-3-fluoropyrrolidine for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-(cyclobutylamino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

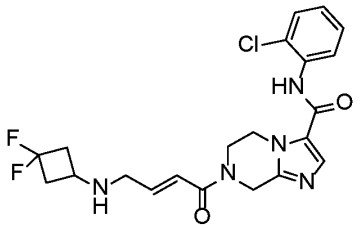
LCMS: *m/z* 432.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.6 Hz, 1H), 6.52 (d, *J* = 15.0 Hz, 1H), 5.19 (dt, *J* = 11.0, 6.1 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.19 – 3.88 (m, 2H), 3.34 (d, *J* = 4.4 Hz, 2H), 3.01 – 2.66 (m, 3H), 2.57 – 2.45 (m, 1H), 2.31 – 1.96 (m, 2H).

Example 135. Synthesis of (*E*)-7-(4-(4-acetyl-1,4-diazepan-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



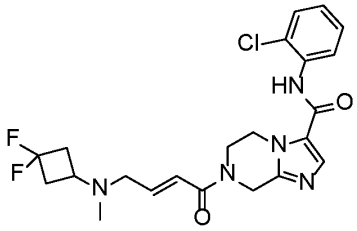
[0975] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 1-(1,4-diazepan-1-yl)ethan-1-one for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-7-(4-(4-acetyl-1,4-diazepan-1-yl)but-2-enoyl)-*N*-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 485.2$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.12 – 7.06 (m, 1H), 6.96 (dt, *J* = 15.0, 5.7 Hz, 1H), 6.49 (d, *J* = 15.5 Hz, 1H), 4.94 (s, 2H), 4.51 (s, 2H), 4.15 – 3.95 (m, 2H), 3.70 – 3.60 (m, 2H), 3.56 – 3.48 (m, 2H), 3.31 (t, *J* = 4.1 Hz, 2H), 2.76 – 2.58 (m, 4H), 2.11 (d, *J* = 3.2 Hz, 3H), 1.95 – 1.84 (m, 2H).

Example 136. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



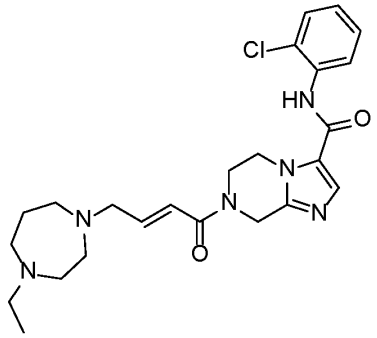
[0976] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of 3,3-difluorocyclobutan-1-amine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product (*E*)-*N*-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 450.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.94 – 6.84 (m, 1H), 6.70 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 23.9 Hz, 2H), 4.52 – 4.38 (m, 2H), 4.14 – 4.05 (m, 2H), 3.38 (dd, *J* = 5.6, 1.5 Hz, 2H), 3.27 – 3.18 (m, 1H), 2.85 – 2.72 (m, 2H), 2.45 – 2.27 (m, 2H).

Example 137. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



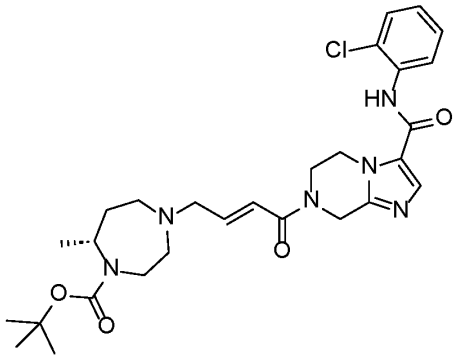
[0977] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of 3,3-difluorocyclobutan-1-amine hydrochloride for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the (*E*)-*N*-(2-chlorophenyl)-7-(4-((3,3-difluorocyclobutyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 464.1[M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.80 – 6.67 (m, 1H), 4.94 (d, *J* = 24.7 Hz, 2H), 4.53 – 4.39 (m, 2H), 4.09 (t, *J* = 5.4 Hz, 2H), 3.20 (d, *J* = 5.8 Hz, 2H), 2.91 – 2.80 (m, 1H), 2.75 – 2.63 (m, 2H), 2.50 – 2.35 (m, 2H), 2.19 (s, 3H).

Example 138. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-ethyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



[0978] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of acetaldehyde for formaldehyde to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-ethyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 471.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.99 (dt, *J* = 15.1, 5.8 Hz, 1H), 6.48 (d, *J* = 14.4 Hz, 1H), 4.92 (d, *J* = 20.3 Hz, 2H), 4.50 (s, 2H), 4.08 (s, 2H), 3.42 – 3.24 (m, 2H), 2.77 – 2.65 (m, 8H), 2.59 – 2.52 (m, 2H), 1.83 (dt, *J* = 11.7, 5.9 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H).

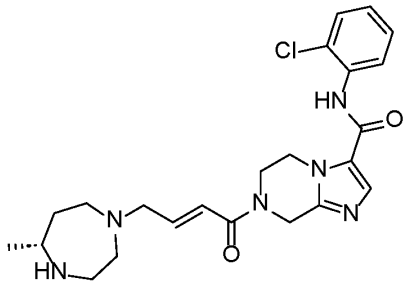
Example 139. Synthesis of *tert*-butyl (7*R*)-4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-7-methyl-1,4-diazepane-1-carboxylate.



[0979] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *tert*-butyl (7*R*)-7-methyl-1,4-diazepane-1-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *tert*-butyl (7*R*)-4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazin-7-yl]-4-oxo-but-2-enyl]-7-methyl-1,4-diazepane-1-carboxylate. LCMS: *m/z* 557.3[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.11 (s, 1H), 7.64 (s,

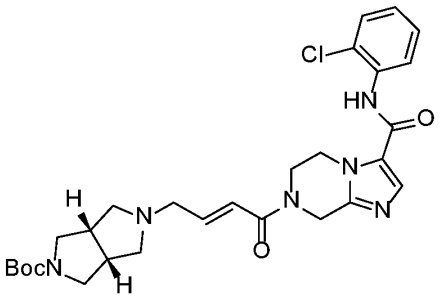
1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.1 Hz, 1H), 6.97 (dd, *J* = 14.9, 4.2 Hz, 1H), 6.46 (d, *J* = 14.5 Hz, 1H), 4.94 (s, 2H), 4.50 (s, 2H), 4.13 (dd, *J* = 60.9, 35.9 Hz, 3H), 3.91 – 3.59 (m, 1H), 3.22 (s, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.90 – 2.72 (m, 2H), 2.38 – 2.14 (m, 2H), 2.00 (s, 1H), 1.68 (dd, *J* = 20.3, 6.6 Hz, 1H), 1.47 (d, *J* = 2.1 Hz, 9H), 1.07 (dd, *J* = 6.2, 2.6 Hz, 3H).

Example 140. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-[(5*R*)-5-methyl-1,4-diazepan-1-yl]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



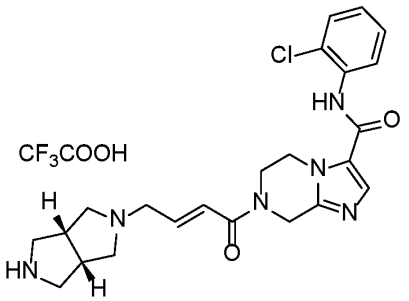
[0980] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (7*R*)-7-methyl-1,4-diazepane-1-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *N*-(2-chlorophenyl)-7-[(*E*)-4-[(5*R*)-5-methyl-1,4-diazepan-1-yl]but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 457.1[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.11 (s, 1H), 7.64 (d, *J* = 5.5 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 4.85 (dd, *J* = 34.7, 14.7 Hz, 2H), 4.45 (s, 2H), 4.00 (d, *J* = 61.8 Hz, 2H), 3.66 – 3.47 (m, 1H), 3.38 – 2.55 (m, 10H), 2.50 – 2.27 (m, 1H), 1.74 (s, 2H), 1.04 (dd, *J* = 34.9, 6.5 Hz, 2H), 0.89 (dd, *J* = 15.9, 6.4 Hz, 1H).

Example 141. Synthesis of *tert*-butyl (3a*R*,6a*S*)-5-((*E*)-4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate.



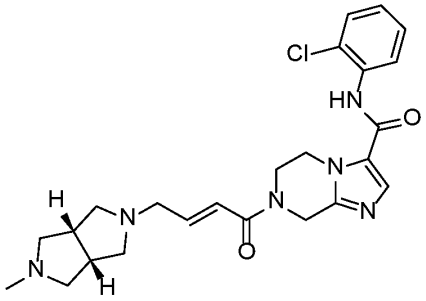
[0981] The method as described for the synthesis of *tert*-butyl 4-[(*E*)-4-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate was applied with substitution of *tert*-butyl (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *tert*-butyl (3a*R*,6a*S*)-5-((*E*)-4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate. LCMS: *m/z* 555.2[M+H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0, 0.6 Hz, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.11 – 7.06 (m, 1H), 7.01 – 6.93 (m, 1H), 6.51 – 6.44 (m, 1H), 4.98 – 4.90 (m, 2H), 4.54 – 4.47 (m, 2H), 4.12 – 4.02 (m, 2H), 3.57 – 3.49 (m, 2H), 3.32 – 3.20 (m, 4H), 2.84 – 2.71 (m, 4H), 2.42 (s, 2H), 1.46 (s, 9H).

Example 142. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-4-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide 2,2,2-trifluoroacetate.



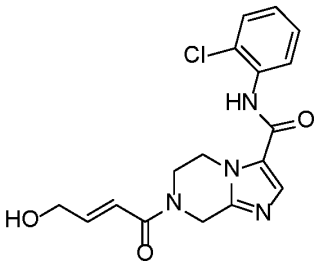
[0982] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-a]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate and purified by Prep-HPLC under acidic condition to provide the product *N*-(2-chlorophenyl)-7-((*E*)-4-((3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide 2,2,2-trifluoroacetate. LCMS: *m/z* 455.1 [M+H]$^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.03 – 7.94 (m, 1H), 7.69 – 7.63 (m, 1H), 7.52 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.40 – 7.24 (m, 2H), 5.09 – 5.00 (m, 1H), 4.94 – 4.91 (m, 1H), 4.60 – 4.54 (m, 1H), 4.48 – 4.42 (m, 1H), 4.15 – 3.45 (m, 14H), 3.18 – 2.94 (m, 2H).

Example 143. Synthesis of *N*-(2-chlorophenyl)-7-((*E*)-4-((3a*R*,6a*S*)-5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.



[0983] The method as described for the synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-(4-methyl-1,4-diazepan-1-yl)but-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide was applied with substitution of *tert*-butyl (3a*R*,6a*S*)-hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate for *tert*-butyl 1,4-diazepane-1-carboxylate to provide the product *N*-(2-chlorophenyl)-7-((*E*)-4-((3a*R*,6a*S*)-5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 469.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.09 (td, *J* = 7.9, 1.5 Hz, 1H), 7.00 (dt, *J* = 15.1, 5.8 Hz, 1H), 6.47 (d, *J* = 14.9 Hz, 1H), 4.94 (s, 2H), 4.57 – 4.42 (m, 2H), 4.16 – 3.93 (m, 2H), 3.26 (dd, *J* = 5.8, 1.1 Hz, 2H), 2.81 – 2.66 (m, 4H), 2.59 – 2.49 (m, 2H), 2.45 – 2.34 (m, 4H), 2.33 (s, 3H).

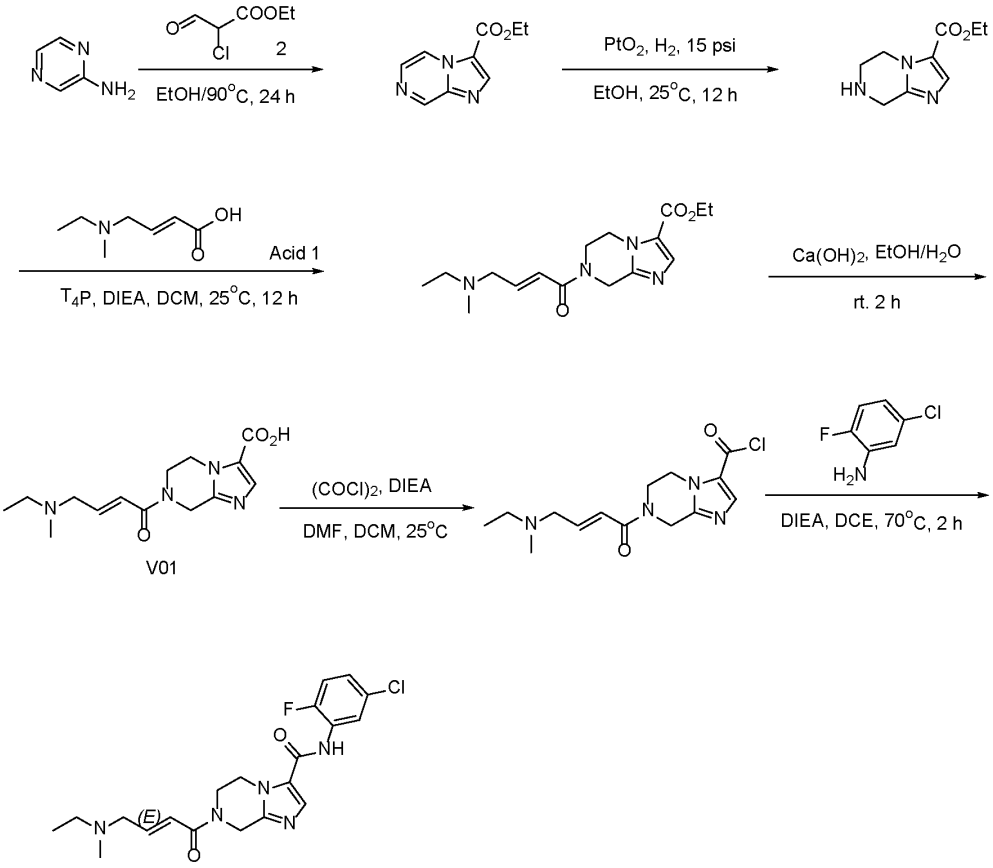
Example 144. Synthesis of *N*-(2-chlorophenyl)-7-[(*E*)-4-hydroxybut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide.



[0984] To a solution of 7-[(*E*)-4-bromobut-2-enoyl]-*N*-(2-chlorophenyl)-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (105.92 mg, 0.25 mmol) in THF (5 mL) was added benzyloxysodium (65.06 mg, 500.00 μmol) in THF (0.75 mL) dropwise at 0 °C. The resulting mixture was stirred at room temperature overnight, quenched with water (1 mL) and concentrated. The residue was purified by Prep-HPLC under basic condition to give *N*-(2-chlorophenyl)-7-[(*E*)-4-hydroxybut-2-enoyl]-6,8-dihydro-5*H*-imidazo[1,2-*a*]pyrazine-3-carboxamide (45 mg, 124.72 μmol, 49.89% yield, 100% purity) as white solid. LCMS: *m/z* 361.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.1 Hz, 1H), 8.12 (s, 1H), 7.64 (s,

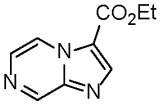
1H), 7.42 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.35 – 7.28 (m, 1H), 7.14 – 7.03 (m, 2H), 6.65 (d, *J* = 14.6 Hz, 1H), 4.96 (s, 2H), 4.50 (s, 2H), 4.42 (s, 2H), 4.18 – 3.91 (m, 2H).

General method K



Example 145. Synthesis of N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

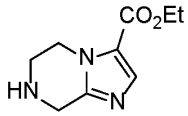
Step 1.1 Synthesis of ethyl imidazo[1,2-a]pyrazine-3-carboxylate



[0985] To a solution of pyrazin-2-amine (20 g, 210.30 mmol, 1 eq) in EtOH (20 mL) was added ethyl 2-chloro-3-oxo-propanoate (38.00 g, 252.36 mmol, 1.2 eq) at 25°C. The mixture was heated to 90°C and was stirred at 90°C for 24 hr. LCMS showed the reaction was complete. The reaction mixture was cooled to 25°C and the reaction mixture was concentrated under reduced pressure to give a residue, the residue was diluted with H_2O (50 mL) and adjusted pH = 7 by aq. $NaHCO_3$, then the reaction mixture was extracted with

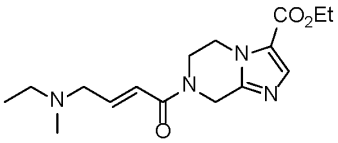
EtOAc (100 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 150 mL/min). Compound ethyl imidazo[1,2-a]pyrazine-3-carboxylate (19 g, 99.38 mmol, 47.26% yield) was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.30 (d, J = 1.6 Hz, 1H), 9.11 (d, J = 4.4 Hz, 1H), 8.43 (s, 1H), 8.23 (d, J = 4.4 Hz, 1H), 4.40 (q, J = 7.2 Hz, 1H), 1.36 (t, J = 6.8 Hz, 1H).

Step 1.2 Synthesis of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxylate



[0986] The PtO_2 (7.50 g, 33.03 mmol, 0.42 eq) was added into flask stand-up bottom under Ar atmosphere at 25°C, then EtOH (300 mL) was added into flask stand-up bottom, then reaction mixture was added ethyl imidazo[1,2-a]pyrazine-3-carboxylate (15 g, 78.46 mmol, 1 eq) and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 25°C for 12 hr under H_2 atmosphere. LCMS showed the reaction was complete. The reaction solution was filtered and the filtration was concentrated to give yellow oil. Without purification. Compound ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (15 g, 76.84 mmol, 97.93% yield) was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (s, 1H), 4.23 (q, J = 6.8 Hz, 2H), 4.09 (t, J = 5.6 Hz, 1H), 3.88 (s, 2H), 3.05 (q, J = 5.6 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H).

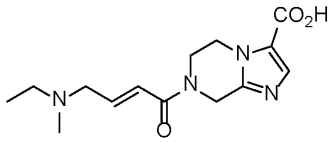
Step 1.3 Synthesis of ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylate



[0987] To a solution of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (818.22 mg, 4.19 mmol, 1 eq) in DCM (10 mL) were added (E)-4-[ethyl(methyl)amino]but-2-enoic acid (1.28 g, 7.13 mmol, 1.7 eq, HCl), T_4P (6.64 g, 9.22 mmol, 50% purity, 2.2 eq) and DIEA (2.17 g, 16.77 mmol, 2.92 mL, 4 eq) at 25°C. The reaction mixture was stirred at 25°C for 1hr. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel

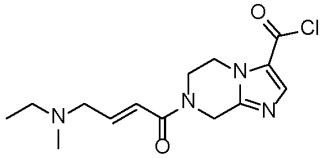
chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% DCM/MeOH gradient @ 100 mL/min). Compound ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate (3 g, crude) was obtained as a black oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.70 (s, 1H), 7.05-6.92 (m, 2H), 4.63 (s, 1H), 4.33-4.28 (q, J = 7.2 Hz, 2H), 4.07 (s, 2H), 3.76-3.71 (m, 2H), 3.65-3.59 (m, 2H), 3.09-3.03 (m, 2H), 2.58-2.51 (m, 2H), 1.36-1.32 (m, 3H), 1.25-1.20 (m, 3H).

Step 1.4 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



[0988] To a solution of ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylate (5 g, 15.61 mmol, 1 eq) in H_2O (20 mL) and EtOH(40 ml) was added $Ca(OH)_2$ (4.63 g, 62.42 mmol, 2.06 mL, 4 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hr. LCMS showed the reaction was complete. The reaction mixture was concentrated to remove the EtOH, then the reaction mixture was filtered and filtration was adjusted pH = 5 by 2N HCl, then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250*70mm,15 um); mobile phase: [H_2O (0.04% HCl)-ACN]; B%:0%, isocratic elution mode). Compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (1.5 g, 5.13 mmol, 32.88% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.20-11.12 (m, 1H), 8.87-7.96 (m, 1H), 7.14-6.99 (m, 1H), 6.80-6.73 (m, 1H), 5.05-4.93 (m, 2H), 4.41-4.31 (m, 1H), 4.11-4.05 (m, 2H), 4.40-3.93 (m, 2H), 3.87-3.78 (m, 2H), 3.19-3.00 (m, 2H), 2.68 (d, J = 4.4 Hz, 3H), 1.26 (t, J = 7.6 Hz, 3H).

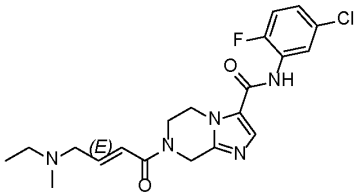
Step 1.5 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride



[0989] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (400 mg, 1.22 mmol, 1 eq, HCl) in DCM (4 mL) were

added DIEA (314.47 mg, 2.43 mmol, 423.81 µL, 2 eq), $(COCl)_2$ (435.00 mg, 3.43 mmol, 0.3 mL, 2.82 eq) and DMF (8.89 mg, 121.66 µmol, 9.36 µL, 0.1 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hr. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to give a residue. Without purification. Compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (400 mg, crude) was obtained as a black oil.

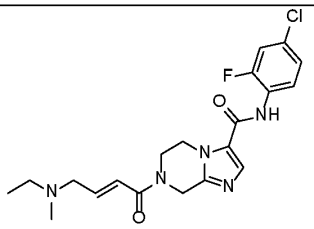
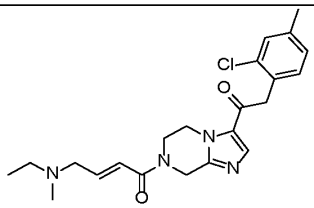
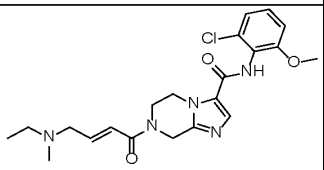
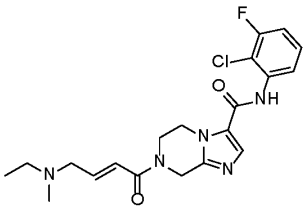
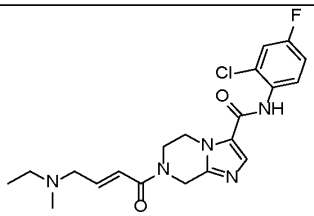
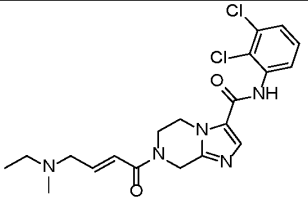
Step 1.6 Synthesis of N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

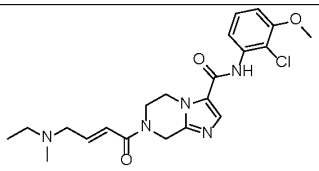
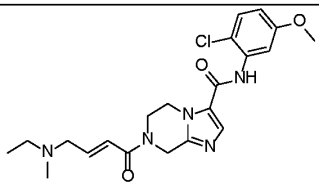
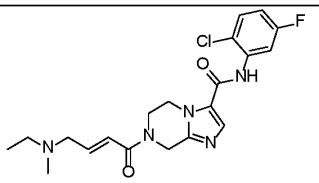
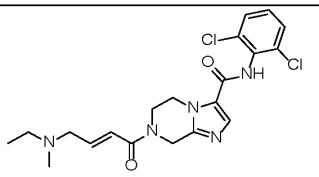
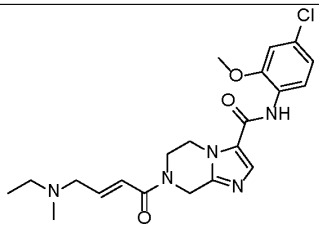
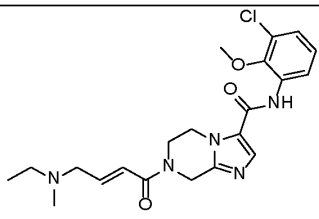


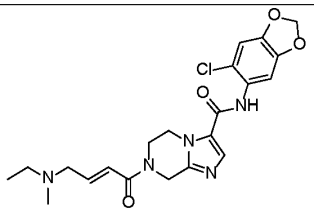
[0990] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride (200 mg, 643.55 µmol, 1 eq) in DCE (2 mL) were added DIEA (83.17 mg, 643.55 µmol, 112.09 µL, 1 eq) and 5-chloro-2-fluoro-aniline (140.51 mg, 965.32 µmol, 1.5 eq) at 25°C. The mixture was heated to 70°C and was stirred at 70 °C for 12hr. LC-MS showed 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride consumed and ~60% of desired compound was detected. The reaction mixture was cooled to 25° C and was quenched by addition H_2O (0.5 mL) at 25°C, and then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 100*30mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 10%-40% B over 8.0 min). Compound N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was obtained as a white solid. LCMS: *m/z* 420.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.87 (s, 1H), 7.73-7.72 (m, 1H), 7.36-7.30 (m, 2H), 6.72-6.70 (m, 2H), 4.91-4.75 (m, 2H), 4.32 (s, 2H), 4.01-3.96 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).

[0991] Compounds in Table E were synthesized following the procedure for N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

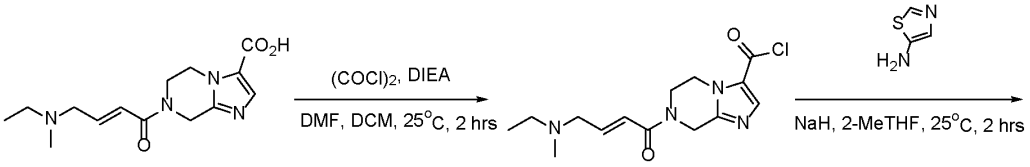
Table E

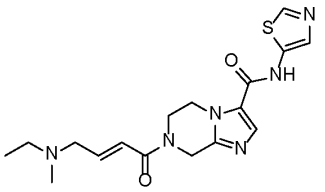
Name	Structure	NMR	LCMS
N-(4-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.00 (s, 1H), 7.85 (s, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.37 (dd, J = 10.8 Hz, 2.4 Hz, 1H), 7.31-7.29 (m, 1H), 6.72-6.70 (m, 2H), 4.91 (s, 1H), 4.75 (s, 1H), 4.31 (s, 2H), 4.00-3.95 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 420.2 $[M+H]^+$
N-(2-chloro-4-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.77 (s, 1H), 7.84 (s, 1H), 7.39-7.33 (m, 1H), 7.18-7.16 (m, 1H), 6.75-6.66 (m, 2H), 4.91-4.69 (m, 2H), 4.31 (s, 2H), 4.00-3.95 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 416.2 $[M+H]^+$
N-(2-chloro-6-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.03 (s, 1H), 9.73 (s, 1H), 8.09 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 7.14-7.09 (m, 2H), 7.06 (d, J = 15.2 Hz, 1H), 6.79-6.72 (m, 1H), 4.95 (s, 2H), 4.41-4.40 (m, 2H), 4.08-4.07 (m, 2H), 3.92-3.85 (m, 2H), 3.87 (s, 3H), 3.17-3.08 (m, 2H), 2.71 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H).	LCMS: m/z 432.2 $[M+H]^+$
N-(3-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ10.09 (s, 1H), 7.86 (s, 1H), 7.51-7.42 (m, 2H), 7.24 (td, J = 8.0 Hz, 0.8 Hz, 1H), 6.76-6.66 (m, 2H), 4.91 (s, 1H), 4.75 (s, 1H), 4.29 (m, 2H), 4.00-3.96 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.37 (q, J = 11.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 420.2 $[M+H]^+$
N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d$_6$, 400 MHz) δ 9.89-9.85 (m, 1H), 7.80 (s, 1H), 7.56-7.54 (m, 2H), 7.24-7.22 (m, 1H), 6.71-6.69 (m, 2H), 4.90-4.73 (m, 2H), 4.32-4.29 (m, 2H), 4.00-3.99 (m, 2H), 3.12 (d, J = 4.8 Hz, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 420.2 $[M+H]^+$
N-(2,3-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.40 (s, 1H), 7.88 (s, 1H), 7.56-7.51 (m, 1H), 7.42-7.38 (m, 1H), 6.76-6.70 (m, 2H), 4.92-4.75 (m, 2H), 4.31-4.28 (m, 2H), 4.01-3.95 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.14 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 436.2 $[M+H]^+$

Name	Structure	NMR	LCMS
N-(2-chloro-3-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.74 (s, 1H), 7.86 (s, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.71-6.70 (m, 2H), 4.90-4.75 (m, 2H), 4.31-4.30 (m, 2H), 4.00-3.95 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.35 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 432.2 $[M+H]^+$
N-(2-chloro-5-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.91 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 6.97 (d, J = 15.2 Hz, 1H), 6.87 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 6.69-6.62 (m, 1H), 4.86 (s, 2H), 4.37-4.36 (m, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.92-3.88 (m, 2 H), 3.75 (s, 3H), 3.17-3.09 (m, 2H), 2.74 (s, 3H), 1.24 (t, J = 7.6 Hz, 3H).	LCMS: m/z 432.2 $[M+H]^+$
N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.89 (s, 1H), 7.88 (s, 1H), 7.62-7.54 (m, 2H), 7.16 (t, J = 2.4 Hz, 1H), 6.74-6.72 (m, 2H), 4.93-4.77 (m, 2H), 4.35-4.29 (m, 2H), 4.03-3.97 (m, 2H), 3.15 (d, J = 4.4 Hz, 2H), 2.39 (q, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.01 (t, J = 6.8 Hz, 3H).	LCMS: m/z 420.2 $[M+H]^+$
(E)-N-(2,6-dichlorophenyl)-7-(4-(ethyl(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1 ,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.11 (s, 1H), 7.89 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 6.71-6.69 (m, 2H), 4.91-4.75 (m, 2H), 4.30-4.29 (m, 2H), 4.01-3.96 (m, 2H), 3.13 (d, J = 4.8 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.13 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 436.1 $[M+H]^+$
N-(4-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.14 (s, 1H), 9.40 (s, 1H), 8.10 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 7.03-6.99 (m, 2H), 6.99-6.78 (m, 1H), 4.96 (s, 2H), 4.32 (t, J = 4.4 Hz, 2H), 4.07 (t, J = 7.2 Hz, 2H), 3.92-3.88 (m, 2H), 3.87 (s, 3H), 3.21-3.06 (m, 2H), 2.71 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H).	LCMS: m/z 432.2 $[M+H]^+$
N-(3-chloro-2-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.64 (s, 1H), 7.89 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 6.8 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 6.72-6.70 (m, 1H), 4.92-4.76 (m, 2H), 4.33-4.30 (m, 2H), 4.01-3.94 (m, 2H), 3.76 (s, 3H), 3.13 (d, J = 4.8 Hz, 1H), 2.37 (q, J = 6.8 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H).	LCMS: m/z 432.2 $[M+H]^+$

Name	Structure	NMR	LCMS
N-(6-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.15 (s, 1H), 9.88 (s, 1H), 8.12 (s, 1H), 7.12 (s, 1H) 7.08-7.03 (m, 2H), 6.80-6.72 (m, 1H), 6.10 (s, 1H), 4.96 (s, 2H), 4.42-4.41 (m, 2H), 4.08-4.07 (m, 2H), 3.92-3.91 (m, 2H), 3.18-3.06 (m, 2H), 2.71 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H).	LCMS: m/z 446.2 $[M+H]^+$

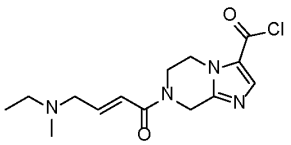
General method L





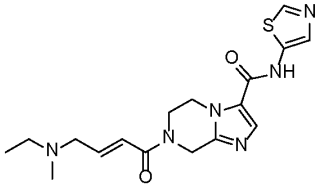
Example 146. Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride



[0992] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (2.5 g, 7.60 mmol, 1 eq, HCl) in DCM (25 mL) were added DIEA (1.97 g, 15.21 mmol, 2.65 mL, 2 eq) and DMF (55.58 mg, 760.36 µmol, 58.50 µL, 0.1 eq) at 25°C. And then oxalyl dichloride (2.90 g, 22.81 mmol, 2.00 mL, 3 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed the reaction was complete after quenching with MeOH. The reaction mixture was concentrated under reduced pressure to give compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (2.5 g, crude) as a brown solid. LCMS: m/z 307.2 $[M+H]^+$

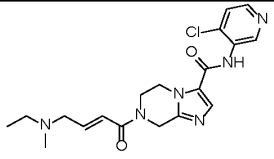
Step 1.2 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

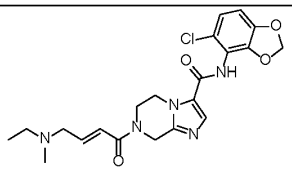


[0993] To a solution of thiazol-5-amine (96.67 mg, 965.32 μmol, 1.2 eq) in 2-MeTHF (2 mL) was added NaH (45.05 mg, 1.13 mmol, 60% purity, 1.4 eq) in portions at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was heated to 60°C and stirred at 60°C for 2 hrs. And then the reaction mixture was cooled to 25°C, then 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (0.25 g, 804.43 μmol, 1 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS and HPLC showed the reaction completed. The reaction mixture was cooled to 0°C and quenched with sat. aq. NH_4Cl (2 mL) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed up to 25°C. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 1%-35% B over 8.0 min). The residue was dried over lyophilization to give compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (56 mg, 141.46 μmol, 17.58% yield, 94.59% purity) as a brown solid. LCMS: m/z 375.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.51 (s, 1H), 8.59 (s, 1H), 7.86 (s, 1H), 7.72 (s, 1H), 6.77-6.68 (m, 2H), 4.93-4.77 (m, 2H), 4.38-4.31 (m, 2H), 4.02-3.97 (m, 2H), 3.15 (d, J = 4.4 Hz, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.00 (t, J = 7.2 Hz, 3H).

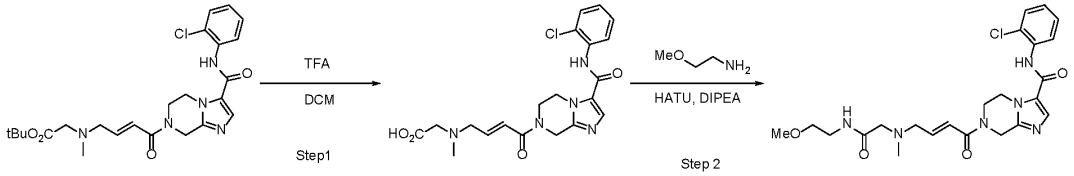
[0994] Compounds in Table F were synthesized following the procedure for 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-thiazol-5-yl-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table F

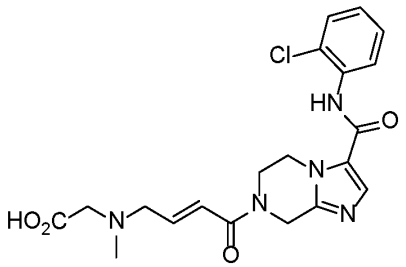
Name	Structure	NMR	LCMS
N-(4-chloro-3-pyridyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-		^1H NMR (DMSO-d_6, 400 MHz) δ 10.82 (s, 1 H), 10.21 (s, 1H), 8.70 (s, 1H), 8.44 (d, J = 5.6 Hz, 1H), 8.12 (s, 1H), 7.66 (d, J = 5.2 Hz, 1H), 7.06 (d, J = 15.2 Hz, 1H), 6.78-6.71 (m, 1H), 4.94 (s, 2H), 4.41 (t, J = 5.2 Hz, 2H),	LCMS: m/z 403.2 $[M+H]^+$

Name	Structure	NMR	LCMS
a]pyrazine-3-carboxamide		4.06 (t, *J* = 4.4 Hz, 2H), 3.93-3.72 (m, 2H), 3.17-3.07 (m, 2H), 2.72 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H).	
N-(5-chloro-1,3-benzodioxol-4-yl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.29 (s, 1 H), 10.14 (s, 1H), 8.21 (s, 1H), 7.07-7.00 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 6.80-6.75 (m, 1H), 6.09 (s, 2H), 4.98 (s, 2H), 4.43 (t, *J* = 5.2 Hz, 2H), 3.90 (t, *J* = 5.2 Hz, 2H), 3.92-3.85 (m, 2H), 3.16-3.07 (m, 2H), 2.70 (s, 3H), 1.29 (t, *J* = 7.6 Hz, 3H).	LCMS: m/z 446.2 $[M+H]^+$

Example 147. Synthesis of (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-((2-methoxyethyl)amino)-2-oxoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide.

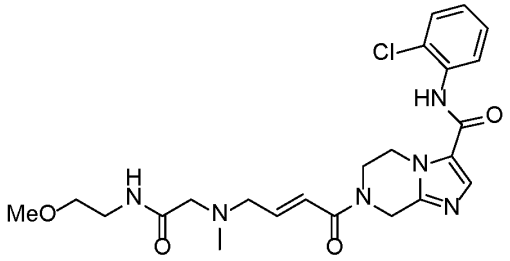


Step 1: Synthesis of (E)-N-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)-4-oxobut-2-en-1-yl)-N-methylglycine

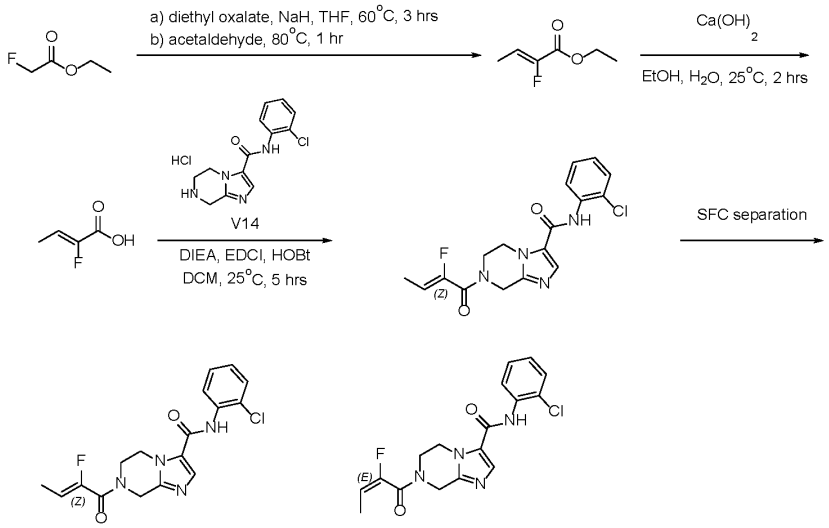


[0995] To a solution of *tert*-butyl (*E*)-*N*-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-*N*-methylglycinate (130 mg, 266.41 μmol) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at room temperature overnight. The reaction solution was concentrated, the residue was purified by Prep-HPLC under basic condition to give to give (*E*)-*N*-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-*N*-methylglycine (80 mg, 185.24 μmol, 69.53% yield, 100% purity) as white solid. LCMS: *m/z* 432.1 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.68 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.8, 1.5 Hz, 1H), 7.25 (td, *J* = 7.8, 1.6 Hz, 1H), 7.06 – 6.93 (m, 1H), 6.89 – 6.77 (m, 1H), 5.01 – 4.91 (m, 2H), 4.56 – 4.38 (m, 2H), 4.15 – 4.05 (m, 2H), 3.97 (d, *J* = 7.0 Hz, 2H), 3.64 (s, 2H), 2.88 (s, 3H).

Step 2: Synthesis of (E)-N-(2-chlorophenyl)-7-(4-((2-((2-methoxyethyl)amino)-2-oxoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

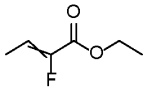


[0996] To a solution of 2-methoxyethanamine (7.83 mg, 104.20 μmol, 9.06 μL) , (*E*)-*N*-(4-(3-((2-chlorophenyl)carbamoyl)-5,6-dihydroimidazo[1,2-*a*]pyrazin-7(8*H*)-yl)-4-oxobut-2-en-1-yl)-*N*-methylglycine (30 mg, 69.47 μmol) and HATU (52.83 mg, 138.93 μmol) in DMF (3 mL) was added DIPEA (17.96 mg, 138.93 μmol, 24.20 μL). The resulting mixture was stirred at room temperature overnight and then purified by Prep-HPLC under basic condition to give (*E*)-*N*-(2-chlorophenyl)-7-(4-((2-((2-methoxyethyl)amino)-2-oxoethyl)(methyl)amino)but-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine-3-carboxamide (30 mg, 61.35 μmol, 88.32% yield, 100% purity) as a white solid. LCMS: *m/z* 489.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.7 Hz, 1H), 8.12 (s, 1H), 7.64 (s, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 (s, 1H), 7.34 – 7.29 (m, 1H), 7.09 (td, *J* = 7.8, 1.5 Hz, 1H), 7.01 – 6.91 (m, 1H), 6.47 (d, *J* = 15.3 Hz, 1H), 4.94 (s, 2H), 4.51 (s, 2H), 4.20 – 3.87 (m, 2H), 3.50 – 3.45 (m, 4H), 3.36 (s, 3H), 3.25 (d, *J* = 6.1 Hz, 2H), 3.06 (s, 2H), 2.33 (s, 3H).



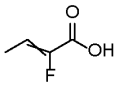
Example 148. Synthesis of N-(2-chlorophenyl)-7-[2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide, N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7-[(E)-2- fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of 2-fluorobut-2-enoic acid



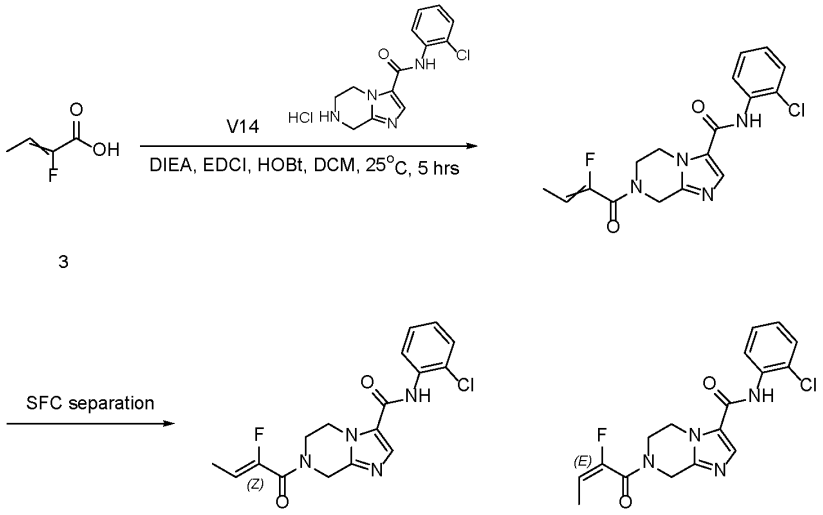
[0997] To a solution of NaH (3.77 g, 94.25 mmol, 60% purity, 1 *eq*) in THF (50 mL) were added ethyl 2-fluoroacetate (2 g, 18.85 mmol, 1.83 mL, 0.2 *eq*) and diethyl oxalate (13.77 g, 94.25 mmol, 12.87 mL, 1 *eq*) in portions at 0°C, nitrogen atmosphere protection was applied. Then ethyl 2-fluoroacetate (8.00 g, 75.40 mmol, 7.33 mL, 0.8 *eq*) was added to the reaction mixture dropwise at 25°C. The reaction mixture was heated to 60°C and stirred at 60°C for 3 hrs. The reaction mixture was cooled to 0°C. And then acetaldehyde (5 M, 19.23 mL, 1.02 *eq*) was added to the reaction mixture dropwise at 0°C. The reaction mixture was heated to 80°C and stirred at 80°C for 1 hr. HPLC showed the reaction was complete. The reaction mixture was cooled to 25°C and poured into ice water (60 mL) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed up to 25°C, the organic phase was separated, and then the aqueous phase was extracted with DCM (20 mL x 3), the combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give ethyl 2-fluorobut-2-enoate (17 g, crude) was obtained as brown oil.

Step 1.2 Synthesis of 2-fluorobut-2-enoic acid



[0998] To a solution of ethyl 2-fluorobut-2-enoate (3 g, 22.70 mmol, 1 eq) in EtOH (15 mL) and H_2O (30 mL) was added $Ca(OH)_2$ (5.55 g, 74.92 mmol, 2.48 mL, 3.3 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was cooled to 0°C and adjusted pH to 3 with HCl (2 M) at 0°C. Then the reaction mixture was concentrated under reduced pressure to give 2-fluorobut-2-enoic acid (2 g, crude) was obtained as yellow oil. LCMS: m/z 103.3 $[M-H]^-$. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 5.88-5.76 (m, 1H, cis), 5.48-5.39 (m, 0.8H, trans), 1.93-1.90 (m, 2H, cis), 1.60-1.57 (m, 3H, trans).

Step 1.3 Synthesis of N-(2-chlorophenyl)-7-[2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide, N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7-[(E)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



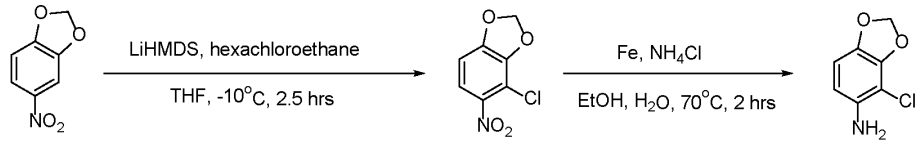
[0999] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (50 mg, 159.65 μmol, 1 eq, HCl) in DCM (0.5 mL) were added 2-fluorobut-2-enoic acid (166.16 mg, 1.60 mmol, 10 eq), DIEA (123.80 mg, 957.91 μmol, 166.85 μL, 6 eq), HOBt (32.36 mg, 239.48 μmol, 1.5 eq) and EDCI (39.79 mg, 207.55 μmol, 1.3 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 5 hrs. The reaction mixture was poured into water (0.1 mL) and stirred for 2 min at 25°C, concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100*30mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide (100 mg, 27.01 μmol, 1 eq) as an off-white solid, 90 mg was separated by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [CO_2-EtOH]; B%: 50%, isocratic elution mode) to give N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (30 mg, 80.46 μmol, 32.43% yield, 97.3% purity) as a white solid and N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (21 mg, 56.55 μmol, 22.80% yield, 97.7% purity) as a white solid.

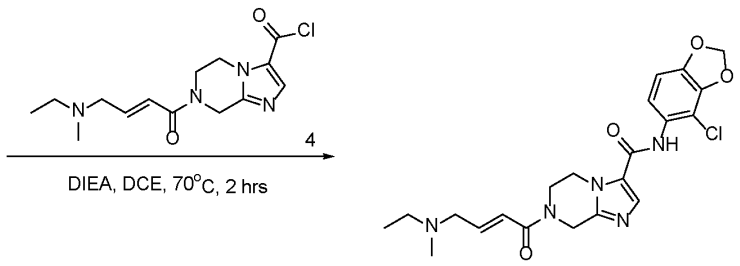
[01000] *N-(2-chlorophenyl)-7-[2-fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxamide*: LCMS: m/z 363.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.86 (s, 1H), 7.55-7.53 (m, 2H), 7.37 (t, J = 6.4 Hz, 1H), 7.27 (t, J = 6.8 Hz,

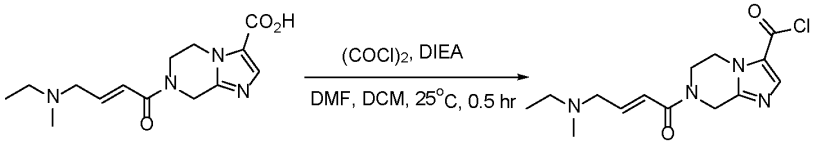
1H), 5.85-5.74 (m, 1H), 4.78 (s, 2H), 4.34-4.33 (m, 2H), 3.97-3.92 (m, 2H), 1.74-1.65 (m, 3H).

[01001] *N-(2-chlorophenyl)-7-[(Z)-2-fluorobut-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide*: LCMS: m/z 363.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.87 (s, 1H), 7.54 (t, J = 6.4 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 1.2 Hz, 1H), 5.80 (dq, J = 37.2 Hz, 6.8 Hz, 1H), 4.78 (s, 2H), 4.34 (t, J = 4.8 Hz, 2H), 3.95 (t, J = 5.2 Hz, 2H), 1.73 (dd, J = 6.8 Hz, 2.4 Hz, 3H).

[01002] *N-(2-chlorophenyl)-7-[(E)-2- fluorobut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide*: LCMS: m/z 363.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.88 (s, 1H), 7.54 (t, J = 5.6 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 5.84-5.74 (m, 1H), 4.78 (s, 2H), 4.34 (s, 2H), 4.01-3.92 (m, 2H), 1.65-1.64 (m, 3H).

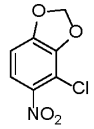






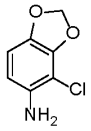
Example 149. Synthesis of N-(4-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl (methyl)amino]but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of 4-chloro-5-nitro-1,3-benzodioxole



[01003] To a solution of 5-nitro-1,3-benzodioxole (1 g, 5.98 mmol, 1 eq) in THF (10 mL) was added LiHMDS (1 M, 8.98 mL, 1.5 eq) dropwise at -10°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -10°C for 0.5 hr. Then hexachloroethane (2.12 g, 8.98 mmol, 1.02 mL, 1.5 eq) was added to the reaction mixture in portions at -10°C. The reaction mixture was stirred at -10°C for 2 hrs. LCMS and HPLC showed the reaction was complete. The reaction mixture was warmed to 0°C and quenched with sat. aq. NH_4Cl (10 mL) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed to 25°C and to the reaction mixture was added water (30 mL) 25°C. The reaction mixture was extracted with EtOAc (15 mL x 3), the combined organic phase was washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~15% Petroleum ether: Ethyl acetate gradient @ 45 mL/min). The eluent was removed under reduced pressure to give 4-chloro-5-nitro-1,3-benzodioxole (0.5 g, 2.48 mmol, 41.46% yield) as a yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.81 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.34 (s, 2H).

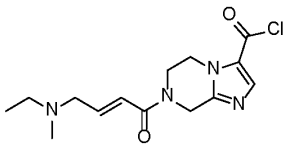
Step 1.2 Synthesis of tert-butyl 4-chloro-1,3-benzodioxol-5-amine



[01004] To a solution of 4-chloro-5-nitro-1,3-benzodioxole (0.2 g, 992.24 μmol, 1 eq) in EtOH (3 mL) and H_2O (1.5 mL) was added NH_4Cl (265.38 mg, 4.96 mmol, 5 eq) at 25°C, nitrogen atmosphere protection was applied. Then Fe (554.12 mg, 9.92 mmol, 10 eq) was added to the reaction mixture in portions at 25°C. The reaction mixture was heated to 70°C and stirred at 70°C for 2 hrs. LCMS and HPLC showed the reaction was complete. The reaction mixture was cooled to 25°C. The reaction mixture was filtered. To the filtrate was added water (30 mL) and the reaction mixture was extracted with EtOAc (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound 4-chloro-1,3-benzodioxol-5-amine (0.12 g, 699.38 μmol, 70.48% yield) was obtained as a brown solid.

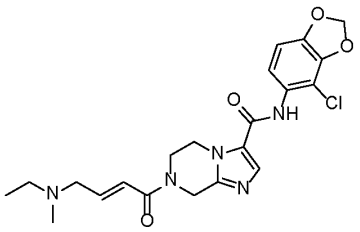
^1H NMR (DMSO-d_6, 400 MHz) δ 6.65 (d, J = 8.4 Hz, 1H), 6.24 (d, J = 8.4 Hz, 1H), 5.94 (s, 2H), 4.99 (s, 2H).

Step 1.3 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride



[01005] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (0.16 g, 486.63 μmol, 1 eq, HCl) in DCM (2 mL) were added DIEA (125.79 mg, 973.25 μmol, 169.52 μL, 2 eq) and DMF (3.56 mg, 48.66 μmol, 3.74 μL, 0.1 eq) at 25°C. And then oxalyl dichloride (185.30 mg, 1.46 mmol, 127.79 μL, 3 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 0.5 hr. LCMS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to give 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (0.15 g, crude) as a brown solid. LCMS: m/z 307.2 $[M+H]^+$.

Step 1.4 Synthesis of N-(4-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl (methyl)amino]but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

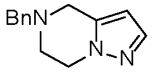


[01006] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride (0.15 g, 482.66 μmol, 1 eq) in DCE (2 mL) was added 4-chloro-1,3-benzodioxol-5-amine (119.25 mg, 695.03 μmol, 1.44 eq) at 25°C. And then DIEA (187.14 mg, 1.45 mmol, 252.21 μL, 3 eq) was added to the reaction mixture at 25°C. The reaction mixture was heated to 70°C and stirred at 70°C for 2 hrs. LCMS and HPLC showed the reaction completed. The reaction mixture was cooled to 25°C, quenched with water (0.1 mL) at 25°C and concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3)-ACN]; gradient: 30%-60% B over 8.0 min). The residue was dried over lyophilization to give N-(4-chloro-1,3-benzodioxol-5-yl)-7-[(E)-4-[ethyl (methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (73 mg, 159.95 μmol, 33.14% yield, 97.76% purity) as a yellow solid. LCMS: m/z 446.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.81 (s, 1H), 7.82 (s, 1H), 6.94-6.88 (m, 2H), 6.75-6.65 (m, 2H),

6.17 (s, 2H), 4.90-4.74 (m, 2H), 4.30-4.29 (m, 2H), 4.00-3.95 (m, 2H), 3.14 (d, *J* = 4.4 Hz, 2H), 2.38 (q, *J* = 7.6 Hz, 2H), 2.15 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

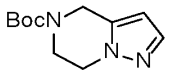
Example 150. Synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.

Step 1. Synthesis of 5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine



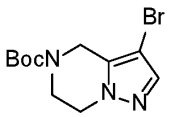
[01007] To a mixture 2-(((1*H*-pyrazol-1-yl)methyl)(benzyl)amino)ethan-1-ol (34 g, 147.00 mmol), Triphenylphosphine (50 g, 191.10 mmol) in toluene (300 mL) was stirred at 100°C for 2h. The mixture was concentrated and the residue was purified on silica flash chromatography with a gradient of EtOAc/DCM (0 to 40 percent, 40 g, Biotage) to obtain crude 5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (29 g) as a colorless oil. LCMS: *m/z* 214.2 $[M+H]^+$.

Step 2. Synthesis of tert-butyl 6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate



[01008] To a solution of 5-benzyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (17.86 g, 83.74 mmol) in Methanol (200 mL) was added 10% Pd/C (1.84 g, 15.19 mmol) and Di-*tert*-butyl dicarbonate (27.41 g, 125.61 mmol, 28.83 mL). The mixture was stirred at room temperature for 16 h under atmosphere of H_2. The mixture was filtered through Celite, washed with methanol. The filtrate was concentrated and the residue was purified on silica flash with a gradient of EtOAc/DCM (0 to 40 percent, 330 g, Biotage) to obtain *tert*-butyl 6,7-dihydropyrazolo[1,5-a]pyrazine-5(4*H*)-carboxylate (10.45 g, 46.80 mmol, 55.89% yield) as a colorless oil. LCMS: *m/z* 224.1 $[M+H]^+$.

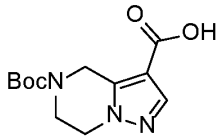
Step 3. Synthesis of tert-butyl 3-bromo-6,7-dihydro-4H-pyrazolo[1,5-a]pyrazine-5-carboxylate



[01009] To a solution of *tert*-butyl 6,7-dihydro-4H-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (10.4 g, 46.58 mmol) in DCM (200 mL) was added NBS (8.29 g, 46.58 mmol) slowly. The mixture was stirred at rt for 2 h. The mixture was poured into water (400 mL) and extracted with DCM (200 mL x 3). The organic layers was washed with brine (100 mL x 1), dried over Na_2SO_4, concentrated and purified on silica flash chromatography with a gradient of

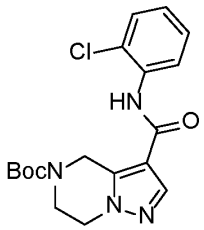
EtOAc/petroleum ether (0 to 20 percent, 40 g, Biotage) to give *tert*-butyl 3-bromo-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (6.4 g, 21.18 mmol, 45.47% yield) as yellow oil. LCMS: *m/z* 304.0[M+H]$^+$.

Step 4. Synthesis of 5-(tert-butoxycarbonyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxylic acid



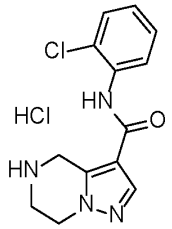
[01010] To a solution of *tert*-butyl 3-bromo-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (0.52 g, 1.72 mmol) in THF (10 mL) was added *n*-BuLi /THF(0.5 mL, 1.25 mmol) at -78 °C. The mixture was stirred for 30 min, then dry ice (757.36 mg, 17.21 mmol) was added. The resulting mixture was stirred for more 30 min. The reaction was quenched with water and adjusted with 1 N HCl to pH 4. The mixture was extracted with EtOAc (30 mL x 2). The extracts were dried over Na_2SO_4, filtered and concentrated to give 5-*tert*-butoxycarbonyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxylic acid (0.4 g, crude) as a yellow solid. LCMS: *m/z* 268.3[M+H]$^+$.

Step 5. Synthesis of tert-butyl 3-((2-chlorophenyl)carbamoyl)-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate



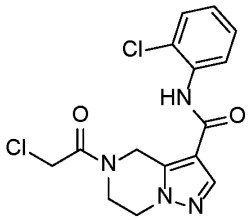
[01011] To a solution of 5-*tert*-butoxycarbonyl-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxylic acid (2.08 g, 7.78 mmol) in DMF (20 mL) were added 2-chloroaniline (1.99 g, 15.56 mmol) , *N*,*N*,*N*′,*N*′-Tetramethylchloroformamidinium hexafluorophosphate (4.37 g, 15.56 mmol) and 1-methylimidazole (2.56 g, 31.13 mmol, 2.48 mL). The mixture was stirred at 60 °C for 1 h. The mixture was concentrated and the residue was purified on silica flash chromatography with a gradient of EtOAc/PE (0 to 20 percent, 40 g, Biotage) to give *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-5-carboxylate (1.99 g, 2.64 mmol, 33.93% yield, 50% purity) as yellow oil. LCMS: *m/z* 268.3[M-Boc]$^+$.

Step 6. Synthesis of N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide hydrochloride (V15)



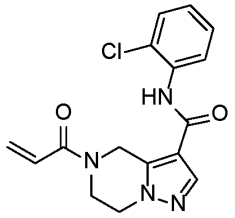
[01012] A mixture of *tert*-butyl 3-[(2-chlorophenyl)carbamoyl]-6,7-dihydro-4*H*-pyrazolo[1,5-a]pyrazine-5-carboxylate (0.18 g, 477.66 μmol) in 4M HCl/Dioxane (10 mL) was stirred at room temperature for 4 h. The mixture was concentrated to give *N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide (V15) (0.14 g, 447.02 μmol, 93.59% yield, CL) as off-white solid. LCMS: *m/z* 279.1[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.21 (s, 1H), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.35 (td, *J* = 7.7, 1.4 Hz, 1H), 7.26 (td, *J* = 7.8, 1.5 Hz, 1H), 4.77 (s, 2H), 4.50 (t, *J* = 5.8 Hz, 2H), 3.85 – 3.79 (m, 2H).

Step 7. Synthesis of 5-(2-chloroacetyl)-N-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide



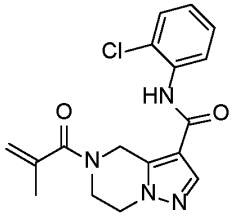
[01013] To a solution of *N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide (30 mg, 95.79 μmol, CL) and TEA (19.39 mg, 191.58 μmol, 26.70 μL) in DCM (3 mL) was added 2-chloroacetyl chloride (10.82 mg, 95.79 μmol, 7.64 μL) slowly. The mixture was stirred at rt for 1 h. The mixture was blow-dried with nitrogen and purified on prep-HPLC basic condition to give 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide (19.4 mg, 54.93 μmol, 57.34% yield) as white solid. LCMS: *m/z* 354.1[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.13 (d, *J* = 3.5 Hz, 1H), 7.70 (td, *J* = 7.2, 1.5 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 6.8 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 2H), 4.41 (d, *J* = 6.4 Hz, 2H), 4.34 (t, *J* = 5.5 Hz, 1H), 4.25 (t, *J* = 5.4 Hz, 1H), 4.11 (dt, *J* = 10.5, 4.9 Hz, 2H).

Example 151. Synthesis of 5-acryloyl-*N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



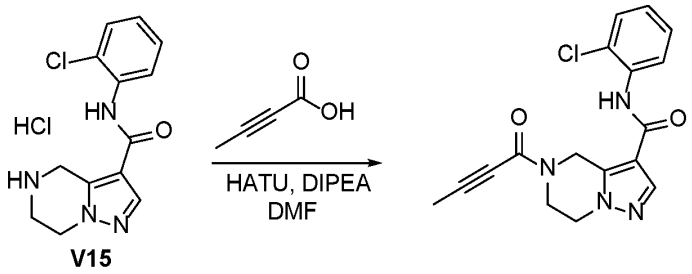
[01014] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of acryloyl chloride for 2-chloroacetyl chloride to a solution of *N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide (30 mg, 95.79 μmol, CL) and TEA (19.39 mg, 191.58 μmol, 26.70 μL) in DCM (3 mL) was added acryloyl chloride (8 mg, 95.79 μmol, 7.64 μL) slowly. The mixture was stirred at rt for 1 h. The mixture was blow-dried with nitrogen and purified on prep-HPLC basic condition to give provide the product 5-acryloyl-*N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 331.2 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.71 (s, 1H), 7.50 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.35 (td, *J* = 7.8, 1.4 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.95-6.76 (m, 1H), 6.29 (dd, *J* = 16.8, 1.7 Hz, 1H), 5.83 (dd, *J* = 10.7, 1.8 Hz, 1H), 5.16 (d, *J* = 11.4 Hz, 2H), 4.33-4.22 (m, 2H), 4.16 (t, *J* = 5.3 Hz, 2H).

Example 152. Synthesis of *N*-(2-chlorophenyl)-5-methacryloyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



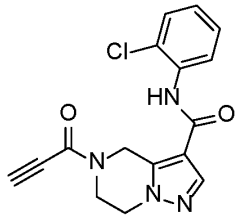
[01015] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of methacryloyl chloride to provide the product *N*-(2-chlorophenyl)-5-methacryloyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 345.3 $[M+H]^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.5 Hz, 1H), 7.24 (td, *J* = 7.8, 1.6 Hz, 1H), 5.37 (s, 1H), 5.21 (s, 1H), 5.12 (s, 2H), 4.27 (t, *J* = 5.3 Hz, 2H), 4.12 (t, *J* = 5.1 Hz, 2H), 1.98 (s, 3H).

Example 153. Synthesis of 5-(but-2-ynoyl)-*N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide.



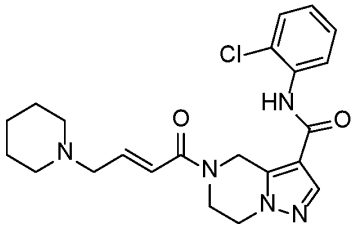
[01016] To a solution of *N*-(2-chlorophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide (30 mg, 95.79 μmol, CL), but-2-ynoic acid (8.05 mg, 95.79 μmol) and HATU (47.35 mg, 124.53 μmol) in DMF (2 mL) was added DIPEA (37.14 mg, 287.37 μmol, 50.05 μL). The mixture was stirred at rt for 1 h. The mixture was purified on prep-HPLC basic condition to give 5-but-2-ynoyl-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide (6.5 mg, 18.96 μmol, 19.80% yield) as white solid. LCMS: *m/z* 342.7[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, *J* = 20.8 Hz, 1H), 8.22 (d, *J* = 5.7 Hz, 1H), 7.58-7.52 (m, 2H), 7.41-7.33 (m, 1H), 7.32-7.24 (m, 1H), 5.16 (s, 1H), 4.91 (s, 1H), 4.28-4.23 (m, 1H), 4.22-4.12 (m, 2H), 4.00 (d, *J* = 6.0 Hz, 1H), 2.06 (d, *J* = 11.8 Hz, 3H).

Example 154. Synthesis of *N*-(2-chlorophenyl)-5-propioloyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



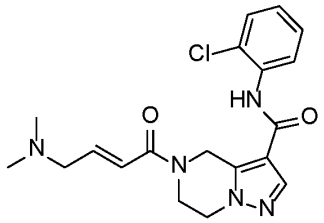
[01017] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of propiolic acid for but-2-ynoic acid to provide the product *N*-(2-chlorophenyl)-5-propioloyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 329.3[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.14 (d, *J* = 3.3 Hz, 1H), 7.70 (ddd, *J* = 8.0, 3.2, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.2, 3.1, 1.5 Hz, 1H), 7.39-7.31 (m, 1H), 7.27-7.20 (m, 1H), 5.35 (s, 1H), 5.10 (s, 1H), 4.34 (s, 2H), 4.25 (t, *J* = 5.4 Hz, 1H), 4.15 (dd, *J* = 9.9, 6.2 Hz, 2H).

Example 155. Synthesis of (*E*)-*N*-(2-chlorophenyl)-5-(4-(piperidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



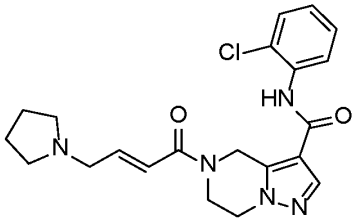
[01018] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(piperidin-1-yl)but-2-enoic acid for but-2-ynoic acid to provide the product (*E*)-*N*-(2-chlorophenyl)-5-(4-(piperidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 428.3[M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.70 (t, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.35 (td, *J* = 7.8, 1.3 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.90-6.73 (m, 2H), 5.15 (d, *J* = 10.3 Hz, 2H), 4.33-4.22 (m, 2H), 4.18-4.13 (m, 2H), 3.41 (t, *J* = 8.0 Hz, 2H), 2.81-2.59 (m, 4H), 1.68 (s, 4H), 1.53 (d, *J* = 3.4 Hz, 2H).

Example 156. Synthesis of (*E*)-*N*-(2-chlorophenyl)-5-(4-(dimethylamino)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



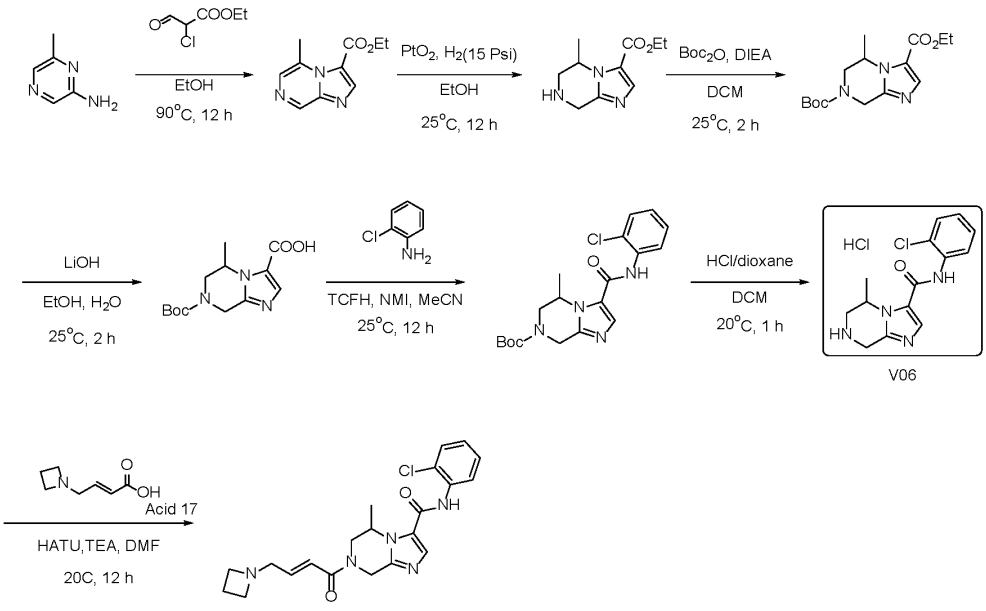
[01019] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(dimethylamino)but-2-enoic acid hydrochloride for but-2-ynoic acid to provide the product (*E*)-*N*-(2-chlorophenyl)-5-(4-(dimethylamino)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-3-carboxamide. LCMS: *m/z* 388.1 [M+H]$^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 6.3 Hz, 1H), 6.88-6.70 (m, 2H), 5.15 (d, *J* = 12.7 Hz, 2H), 4.28 (d, *J* = 14.3 Hz, 2H), 4.16 (t, *J* = 5.3 Hz, 2H), 3.34 (s, 2H), 2.41 (s, 6H).

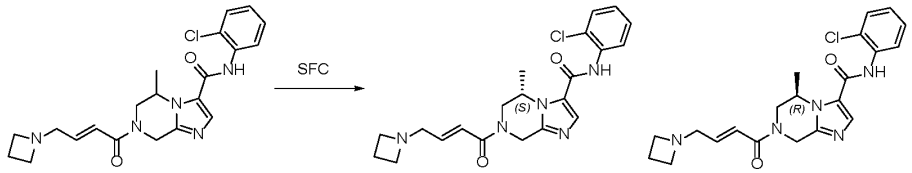
Example 157. Synthesis of (*E*)-*N*-(2-chlorophenyl)-5-(4-(pyrrolidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide.



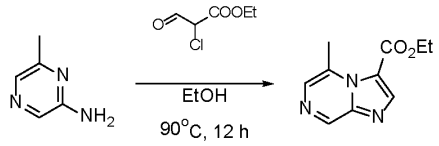
[01020] The method as described for the synthesis of 5-(2-chloroacetyl)-*N*-(2-chlorophenyl)-6,7-dihydro-4*H*-pyrazolo[1,5-*a*]pyrazine-3-carboxamide was applied with substitution of (*E*)-4-(pyrrolidin-1-yl)but-2-enoic acid hydrochloride for but-2-ynoic acid to provide the product (*E*)-*N*-(2-chlorophenyl)-5-(4-(pyrrolidin-1-yl)but-2-enoyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine-3-carboxamide. LCMS: *m/z* 414.1 $[M+H]^+$. ^{1}HNMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.35 (td, *J* = 7.8, 1.3 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.93-6.65 (m, 2H), 5.15 (d, *J* = 14.7 Hz, 2H), 4.37-4.21 (m, 2H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.40 (d, *J* = 6.2 Hz, 2H), 2.66 (s, 4H), 1.85 (s, 4H).

Example 158. Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-N-(2-chlorophenyl) -5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide





Step 1.1. Synthesis of ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate

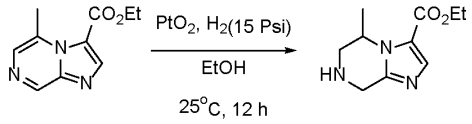


1 2

[01021] To a solution of 6-methylpyrazin-2-amine (20 g, 183.27 mmol, 1 eq) in EtOH (200 mL) was added ethyl 2-chloro-3-oxo-propanoate (33.11 g, 219.92 mmol, 1.2 eq) at 25°C. The reaction mixture was heated to 90°C and stirred at 90°C for 12 hours. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. The reaction mixture was diluted with water (400 mL), then the reaction mixture was adjusted pH = 8 by sat.aq. NaOH at 0°C. The reaction mixture was warmed to 25°C and extracted with EtOAc (250 mL x 3), the combined organic phase was washed with brine (250 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 220 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Petroleum ether: Ethyl acetate gradient @ 150 mL/min). The eluent was removed under

reduced pressure to give ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (22 g, 107.21 mmol, 58.50% yield) as a brown solid. LCMS: m/z 206.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.09 (s, 1H), 8.36 (s, 1H), 7.98 (s, 1H), 4.34 (q, J = 6.4 Hz, 2H), 2.75 (s, 3H), 1.37 (t, J = 6.8 Hz, 3H).

Step 1.2. Synthesis of ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate



2 3

[01022] To a solution of PtO_2 (0.9 g, 3.96 mmol) in EtOH (500 mL) was added ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (22 g, 107.21 mmol, 1 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 12 hr under H_2 (15 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxylate (22 g, crude) as brown oil. LCMS: m/z 210.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.59 (s, 1H), 4.69-4.64 (m, 1H), 4.28-4.21 (m, 3H), 4.00-3.96 (m, 1H), 3.86-3.82 (m, 1H), 3.07-3.04 (m, 1H), 2.99-2.96 (m, 1H), 1.38 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 6.8 Hz, 3H).

Step 1.3. Synthesis of O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine- 3,7-dicarboxylate

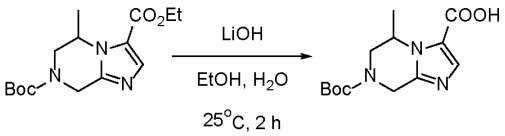


3 4

[01023] To a solution of ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (22 g, 105.14 mmol, 1 eq) in DCM (220 mL) was added DIEA (20.38 g, 157.71 mmol, 27.47 mL, 1.5 eq) at 25°C. Then Boc_2O (27.54 g, 126.17 mmol, 28.99 mL, 1.2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was cooled to 0°C and was adjusted pH = 6 by sat.aq. citric acid at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed up to 25°C and to the reaction mixture was added water (300 mL). The organic phase was separated, the aqueous phase was extracted with DCM (100 mL x 3), the combined organic phase was washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (28 g, crude) as a brown solid. LCMS: m/z 310.1 $[M+H]^+$ ^1H NMR (DMSO-d_6,

400 MHz) δ 7.64 (s, 1H), 4.90-4.88 (m, 3H), 4.29-4.22 (m, 4H), 1.44-1.42 (m, 12H), 1.28-1.26 (m, 3H).

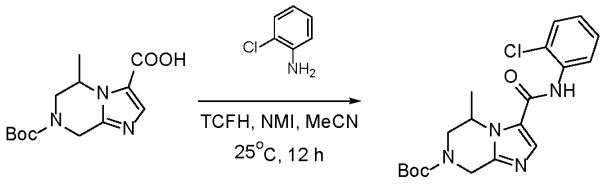
Step 1.4. Synthesis of 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



4 5

[01024] To a solution of O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3,7-dicarboxylate (28 g, 90.51 mmol, 1 *eq*) in EtOH (200 mL) was added a solution of $LiOH{\cdot}H_2O$ (11.39 g, 271.53 mmol, 3 *eq*) in H_2O (100 mL) at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hours. The reaction mixture was concentrated under reduced pressure and then cooled to 0°C, then the reaction mixture was adjusted pH = 4 by 1 M HCl at 0°C. The reaction mixture was warmed up to 25°C and to the reaction mixture was added water (200 mL). The reaction mixture was extracted with DCM (70 mL x 3), the combined organic phase was washed with brine (70 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was triturated with Petroleum ether (70 mL) at 25°C for 30 mins. Compound 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3- carboxylic acid (26 g, crude) was obtained as a brown solid. LCMS: m/z 282.1 $[M+H]^+$ ^1H NMR (DMSO-d_6, 400 MHz) δ 7.56 (s, 1H), 4.91-4.90 (m, 2H), 4.27-4.05 (m, 2H), 3.68-3.62 (m, 1H), 1.44 (s, 9H), 1.28-1.26 (m, 3H).

Step 1.5. Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate

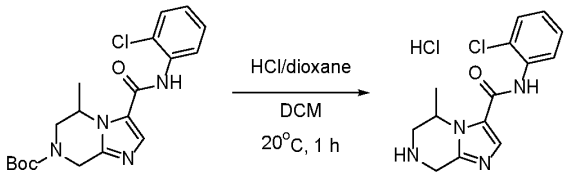


5 6

[01025] To a solution of 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (1 g, 3.55 mmol, 1 eq) in MeCN (10 mL) was added NMI (875.56 mg, 10.66 mmol, 850.05 µL, 3 eq) dropwise at 0°C, nitrogen atmosphere protection was applied. Then 2-chloroaniline (680.24 mg, 5.33 mmol, 562.18 µL, 1.5 eq) and TCFH (2.99 g, 10.66 mmol, 3 eq) were added to the reaction mixture at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 12 hours. To the reaction mixture was added water (30 mL) at

25°C and the reaction mixture was extracted with EtOAc (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Petroleum ether: Ethyl acetate gradient @ 40 mL/min). The eluent was removed under reduced pressure to give tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (1.5 g, crude) was obtained as yellow oil. LCMS: m/z 391.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.95 (s, 1H), 7.97 (s, 1H), 7.57-7.52 (m, 2H), 7.39-7.28 (m, 2H), 5.04-4.94 (m, 2H), 4.42-4.31 (m, 1H), 4.20-4.08 (m, 1H), 3.57-3.40 (m, 1H), 1.45 (s, 9H), 1.31 (d, J = 6.0 Hz, 3H).

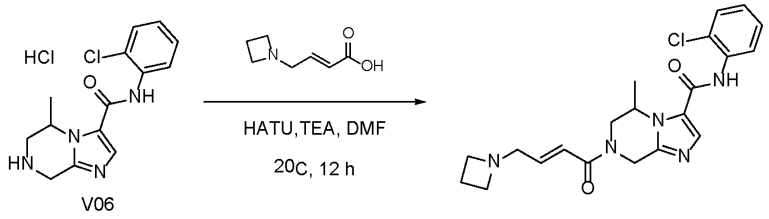
Step 1.6. Synthesis of N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide



6 V06

[01026] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate (1.5 g, 1.92 mmol, 1 eq) in DCM (8 mL) was added HCl/dioxane (4 M, 7.5 mL) at 20°C. The reaction mixture was stirred at 20°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (0.6 g, crude, HCl) was obtained as a yellow solid. LCMS: m/z 291.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.64 (s, 1H), 8.41 (s, 1H), 7.58-7.49 (m, 2H), 7.41-7.37 (m, 2H), 5.28-5.25 (m, 1H), 3.75-3.56 (m, 5H), 1.60 (t, J = 6.8 Hz, 3H).

Step 1.7. Synthesis of 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

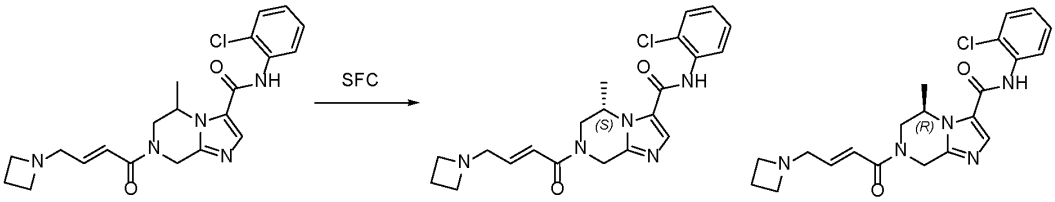


V06

[01027] To the reaction mixture of N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (300.00 mg, 916.85 μmol, 1 eq, HCl), (E)-

4-(azetidin-1-yl)but-2-enoic acid (244.29 mg, 1.38 mmol, 1.5 eq) in DMF (3 mL) were added HATU (871.53 mg, 2.29 mmol, 2.5 eq), TEA (371.10 mg, 3.67 mmol, 510.45 µL, 4 eq) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed to 20°C and stirred at 20°C for 12 hours. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm *10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 8.0 min). The residue was dried over lyophilization. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 5:1). Compound 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (7 mg, 16.10 µmol, 1.76% yield, 95.19% purity) was obtained as a white solid. LCMS: m/z 414.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38-7.29 (m, 2H), 6.68-6.62 (m, 2H), 5.28-5.19 (m, 1H), 5.15-5.14 (m, 1H), 4.66-4.60 (m, 1H), 4.29-4.25 (m, 1H), 3.72-3.68 (m, 1H), 3.24-3.12 (m, 6H), 2.02-1.95 (m, 2H), 1.29-1.25 (m, 3H).

Step 1.8. Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-N-(2-chlorophenyl) -5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

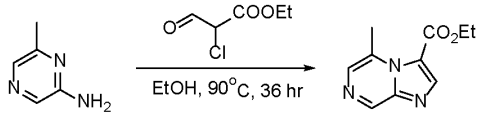


[01028] To the reaction mixture of N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.55 g, 1.68 mmol, 1 eq, HCl), (E)-4-(azetidin-1-yl)but-2-enoic acid (237.29 mg, 1.68 mmol, 1 eq) in DMF (5 mL) was added DIEA (1.09 g, 8.40 mmol, 1.46 mL, 5 eq) at 20°C, nitrogen atmosphere protection was applied. Then HOBt (499.67 mg, 3.70 mmol, 2.2 eq), EDCI (805.56 mg, 4.20 mmol, 2.5 eq) were added to the reaction mixture. The reaction mixture was stirred at 20°C for 2 hours. The reaction mixture was quenched with water (0.1 mL). The crude product was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min). The residue was dried over lyophilization. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 5:1). The residue was further separated by SFC (condition: column: Chiral Pak IH, 250 * 30 mm, 10 um; mobile phase: [CO_2 – IPA (0.1% NH_3H_2O)]; B%: 45%, isocratic elution mode). The residue was dried over

lyophilization to give (5R)-N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (11.2 mg, 26.80 μmol, 1.59% yield, 99.04% purity) as a pale yellow solid and (5S)-N-(2-chlorophenyl)-5-methyl-7-[rac-(E)-4-(azetidin-1-yl) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (12.0 mg, 28.97 μmol, 1.72% yield, 99.91% purity) as a pale yellow solid. LCMS: m/z 414.2 $[M+H]^+$; LCMS: m/z 414.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.55-7.53 (m, 2H), 7.39-7.26 (m, 2H), 6.67-6.58 (m, 2H), 5.27-5.07 (m, 2H), 4.71-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.71-3.68 (m, 1H), 3.21-3.12 (m, 6H), 2.02-1.95 (m, 2H), 1.29-1.25 (m, 3H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.55-7.53 (m, 2H), 7.39-7.28 (m, 2H), 6.63-6.58 (m, 2H), 5.28-5.06 (m, 2H), 4.71-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.71-3.68 (m, 1H), 3.25-3.15 (m, 6H), 2.02-1.95 (m, 2H), 1.29-1.25 (m, 3H).

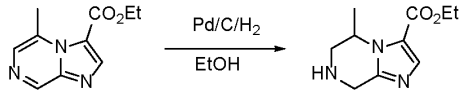
Example 159. Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

Step 1.1 Synthesis of ethyl imidazo[1,2-a]pyrazine-3-carboxylate



[01029] To a solution of 6-methylpyrazin-2-amine (25 g, 229.09 mmol, 1 eq) in EtOH (250 mL) was added ethyl 2-chloro-3-oxo-propanoate (41.39 g, 274.90 mmol, 1.2 eq) at 25°C. The reaction mixture was heated to 90°C and the reaction mixture was stirred at 90 °C for 36 hr. The reaction mixture was cooled to 25°C and the reaction mixture was concentrated under reduced pressure to give a residue, The residue was diluted with H_2O (100 mL) and the reaction mixture was adjusted pH = 7 by 1 M HCl, then the reaction mixture was extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 150 mL/min). Compound ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (27 g, 131.57 mmol, 57.43% yield) was obtained as a yellow solid. LCMS: m/z 192.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.09 (s, 1H), 8.38 (s, 1H), 7.88 (s, 1H), 4.41 (q, J = 7.2 Hz, 1H), 2.86 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H).

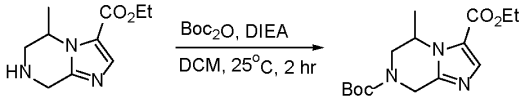
Step 1.2 Synthesis of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate



2 3

[01030] To a solution of ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (27 g, 131.57 mmol, 1 eq) in EtOH (400 mL) was added Pd/C (20 g, 9.40 mmol, 5% purity) at 25°C and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 80°C for 3.3 min under H_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. Compound ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (24 g, 114.70 mmol, 87.18% yield) was obtained as a yellow solid. LCMS: m/z 196.0 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 4.86-4.82 (m, 1H), 4.31 (qd, *J* = 7.2 Hz, 2.4 Hz, 2H), 4.24-4.19 (m, 1H), 4.08-4.04 (m, 1H), 3.21 (dd, *J* = 13.6 Hz, 4.0 Hz, 1H), 3.11-3.08 (m, 1H), 1.48 (d, *J* = 11.6 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

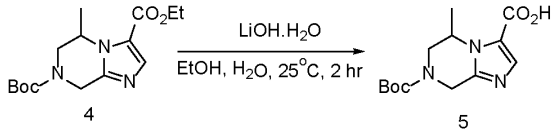
Step 1.3 Synthesis of O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate



3 4

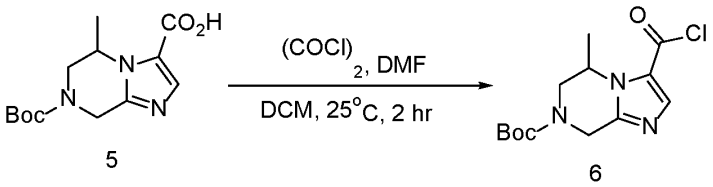
[01031] To a solution of ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (24 g, 114.70 mmol, 1 eq) in DCM (250 mL) were added Boc_2O (30.04 g, 137.64 mmol, 31.62 mL, 1.2 eq) and DIEA (22.24 g, 172.05 mmol, 29.97 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25 °C for 2 hr. The reaction mixture was quenched by addition H_2O (500 mL) at 25 °C and the reaction mixture was adjusted the reaction mixture pH = 5 by sat. aq. citric acid and extracted with EtOAc (200mL x 3). The combined organic layers were washed with brine (400 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (38 g, crude) as a yellow oil. LCMS: m/z 310.0 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 5.30-5.00 (m, 2H), 4.37-4.19 (m, 4H), 3.32-3.22 (m, 1H), 1.51 (s, 9H), 1.42 (d, *J* = 6.4 Hz, 3H).

Step 1.4 Synthesis of 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid



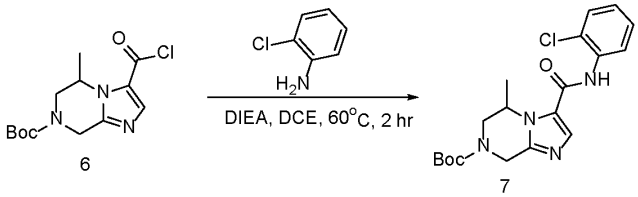
[01032] To a solution of O7-tert-butyl O3-ethyl 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (38 g, 122.83 mmol, 1 eq) in EtOH (360 mL), H_2O (180 mL) were added LiOH.H_2O (15.46 g, 368.50 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue, the residue was added H_2O (200 mL), the reaction mixture was adjusted pH = 4 by 1 M HCl, then filtered and filter cake was concentrated under reduced pressure to give 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (27 g, 95.98 mmol, 78.14% yield) as a white solid. LCMS: m/z 282.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.58 (s, 1H), 4.90 (s, 2H), 4.35-4.09 (m, 2H), 3.70-3.64 (m, 1H), 1.44 (s, 9H), 1.28 (d, J = 6.0 Hz, 3H).

Step 1.5 Synthesis of tert-butyl 3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



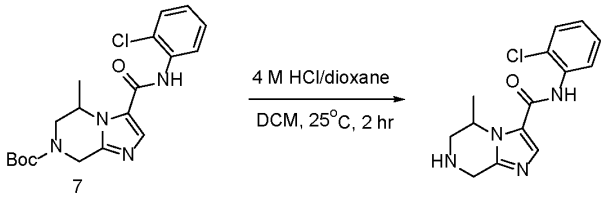
[01033] To a solution of 7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (26 g, 92.43 mmol, 1 eq) in DCM (300 mL) was added DIEA (11.95 g, 92.43 mmol, 16.10 mL, 1 eq), $(COCl)_2$ (23.46 g, 184.85 mmol, 16.18 mL, 2 eq) and DMF (675.54 mg, 9.24 mmol, 711.09 µL, 0.1 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. LC-MS showed the reaction was complete (quenched by MeOH). The reaction mixture was concentrated under reduced pressure to give compound tert-butyl 3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (26 g, 86.74 mmol, 93.85% yield) as a black solid. LCMS: m/z 296.3 $[M+H]^+$

Step 1.6 Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



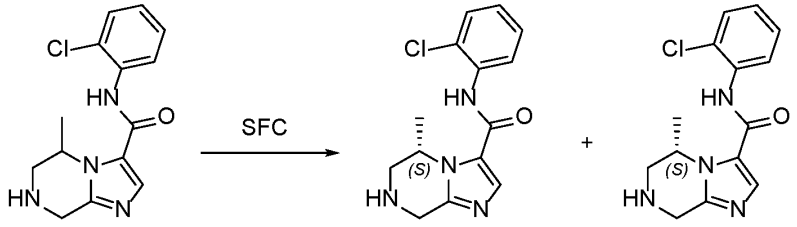
[01034] To a solution of tert-butyl 3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate (26 g, 86.74 mmol, 1 eq) in DCE (300 mL) were added 2-chloroaniline (13.28 g, 104.09 mmol, 10.97 mL, 1.2 eq), DIEA (22.42 g, 173.48 mmol, 30.22 mL, 2 eq) at 25°C. The reaction mixture was heated to 60°C and was stirred at 60°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 120 mL/min). Compound tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (18.5 g, 47.33 mmol, 54.57% yield) was obtained as a yellow solid. LCMS: m/z 391.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.90 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.40 (td, J = 7.6 Hz, 1.0 Hz, 1H), 5.01-4.91 (m, 2H), 4.42-4.26 (m, 1H), 4.10-4.07 (m, 1H), 3.47-3.40 (m, 1H), 1.44 (s, 9H), 1.28 (d, J = 4.8 Hz, 3H).

Step 1.7 Synthesis of N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide



[01035] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H -imidazo[1,2-a]pyrazine-7-carboxylate (18.5 g, 47.33 mmol, 1 eq) in DCM (100 mL) was added HCl/dioxane (4 M, 100 mL) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added H_2O (100 mL), the reaction mixture was adjusted pH = 8 by aq. Na_2CO_3, then filtered and filter cake was concentrated under reduced pressure to give compound N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V06) (11 g, 37.84 mmol, 79.97% yield) as a yellow solid. LCMS: m/z 291.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.08 (s, 1H), 7.93 (s, 1H), 7.59-7.49 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.31 (td, J = 7.6 Hz, 1.2 Hz, 1H), 5.14-5.10 (m, 1H), 4.36 (q, J = 16.0 Hz, 2H), 3.63-3.48 (m, 2H), 1.49 (d, J = 6.4 Hz, 3H).

Step 1.8 Synthesis of (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V06A) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (V06B)



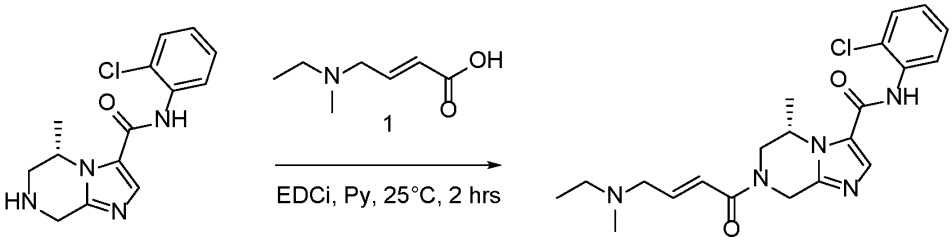
V06 V06A V06B

[01036] 10 g of compound N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide was separation by SFC (column: DAICEL CHIRALPAK AD (250 mm * 50 mm,10 um); mobile phase: [CO_2 – MeOH (0.1% NH_3H_2O)]; B%: 30%, isocratic elution mode). Compound (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V06A) (4 g, 13.76 mmol, 29.07% yield) and compound (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V06B) (4.6 g, 15.82 mmol, 33.43% yield) were obtained as yellow solid.

[01037] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.73 (s, 1H), 7.79 (s, 1H), 7.55-7.53 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.31 (td, J = 7.6 Hz, 1.6 Hz, 1H), 4.78-4.76 (m, 1H), 4.10-4.09 (m, 1H), 3.85-3.81 (m, 1H), 3.06 (dd, J = 13.2 Hz, 4.0 Hz, 1H), 2.93-2.90 (m, 1H), 1.36 (d, J = 6.4 Hz, 3H).

[01038] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.81 (s, 1H), 7.82 (s, 1H), 7.55-7.42 (m, 2H), 7.39-7.35 (m, 1H), 7.30-7.26 (m, 1H), 4.84-4.81 (m, 1H), 4.11-4.05(m, 1H), 4.93-4.89 (m, 1H), 3.13-3.12 (m, 1H), 3.03-3.00 (m, 1H), 1.40 (d, J = 6.4 Hz, 3H).

1.9 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

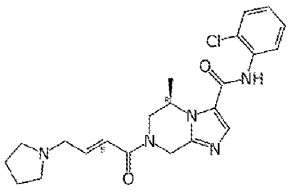
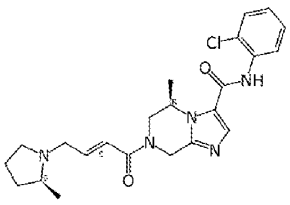


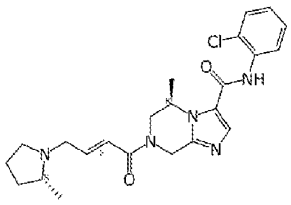
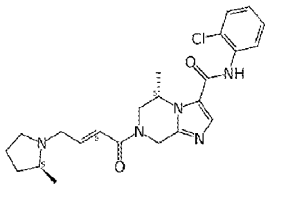
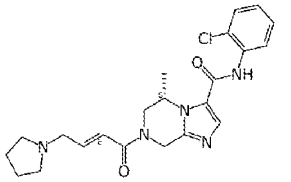
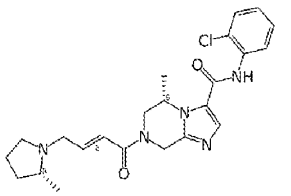
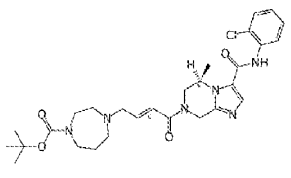
[01039] To a solution of (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (150 mg, 515.91 μmol, 1 *eq*) and (E)-4-[ethyl(methyl)amino]but-2-enoic acid (88.64 mg, 619.09 μmol, 1.2 *eq*) in pyridine (5 mL) was added EDCI (197.80 mg,

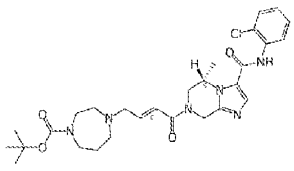
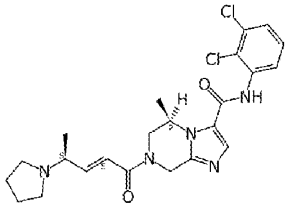
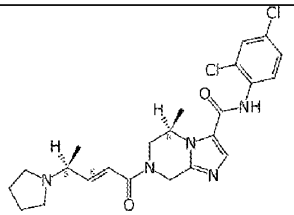
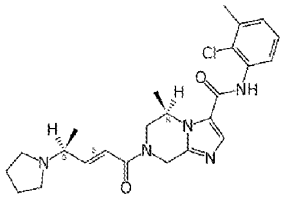
1.03 mmol, 2 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.0852 g, 203.30 μmol, 39.41% yield, 99.245% purity) was obtained as a white solid. LCMS: m/z 416.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.73 (m, *J* = 3.6 Hz, 2H), 5.28-5.18 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.32-4.26 (m, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.14 (d, *J* = 4.4 Hz, 2H), 2.37 (q, *J* = 6.8 Hz, 2H), 2.14 (s, 3H), 1.29-1.26 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

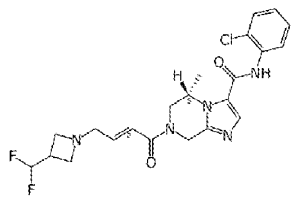
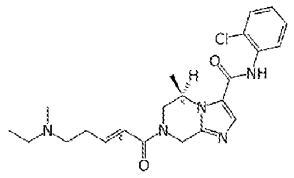
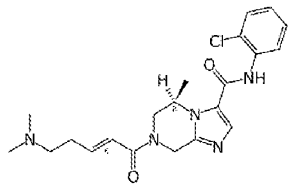
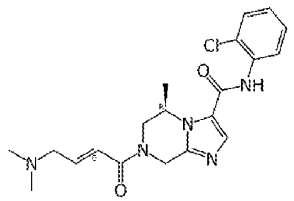
[01040] Compounds in Table G were synthesized following the procedure for (5S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table G

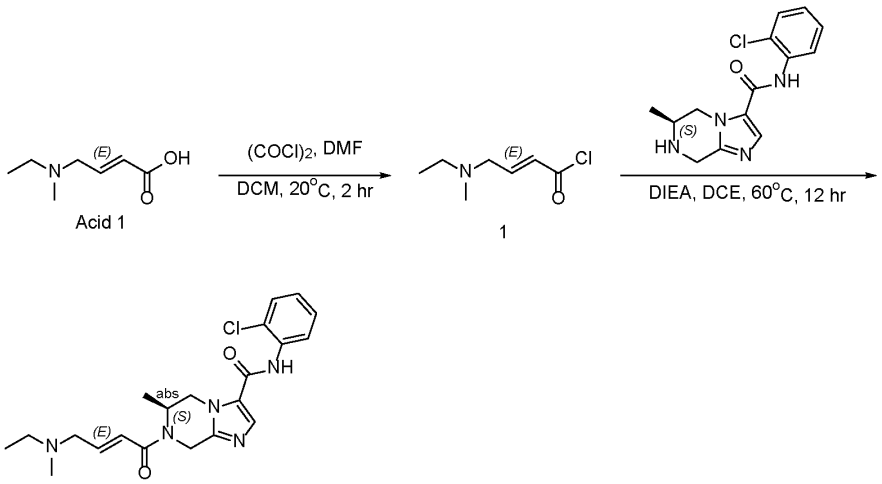
Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br.s,1 H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.39-7.35 (m, 1H), 7.31-7.25 (m, 1H), 6.80-6.66 (m, 2H), 5.28-5.17 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.30-4.25 (m, 1H), 3.74-3.68 (m, 1H), 3.23 (d, *J* = 4.4 Hz, 2H), 2.45 (s, 4H), 1.69 (s, 4H), 1.38-1.18 (m, 3H).	LCMS: m/z 428.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.40-7.38 (m, 1H), 7.31-7.27 (m, 1H), 6.76-6.74 (m, 2H), 5.28-5.18 (m, 1H), 5.06 (s, 1H), 4.70-4.58 (m, 1H), 4.32-4.25 (m, 1H), 3.70 (d, *J* = 15.2 Hz, 1H), 3.56-3.52 (m, 1H), 2.95.2.90 (m, 2H), 2.33-2.31 (m, 1H), 2.13 (q, *J* = 8.4 Hz, 1H), 1.90-1.87 (m, 1H), 1.64-1.61 (m, 2H), 1.29-1.24 (m, 4H), 1.03 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$

Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylpyrrolidin -1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.42-7.34 (m, 1H), 7.32-7.26 (m, 1H), 6.82-6.69 (m, 2H), 5.32-5.15 (m, 1H), 5.10-5.00 (m, 1H), 4.72-4.54 (m, 1H), 4.35-4.23 (m, 1H), 3.75-3.65 (m, 0.4H), 3.54 (d, J = 14.8 Hz, 1H), 3.27-3.19 (m, 0.6H), 3.11-2.85 (m, 2H), 2.35 (d, J = 7.2 Hz, 1H), 2.16-2.09 (m, 1H), 1.94-1.82 (m, 1H), 1.70-1.55 (m, 2H), 1.34-1.22 (m, 4H), 1.04 (d, J = 5.6 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.27 (m, 1H), 6.69-6.68 (m, 2H), 5.29-5.19 (m, 1H), 5.05 (s, 1H), 4.63 (dd, J = 33.2 Hz, 16.8 Hz, 1H), 4.29 (t, J = 15.2 Hz, 1H), 3.69 (d, J = 13.2 Hz, 0.6H), 3.26-3.22 (m, 0.4H), 3.03-3.00 (m, 1H), 2.44-2.41 (m, 4H), 1.66 (s, 4H), 1.29-1.25 (m, 3H), 1.16 (d, J = 6.8 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.55 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 6.4 Hz, 1H), 6.80-6.73 (m, 2H), 5.28-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.58 (m, 1H), 4.30-4.26 (m, 1H), 3.71-3.68 (m, 1H), 3.24-3.23 (m, 2H), 2.45 (s, 4H), 1.69 (s, 4H), 1.34-1.25 (m, 3H).	LCMS: m/z 428.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylpyrrolidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.33-7.23 (m, 1H), 6.85-6.66 (m, 2H), 5.32-5.13 (m, 1H), 5.12-5.00 (m, 1H), 4.77-4.44 (m, 1H), 4.35-4.21 (m, 1H), 3.74-3.66 (m, 0.5H), 3.54 (d, J = 3.2 Hz, 1H), 3.28-3.19 (m, 0.5H), 3.01-2.88 (m, 2H), 2.39-2.34 (m, 1H), 2.15-2.08 (m, 1H), 1.94-1.84 (m, 1H), 1.70-1.55 (m, 2H), 1.37-1.18 (m, 4H), 1.04 (d, J = 6.0 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$
tert-butyl 4-[(E)-4-[(5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.72 (s, 2H), 5.28-5.22 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.30-4.26 (m, 1H), 3.71 (d, J = 13.6	LCMS: m/z 557.2 $[M+H]^+$

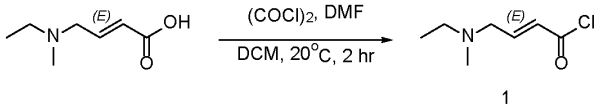
Name	Structure	NMR	LCMS
		Hz, 0.5H), 3.36 (d, *J* = 6.0 Hz, 4H), 3.28 (d, *J* = 3.2 Hz, 1.5H), 2.58 (s, 3H), 1.72 (s, 2H), 1.39 (s, 11H), 1.30-1.25 (m, 3H).	
4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate		^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.71 (m, 2H), 5.28-5.18 (m, 1H), 5.05 (s, 1H), 4.70-4.58 (m, 1H), 4.28 (d, *J* = 16.8 Hz, 1H), 3.71 (d, *J* = 14.0 Hz, 1H), 3.37-3.34 (m, 6H), 3.28 (d, *J* = 4.0 Hz, 2H), 2.59-2.58 (m, 2H), 1.72-1.71 (m, 2H), 1.39 (m, 9H), 1.30-1.25 (m, 3H).	LCMS: m/z 557.2 [M+H]$^+$
(5R)-N-(2,3-dichlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.03 (s, 1H), 7.91 (s, 1H), 7.58-7.52 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 6.70-6.68 (m, 2H), 5.28-5.20 (m, 1H), 5.03 (br.s, 1H), 4.70-4.57 (m, 1H), 4.33-4.26 (m, 1H), 3.69 (d, *J* = 13.6 Hz, 1H), 3.34-3.01 (m, 2H), 3.06-3.01 (m, 1H), 2.44-2.43 (m, 2H), 1.67 (s, 4H), 1.30-1.26 (m, 3H), 1.16 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 476.1/478.1 [M+H]$^+$
(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.68-6.64 (m, 2H), 5.27-5.19 (m, 1H), 5.03 (s, 1H), 4.69-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.70-3.67 (m, 0.5H), 3.25-3.22 (m, 0.5H), 3.03-3.02 (m, 1H), 2.48-2.43 (m, 4H), 1.66 (s, 4H), 1.29-1.25 (m, 3H), 1.16-1.15 (m, 3H).	LCMS: m/z 476.1/478.1 [M+H]$^+$
(5R)-N-(2-chloro-3-methyl-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.80 (s, 1H), 7.88 (s, 1H), 7.38-7.36 (m, 1H), 7.27-7.24 (m, 2H), 6.73-6.68 (m, 2H), 5.27-5.18 (m, 1H), 5.04 (s, 1H), 4.70-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.68 (d, *J* = 13.2 Hz, 0.5H), 3.32-3.27 (m, 0.5H), 3.10-3.01 (m, 1H), 2.47-2.41 (m, 4H), 2.38 (s, 3H), 1.66 (s, 4H), 1.29-1.25 (m, 3H), 1.15 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 456.2 [M+H]

Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-7-[(E)-4-[3-(difluoromethyl)azetidin-1-yl]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.87 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.68-6.58 (m, 2H), 6.38-6.08 (m, 1H), 5.27-5.17 (m, 1H), 5.05 (br.s, 1H), 4.70-4.56 (m, 1H), 4.31-4.24 (m, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.32-3.30 (m, 2H), 3.20 (s, 2H), 3.10 (d, *J* = 5.2 Hz, 2H), 2.95-2.81 (m, 1H), 1.29-1.23 (m, 3H).	LCMS: m/z 464.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-5-[ethyl (methyl)amino] pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d6) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (t, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.84-6.74 (m, 1H), 6.71-6.57 (m, 1H), 5.26-5.22 (m, 1H), 5.03 (s, 1H), 4.70-4.49 (m, 1H), 4.37-4.21 (m, 1H), 3.73-3.63 (m, 0.5H), 3.27-3.18 (m, 0.5H), 2.43 (t, *J* = 7.6 Hz, 2H), 2.39-2.32 (m, 4H), 2.17-2.06 (m, 3H), 1.32-1.20 (m, 3H), 0.96 (t, *J* = 6.8 Hz, 3H).	LCMS: m/z 430.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-5-(dimethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.87 (s, 1H), 7.86 (s, 1H), 7.62-7.50 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz,1H), 7.33-7.26 (m, 1H), 6.78 (d, *J* = 14.8 Hz, 1H), 6.65 (t, *J* = 14.4 Hz, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.12-5.00 (m, 1H), 4.74-4.57 (m, *J* = 7.2 Hz, 1H), 4.36-4.22 (m, 1H), 3.77-3.59 (m, 0.5H), 3.31-3.21 (m, 0.5H), 2.42-2.27 (m, 4H), 2.18-2.06 (m, 6H), 1.35-1.19 (m, 3H).	LCMS: m/z 416.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 6.73-6.72 (m, 2H), 5.28-5.18 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.32-4.26 (m, 1H), 3.69 (d, *J* = 13.2 Hz, 0.6H), 3.28-3.24 (m, 0.4H), 3.06 (d, *J* = 4.0 Hz, 2H), 2.16 (s, 6H), 1.30-1.26 (m, 3H).	LCMS: m/z 402.2 $[M+H]^+$

Example 160: Synthesis of (6S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

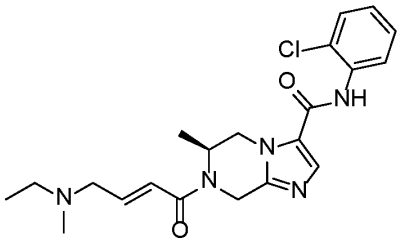


Step 1.1 Synthesis of (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride



[01041] To a solution of (E)-4-[ethyl(methyl)amino]but-2-enoic acid (0.2 g, 1.40 mmol, 1 eq) in DCM (3 mL) was added (COCl)2 (230.49 mg, 1.82 mmol, 158.96 µL, 1.3 eq) and DMF (10.21 mg, 139.68 µmol, 10.75 µL, 0.1 eq) at 20°C. The reaction mixture was stirred at 20 °C for 2hr. The reaction mixture was stirred at 20°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give compound (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.2 g, 1.24 mmol, 88.59% yield) was obtained as a red oil. LCMS: m/z 158.1 $[M+H]^+$.

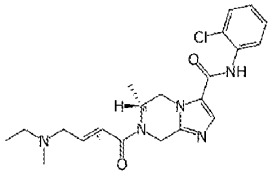
Step 1.2 Synthesis of (6S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01042] To a reaction mixture of (6S)-N-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (200.00 mg, 687.88 µmol, 1.11 eq) in DCE (3 mL) were added (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.2 g, 1.24 mmol, 2 eq), DIEA (159.92 mg, 1.24 mmol, 215.53 µL, 2 eq) at 25°C, and then the reaction mixture was heated to 60°C and was stirred at 60°C for 12 hr. The reaction mixture was concentrated under

reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1% - 40% B over 8.0 min). Compound (6S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (104 mg, 250.05 μmol, 40.42% yield) was obtained as a yellow solid. LCMS: m/z 416.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 8.55 (s, 1H), 7.59-7.51 (m, 2H), 7.41 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.34 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.11-6.95 (m, 1H), 6.82-6.74 (m, 1H), 5.44-5.39 (m, 1H), 5.20-4.98 (m, 1H), 4.75-4.54 (m, 2H), 4.35-4.15 (m, 1H), 3.97-3.82 (m, 2H), 3.20-2.99 (m, 2H), 2.69 (d, J = 4.8 Hz, 3H), 1.28-1.24 (m, 6H).

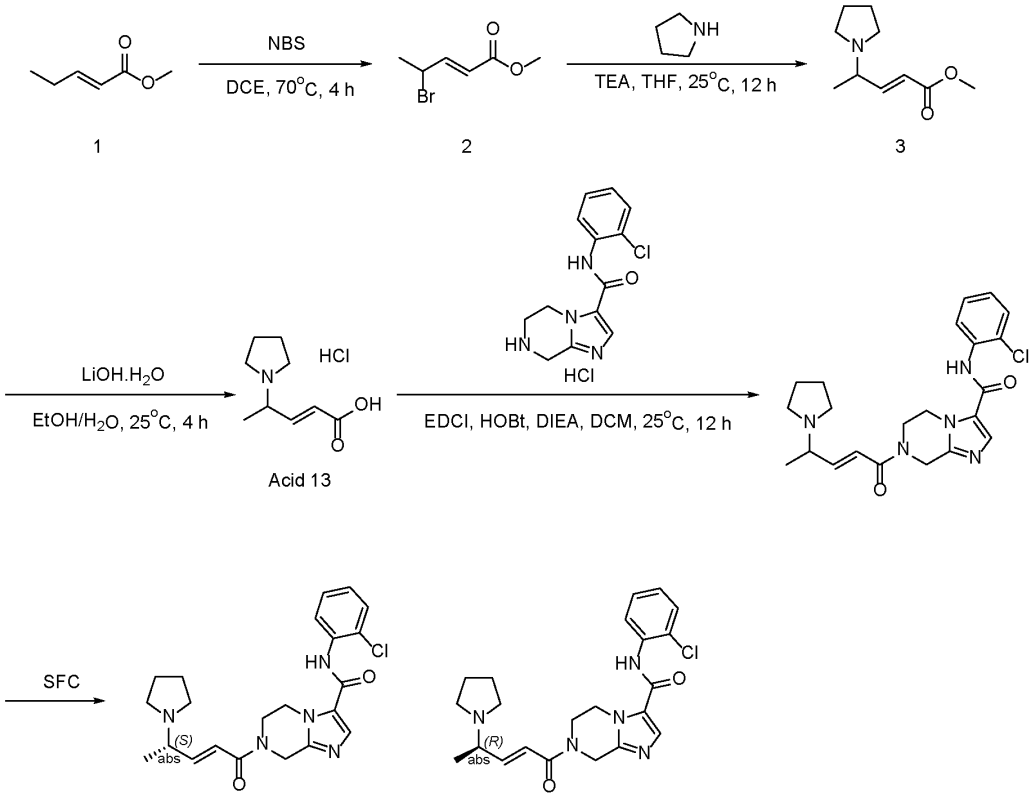
Example 161: Synthesis of (6R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



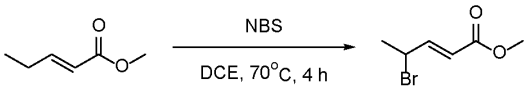
[01043] The method as described for the synthesis (6S)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was applied with substitution of (S)-N-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide for (R)-N-(2-chlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide to provide the product (6R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide. LCMS: m/z 416.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 8.55 (s, 1H), 7.59-7.51 (m, 2H), 7.41 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.34 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.11-6.95 (m, 1H), 6.82-6.74 (m, 1H), 5.44-5.39 (m, 1H), 5.20-4.98 (m, 1H), 4.75-4.54 (m, 2H), 4.35-4.15 (m, 1H), 3.97-3.82 (m, 2H), 3.20-2.99 (m, 2H), 2.69 (d, J = 4.8 Hz, 3H), 1.28-1.24 (m, 6H).

Example 162: Synthesis of *N*-(2-chlorophenyl)-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide.

General method N

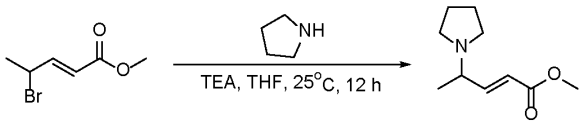


Step 1.1 Synthesis of methyl (E)-4-bromopent-2-enoate-



[01044] To a solution of methyl (E)-pent-2-enoate (5 g, 43.81 mmol, 1 eq) in DCE (50 mL) was added NBS (8.58 g, 48.19 mmol, 1.1 eq) at 25°C. The reaction mixture was heated to 70°C and was stirred at 70°C for 4 hr. The reaction mixture was cooled to 25°C and was quenched by addition H_2O (0.5 mL) at 25°C, concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound methyl (E)-4-bromopent-2-enoate (7 g, 36.26 mmol, 82.78% yield) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (dd, J = 15.6 Hz, 8.4 Hz, 1H), 5.93 (dd, J = 14.8 Hz, 0.8 Hz, 1H), 4.72-4.68 (m, 1H), 3.76 (s, 3H), 1.83 (d, J = 6.8 Hz, 3H).

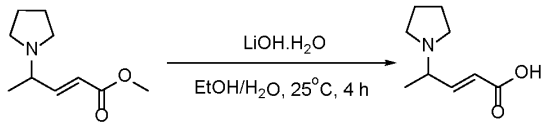
Step 1.2 Synthesis of methyl (E)-4-pyrrolidin-1-ylpent-2-enoate -



2 3

[01045] To a solution of pyrrolidine (884.23 mg, 12.43 mmol, 1.04 mL, 1.2 eq) in THF (10 mL) were added Et_3N (2.98 g, 29.42 mmol, 4.10 mL, 2.84 eq) and methyl (E)-4-bromopent-2-enoate (2 g, 10.36 mmol, 1 eq) at 25°C. The reaction mixture was stirred at 25 °C for 12 hr. The reaction mixture was quenched by addition H_2O (10 mL) at 25°C, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 50 mL/min). Compound methyl (E)-4-pyrrolidin-1-ylpent-2-enoate (0.8 g, 4.37 mmol, 42.14% yield) was obtained as a yellow oil. LCMS: m/z 184.1 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.94 (dd, J = 15.6 Hz, 8.4 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 3.74 (s, 3H), 2.98-2.94 (m, 1H), 2.55-2.53 (m, 4H), 1.80-1.78 (m, 4H), 1.25 (d, J =6.8 Hz, 3H).

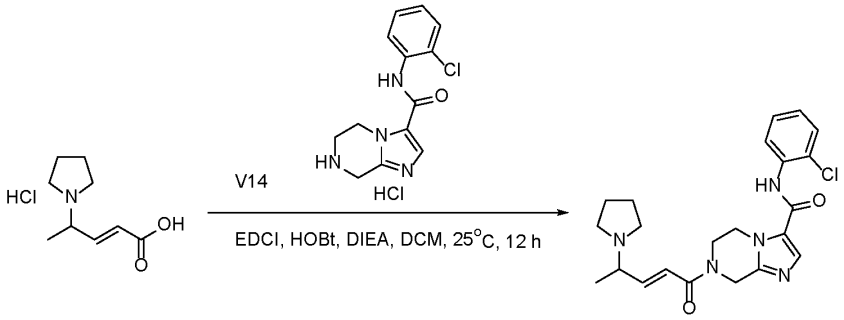
Step 1.3 Synthesis of (E)-3-[(2R)-4-tert-butoxycarbonylmorpholin-2-yl]prop-2-enoic acid



3

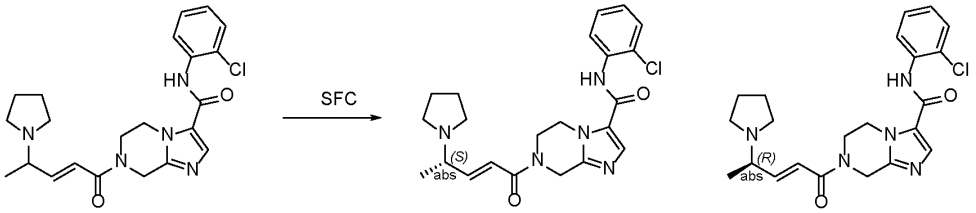
[01046] To a solution of methyl (E)-4-pyrrolidin-1-ylpent-2-enoate (0.8 g, 4.37 mmol, 1 eq) in EtOH (8 mL), H_2O (2 mL) was added $LiOH.H_2O$ (549.60 mg, 13.10 mmol, 3 eq) and at 25°C. The reaction mixture was stirred at 25°C for 4 hr. The reaction mixture was concentrated under reduced pressure to remove EtOH, then the reaction mixture was adjusted pH = 3 by 1 N HCl and extracted with EtOAc (6 mL x 3). The combined organic layers were washed with brine (18 mL x 1), dried over [Na_2SO_4], filtered and give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-10% B over 8.0 min). Compound (E)-4-pyrrolidin-1-ylpent-2-enoic acid (0.5 g, 2.95 mmol, 67.68% yield) was obtained as a yellow oil (HCl salt). LCMS: m/z 170.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.74 (s, 1H), 11.38 (s, 1H), 6.84 (dd, J = 15.6 Hz, 8.8 Hz, 1H), 6.15 (d, J = 15.6 Hz, 1H), 4.10-4.03 (m, 1H), 3.74-3.41 (m, 2H), 2.99-2.98 (m, 2H), 1.92-1.89 (m, 4H), 1.43 (d, J = 6.8 Hz, 3H).

Step 1.4 Synthesis of N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01047] To a reaction mixture of (E)-4-pyrrolidin-1-ylpent-2-enoic acid (118.21 mg, 574.75 μmol, 1.2 eq, HCl), N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.15 g, 478.95 μmol, 1 eq, HCl) in DCM (1 mL) were added EDCI (183.63 mg, 957.91 μmol, 2 eq), HOBT (97.08 mg, 718.43 μmol, 1.5 eq) and DIEA (247.61 mg, 1.92 mmol, 333.70 μL, 4 eq) at 25°C and then the reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (0.5 mL) at 25°C and then concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 50% B over 8.0 min). Compound N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (71 mg, 165.92 μmol, 34.64% yield) was obtained as a white solid. LCMS: m/z 428.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 8.0 Hz, 2.0 Hz, 1H), 6.71-6.62 (m, 2H), 4.92-4.74 (m, 2H), 4.31-4.24 (m, 2H), 4.00-3.95 (m, 2H), 3.92-3.00 (m, 1H), 2.47-2.38 (m, 4H), 1.66-1.63 (m, 4H), 1.15 (d, J =6.4 Hz, 3H).

Step 1.5 Synthesis of N-(2-chlorophenyl)-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide, N-(2-chlorophenyl)-7-[(E,4R)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01048] The compound was separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 um); mobile phase: [CO_2 - MeOH (0.1% NH_3H_2O)]; B%: 65%, isocratic elution

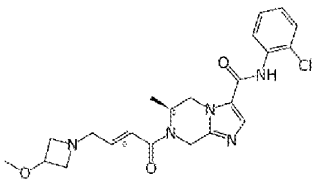
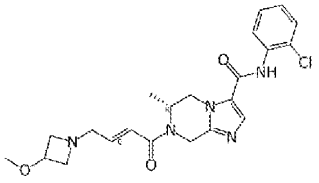
mode). Compound N-(2-chlorophenyl)-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (16 mg, 36.36 μmol, 26.16% yield, 97.25% purity) was obtained as a white solid, and N-(2-chlorophenyl)-7-[(E,4R)-4- pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (16.1 mg, 37.30 μmol, 26.83% yield, 99.14% purity) was obtained as a white solid.

[01049] LCMS: m/z 428.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (td, J = 9.2 Hz, 1.2 Hz, 2H), 7.37 (td, J = 9.2 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.67-6.62 (m, 2H), 4.96-4.74 (m, 2H), 4.31-4.27 (m, 2H), 4.01-3.95 (m, 2H), 3.03-3.00 (m, 1H), 2.49-2.42 (m, 4H), 1.66-1.63 (m, 4H), 1.15 (d, J =6.8 Hz, 3H).

[01050] LCMS: m/z 428.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (td, J = 9.2 Hz, 1.2 Hz, 2H), 7.37 (td, J = 9.2 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.67-6.62 (m, 2H), 4.92-4.74 (m, 2H), 4.32-4.30 (m, 2H), 4.01-3.94 (m, 2H), 3.02-2.99 (m, 1H), 2.47-2.38 (m, 4H), 1.66-1.63 (m, 4H), 1.15 (d, J =6.4 Hz, 3H).

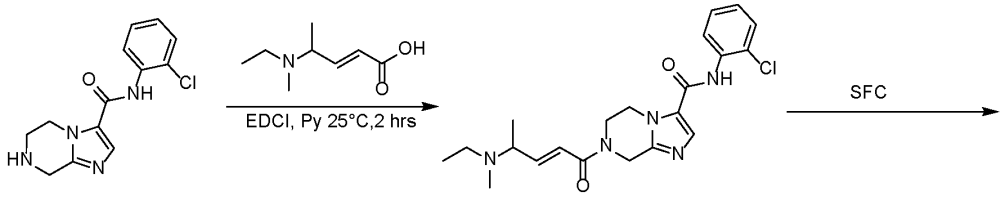
[01051] Compounds in Table H were synthesized following the procedure for *N*-(2-chlorophenyl)-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table H

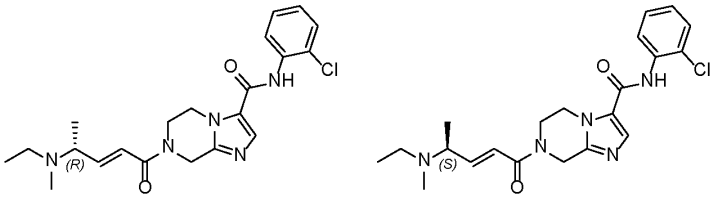
Name	Structure	NMR	LCMS	SFC conditions
(6S)-N-(2-chlorophenyl)-6-methyl-7-[rac-(E)-4-(3-methoxyazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.91 (s, 1H), 7.60-7.54 (m, 2H), 7.39-7.26 (m, 2H), 6.65-6.57 (m, 2H), 5.09 (d, J = 17.2 Hz, 1H), 4.87-4.81 (m, 1H), 4.64 (d, J = 13.6 Hz, 1H), 4.37- 4.16 (m, 2H), 4.01-3.95 (m, 1H), 3.56-3.54 (m, 2H), 3.21- 3.20 (m, 2H), 3.15 (s, 3H), 2.85-2.82 (m, 2H), 1.07 (s, 3H).	LCMS: m/z 444.2 [M+H]+	SFC (condition: column: DAICEL CHIRALCEL OJ (250 mm * 30 mm,10 um); mobile phase: [CO2-EtOH]; B%: 40%, isocratic elution mode)
(6R)-N-(2-chlorophenyl)-6-methyl-7-[rac-(E)-4-(3-methoxyazetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.91 (s, 1H), 7.60-7.54 (m, 2H), 7.39-7.26 (m, 2H), 6.6-6.57 (m, 2H), 5.09 (d, J = 18.0 Hz, 1H), 4.87-4.81 (m, 1H),	LCMS: m/z 444.2 [M+H]+	SFC (condition: column: DAICEL CHIRALCEL OJ (250 mm * 30 mm,10 um); mobile phase: [CO2-

Name	Structure	NMR	LCMS	SFC conditions
		4.64 (d, *J* = 13.6 Hz, 1H), 4.37- 4.16 (m, 2H), 4.01-3.96 (m, 1H), 3.56-3.52 (m, 2H), 3.21- 3.20 (m, 2H), 3.15 (s, 3H), 2.85-2.82 (m, 2H), 1.08 (s, 3H).		EtOH]; B%: 40%, isocratic elution mode)

Example 163: Synthesis of (E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide, (S,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide and (R,E)-N-(2-chlorophenyl)-7-(4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



1



[01052] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (100 mg, 319.30 μmol, 1 eq, HCl) and (E)-4-[ethyl(methyl)amino]pent-2-enoic acid (60.24 mg, 383.16 μmol, 1.2 eq) in Py (1 mL) was added EDCI (122.42 mg, 638.61 μmol, 2 eq) in portions at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduce pressure. The residue was purified by prep-HPLC (basic condition: column: We Pure Biotech XP tC_{18} 150* 40* 7 um; mobile phase: [H_2O (0.05% NH_3H_2O+ 10 mM NH_4HCO_3)- ACN]; gradient: 15%- 45% B over 8.0 min). The residue was dried over lyophilization. The compound was further separated by SFC (condition: column: DAICEL CHIRALPAK AD (250 mm* 30 mm 10 um); mobile phase: [CO_2- EtOH

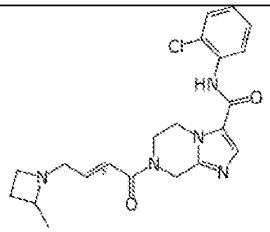
(0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode). The residue was dried over lyophilization. Compound N-(2-chlorophenyl)-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (34.5 mg, 82.95 μmol, 25.98% yield, 100% purity) was obtained as a white solid. Compound N-(2-chlorophenyl)-7-[(E,4S)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (26.4 mg, 62.20 μmol, 19.48% yield, 98% purity) was obtained as a white solid. LCMS: m/z 416.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.91-9.74 (m, 1H), 7.87 (s, 1H), 7.59-7.49 (m, 2H), 7.43-7.23 (m, 2H), 6.77-6.58 (m, 2H), 5.06-4.66 (m, 2H), 4.32 (s, 2H), 4.08-3.87 (m, 2H), 3.31-3.26 (m, 1H), 2.46-2.29 (m, 2H), 2.12 (s, 3H), 1.11 (d, J = 8.0 Hz, 3H), 0.97 (t, J = 8.0 Hz, 3H).

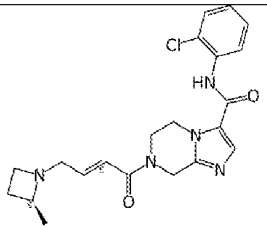
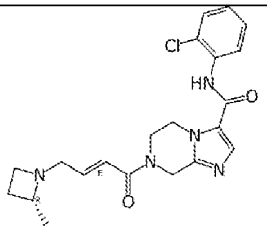
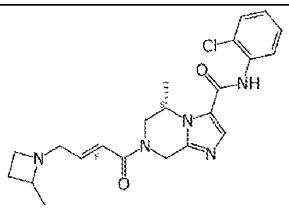
[01053] ^1H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.88 (s, 1H), 7.58-7.50 (m, 2H), 7.42-7.24 (m, 2H), 6.77-6.58 (m, 2H), 4.98-4.71 (m, 2H), 4.38-4.25 (m, 2H), 4.08-3.90 (m, 2H), 3.31-3.27 (m, 1H), 2.48-2.31 (m, 2H), 2.13 (s, 3H), 1.12 (d, J = 8.0 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H).

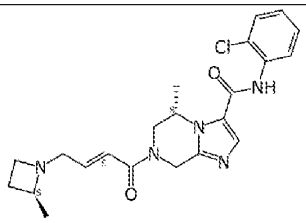
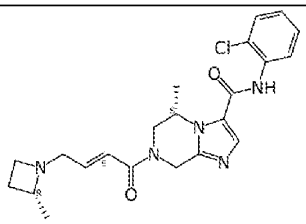
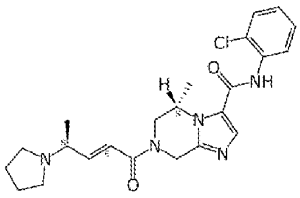
[01054] ^1H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (t, J = 8.4 Hz, 2H), 7.41-7.25 (m, 2H), 6.77-6.58 (m, 2H), 4.98-4.68 (m, 2H), 4.37-4.23 (m, 2H), 4.08-3.90 (m, 2H), 3.26 (br s, 1H), 2.42-2.31 (m, 2H), 2.13 (s, 3H), 1.12 (d, J = 8.0 Hz, 3H), 0.97 (t, J = 8.0 Hz, 3H).

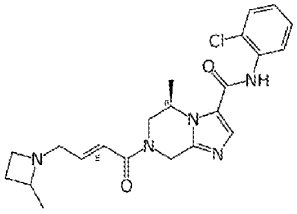
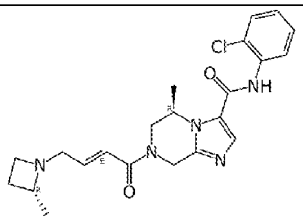
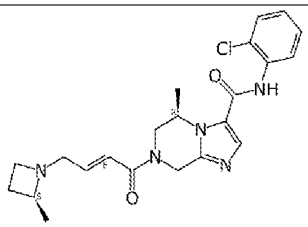
[01055] Compounds in Table I were synthesized following the procedure for *N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide.*

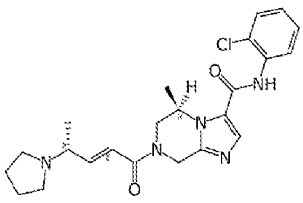
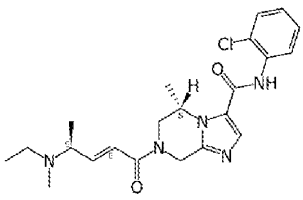
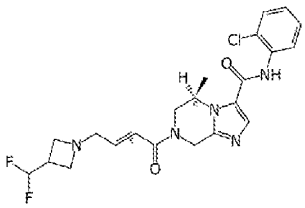
Table I

Name	Structure	NMR	LCMS	SFC conditions
N-(2-chlorophenyl)-7-[(E)-4-(2-methylazetidin-1-yl)but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.56-7.52 (m, 2H), 7.38-7.29 (m, 2H), 6.69-6.62 (m, 2H), 4.91-4.74 (m, 2H), 4.32 (s, 2H), 4.01-3.95 (m, 2H), 3.32-3.28 (m, 2H), 3.27-3.26 (m, 1H), 3.13-3.03 (m, 1H), 2.70-2.68 (m, 1H), 2.02-2.00 (m, 1H), 1.70-1.63 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H).	LCMS : m/z 414.2 $[M+H]^+$	

Name	Structure	NMR	LCMS	SFC conditions
N-(2-chlorophenyl)-7-[(E)-4-[(2S)-2-methylazetidin-1-yl]but-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.56-7.52 (m, 2H), 7.38-7.28 (m, 2H), 6.69-6.62 (m, 2H), 4.90-4.74 (m, 2H), 4.32 (s, 2H), 3.99-3.95 (m, 2H), 3.32-3.28 (m, 2H), 3.27-3.26 (m, 1H), 3.15-3.02 (m, 1H), 2.70-2.68 (m, 1H), 2.02-2.00 (m, 1H), 1.70-1.68(m, 1H), 1.10 (d, J = 6.0 Hz, 3H).	LCMS : m/z 414.2 [M+H]$^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm* 30 mm, 10 um); mobile phase: [CO_2-MeOH (0.1% $NH_3{\cdot}H_2O$)]; B%: 25%, isocratic elution mode)
N-(2-chlorophenyl)-7-[(E)-4- [(2R)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.56-7.52 (m, 2H), 7.39-7.28 (m, 2H), 6.65-6.62 (m, 2H), 4.90-4.74 (m, 2H), 4.32 (s, 2H), 3.99-3.95 (m, 2H), 3.32-3.28 (m, 2H), 3.27-3.26 (m, 1H), 3.15-3.03 (m, 1H), 2.70-2.68 (m, 1H), 2.02-2.00 (m, 1H), 1.70-1.68 (m, 1H), 1.10 (d, J = 6.0 Hz, 3H).	LCMS : m/z 414.2 [M+H]$^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm* 30 mm, 10 um); mobile phase: [CO_2-MeOH (0.1% $NH_3{\cdot}H_2O$)]; B%: 25%, isocratic elution mode)
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-methylazetidin-1-yl)but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (t, J = 6.8 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.71-6.66 (m, 2H), 5.28-5.05 (m, 2H), 4.70-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.72-3.68 (m, 1H), 3.28-3.25 (m, 2H), 3.16-3.12 (m, 1H), 3.08-3.04 (m, 1H), 2.74-2.67 (m, 1H), 2.00 (q, J = 8 Hz, 1H), 1.68 (q, J = 8.8 Hz, 1H), 1.27-1.24 (m, 3H), 1.10 (d, J = 6.4 Hz, 3H).	LCMS : m/z 428.2 [M+H]$^+$	

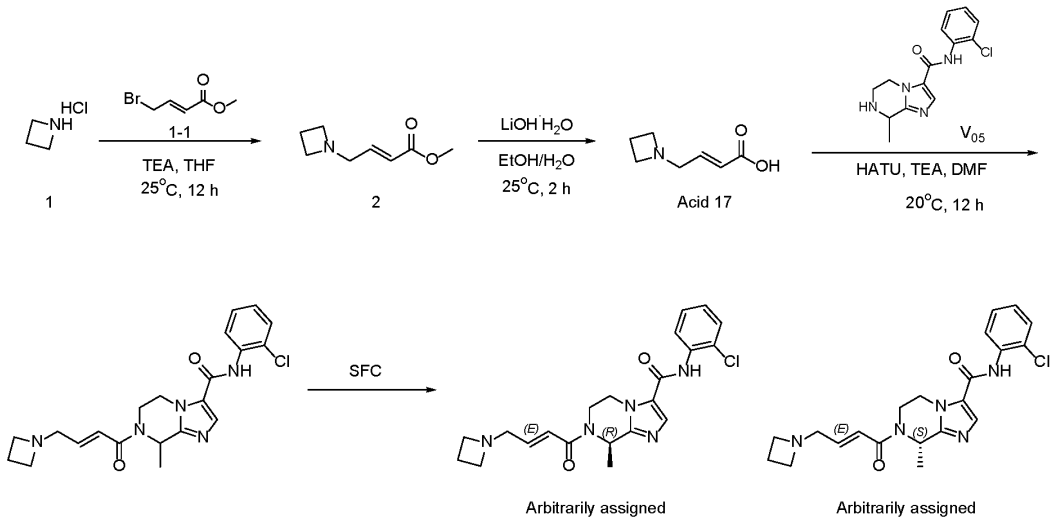
Name	Structure	NMR	LCMS	SFC conditions
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.66 (s, 2H), 5.2-5.05 (m, 2H), 4.70-4.57 (m, 1H), 4.29-4.26 (m, 1H), 3.71-3.68 (m, 1H), 3.29-3.24 (m, 2H), 3.15-3.04 (m, 2H), 2.73-2.65 (m, 1H), 2.02-2.00 (m, 1H), 1.70-1.615 (m, 1H), 1.28-1.25 (m, 3H), 1.09 (d, J = 5.6 Hz, 3H).	LCMS : m/z 428.2 [M+H]$^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 30%, isocratic elution mode)
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.87 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1.2 Hz, 1H), 6.67-6.66 (m, 2H), 5.28-5.05 (m, 2H), 4.70-4.54 (m, 1H), 4.31-4.25 (m, 1H), 3.71-3.68 (m, 0.6H), 3.31-3.25 (m, 2H), 3.22-3.21 (m, 0.4H), 3.15-3.05 (m, 2H), 2.71-2.67 (m, 1H), 2.05-1.99 (m, 1H), 1.73-1.64 (m, 1H), 1.28-1.24 (m, 3H), 1.10-1.09 (m, 3H).	LCMS : m/z 428.2 [M+H]$^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 30%, isocratic elution mode)
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.27 (m, 1H), 6.69-6.68 (m, 2H), 5.29-5.19 (m, 1H), 5.05 (s, 1H), 4.63 (dd, J = 33.2 Hz, 16.8 Hz, 1H), 4.29 (t, J = 15.2 Hz, 1H), 3.69 (d, J = 13.2 Hz, 1H), 3.26-3.22 (m, 1H), 3.03-3.00 (m,	LCMS : m/z 442.2 [M+H]$^+$	

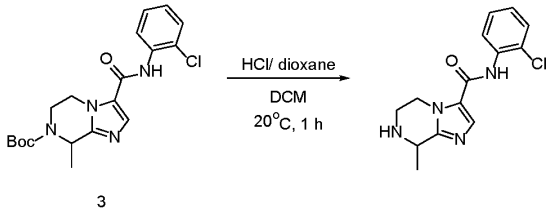
Name	Structure	NMR	LCMS	SFC conditions
		1H), 2.44-2.41 (m, 4H), 1.66 (s, 4H), 1.29-1.25 (m, 3H), 1.16 (d, J = 6.8 Hz, 3H).		
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-methylazetidin-1-yl)but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.58-7.49 (m, 2H), 7.42-7.34 (m, 1H), 7.33-7.25 (m, 1H), 6.66 (s, 2H), 5.32-5.12 (m, 1H), 5.10-4.99 (m, 1H), 4.75-4.52 (m, 1H), 4.27 (d, J = 17.6 Hz, 1H), 3.78-3.62 (m, 1H), 3.30-3.20 (m, 2H), 3.19-2.99 (m, 2H), 2.77-2.63 (m, 1H), 2.06-1.94 (m, 1H), 1.75-1.61 (m, 1H), 1.37-1.19 (m, 3H), 1.10 (d, J = 6.0 Hz, 3H).	LCMS : m/z 428.2 [M+H]$^+$	
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-2-methylazetidin-1-yl] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.59-7.49 (m, 2H), 7.40-7.34 (m, 1H), 7.32-7.26 (m, 1H), 6.66 (s, 2H), 5.31-5.11 (m, 1H), 5.09-4.98 (m, 1H), 4.76-4.52 (m, 1H), 4.27 (d, J = 16.8 Hz, 1H), 3.71-3.64 (m, 1H), 3.28 (s, 2H), 3.19-3.09 (m, 1H), 3.09-3.01 (m, 1H), 2.75-2.64 (m, 1H), 2.06-1.95 (m, 1H), 1.73-1.60 (m, 1H), 1.32-1.19 (m, 3H), 1.09 (d, J = 6.0 Hz, 3H).		purified by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 45%, isocratic elution mode).
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-2-methylazetidin-1-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.58-7.49 (m, 2H), 7.41-7.34 (m, 1H), 7.33-7.26 (m, 1H), 6.65 (s, 2H), 5.32-5.11 (m, 1H), 5.05 (d, J = 3.2 Hz, 1H), 4.75-	LCMS : m/z 428.2 [M+H]$^+$	purified by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile

Name	Structure	NMR	LCMS	SFC conditions
		4.51 (m, 1H), 4.35-4.21 (m, 1H), 3.75-3.63 (m, 1H), 3.30-3.20 (m, 2H), 3.19-3.10 (m, 1H), 3.10-3.01 (m, 1H), 2.77-2.63 (m, 1H), 2.06-1.95 (m, 1H), 1.75-1.61 (m, 1H), 1.35-1.19 (m, 3H), 1.09 (d, J = 6.0 Hz, 3H).		phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 45%, isocratic elution mode).
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (s, 2H), 7.38-7.29 (m, 2H), 6.77-6.53 (m, 2H), 5.33-5.24 (m, 1H), 5.12-5.04 (m, 1H), 4.72-4.53 (m, 1H), 4.38-4.25 (m, 1H), 3.72-3.68 (m, 1H), 3.05 (s, 1H), 2.36 (s, 4H), 1.67 (s, 4H), 1.38-1.09 (m, 6H).	LCMS : m/z 442.2 [M+H]$^+$	
(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-[ethyl(methyl)amino]pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (br.s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.76-6.60 (m, 2H), 5.29-5.21 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.34-4.24 (m, 1H), 3.71-3.68 (m, 1H), 3.28-3.19 (m, 1H), 2.44-2.32 (m, 2H), 2.13 (s, 3H), 1.29-1.23 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.98-0.95 (m, 3H).	LCMS : m/z 430.2 [M+H]$^+$	
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[3-(difluoromethyl)azetidin-1-yl]-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz,	LCMS : m/z 464.2 [M+H]$^+$	

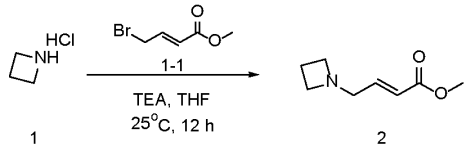
Name	Structure	NMR	LCMS	SFC conditions
		1H), 6.63 (s, 2H), 6.38-6.10 (m, 1H), 5.28-5.17 (m, 1H), 5.06 (s, 1H), 4.70-4.57 (m, 1H), 4.31-4.25 (m, 1H), 3.70 (d, J = 12.8 Hz, 1H), 3.35 (s, 1H), 3.31 (s, 1H), 3.20 (d, J = 2.8 Hz, 2H), 3.10 (d, J = 4.4Hz, 2H), 2.92-2.84 (m, 1H), 1.29-1.25 (m, 3H).		

Example 164: Synthesis of (E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide, (R,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide and (S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.





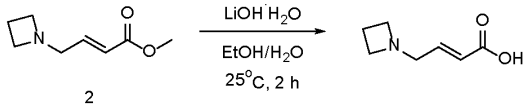
Step 1.1 Synthesis of methyl (E)-4-(azetidin-1-yl)but-2-enoate



1 2

[01056] To a solution of TEA (9.97 g, 98.55 mmol, 13.72 mL, 2.84 eq) in THF (50 mL) was added azetidine;hydrochloride (3.89 g, 41.60 mmol, 1.2 eq) at 25°C. Then a solution of methyl (E)-4-bromobut-2-enoate (7.3 g, 34.66 mmol, 4.80 mL, 1 eq) in THF (50 mL) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 12 hours. To the reaction mixture was added water (120 mL) at 25°C and the organic phase was separated. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Petroleum ether / Ethyl acetate gradient @ 70 mL/min). The eluent was removed under reduced pressure to give methyl (E)-4-(azetidin-1-yl)but-2-enoate (2.5 g, 16.11 mmol, 46.47% yield) as yellow oil. LCMS: m/z 156.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.73 (dt, J = 15.6 Hz, 5.2Hz, 1H), 5.91 (dt, J = 15.6 Hz, 2.0 Hz, 1H), 3.64 (s, 3H), 3.34-3.10 (m, 6H), 2.01-1.94 (m, 2H).

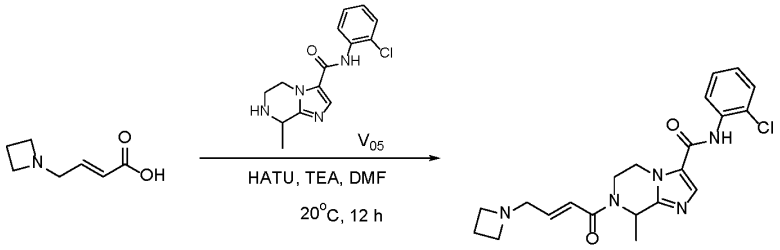
Step 1.2 Synthesis of (E)-4-(azetidin-1-yl)but-2-enoic acid



2

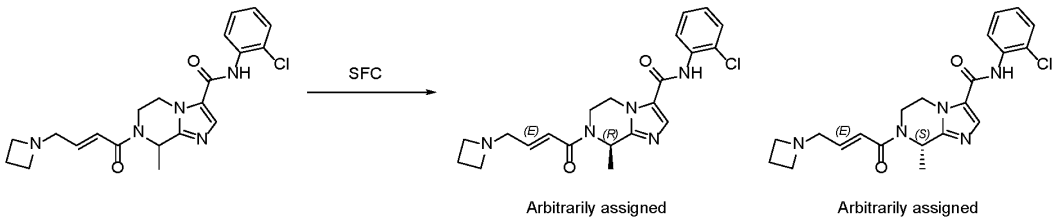
[01057] To a solution of methyl (E)-4-(azetidin-1-yl)but-2-enoate (2.2 g, 14.18 mmol, 1 eq) in EtOH (15 mL) and H_2O (7 mL) was added $LiOH{\cdot}H_2O$ (1.78 g, 42.53 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture concentrated under reduced pressure. The reaction mixture was cooled to 0°C and was adjusted pH = 4 by 1 M HCl at 0°C. The reaction mixture was concentrated under reduce pressure. The crude product was purified by prep-HPLC (column: Phenomenex luna C_{18} (250*70mm,15 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 1%-10% B over 20.0 min). The residue was dried over lyophilization to give (E)-4-(azetidin-1-yl)but-2-enoic acid (1.4 g, 9.92 mmol, 69.96% yield) as a white solid. LCMS: m/z 142.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.83 (s, 1H), 6.65 (dt, J = 15.6 Hz, 6.0Hz, 1H), 6.17 (dt, J = 15.6 Hz, 2.0 Hz, 1H), 4.06-3.92 (m, 6H), 2.36-2.28 (m, 2H).

Step 1.3 Synthesis of 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-8-methyl-6,8 -dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



[01058] To the reaction mixture of N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.3 g, 916.85 μmol, 1 eq, HCl), (E)-4-(azetidin-1-yl)but-2-enoic acid (244.29 mg, 1.73 mmol, 1.89 eq) in DMF (3 mL) were added HATU (871.53 mg, 2.29 mmol, 2.5 eq), TEA (371.10 mg, 3.67 mmol, 510.45 μL, 4 eq) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed to 20°C and stirred at 20°C for 12 hours. The reaction mixture was quenched with water (0.1 mL) and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; gradient: 10%-50% B over 8.0 min) to give 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-8-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (95 mg, 229.52 μmol, 25.03% yield) as a white solid. 90 mg of 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-8-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was further separated by SFC. 5 mg of 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-8-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide ready for delivery. LCMS: m/z 414.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.89 (s, 1H), 7.55-7.51 (m, 2H), 7.38-7.29 (m, 2H), 6.65-6.57 (m, 2H), 5.54-5.41 (m, 1H), 4.61-4.33 (m, 2H), 4.01-3.60 (m, 2H), 3.19-3.11 (m, 6H), 2.02-1.95 (m, 2H), 1.51-1.45 (m, 3H).

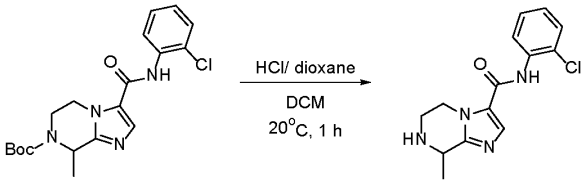
Step 1.4 Synthesis of rac-(8R)-N-(2-chlorophenyl)-8-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and rac-(8R)-N-(2-chlorophenyl)-8-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01059] The 90 mg of 7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-8-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was separated by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm,10 um); mobile phase: [CO_2 – MeOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode) to give rac-(8R)-N-(2-chlorophenyl)-8-methyl- 7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (34.8 mg, 83.92 μmol, 38.59% yield, 99.81% purity) as a white solid and rac-(8S)-N-(2-chlorophenyl)-8-methyl-7-[rac-(E)-4-(azetidin-1-yl)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (39.2 mg, 94.42 μmol, 43.42% yield, 99.70% purity) as a white solid. LCMS: m/z 414.2 $[M+H]^+$; LCMS: m/z 414.2 $[M+H]^+$. HPLC: 99.81%. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.88 (s, 1H), 7.53 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.37-7.28 (m, 2H), 6.65-6.56 (m, 2H), 5.52-5.42 (m, 1H), 4.61-4.33 (m, 2H), 4.01-3.61 (m, 2H), 3.19-3.11 (m, 6H), 2.02-1.95 (m, 2H), 1.58-1.40 (m, 3H).

[01060] ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.89 (s, 1H), 7.53 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.39-7.28 (m, 2H), 6.65-6.61 (m, 2H), 5.54-5.50 (m, 1H), 4.61-4.33 (m, 2H), 4.01-3.60 (m, 2H), 3.21-3.10 (m, 6H), 2.02-1.95 (m, 2H), 1.50-1.46 (m, 3H).

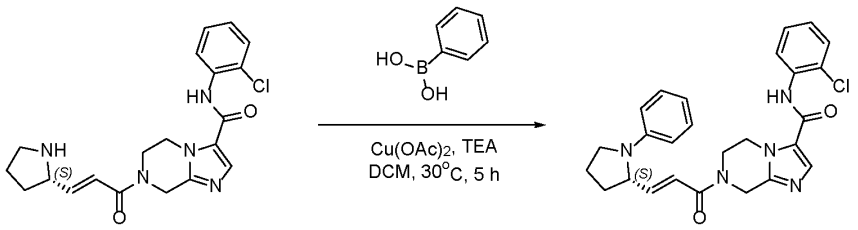
Step 1.5 Synthesis of N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide -



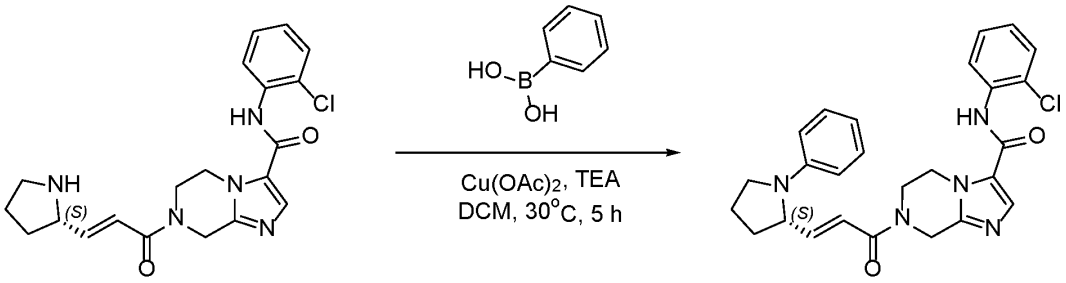
3

[01061] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-8-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (0.8 g, 1.02 mmol, 1 eq) in DCM (4 mL) was added HCl/dioxane (4 M, 4 mL) at 20°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give N-(2-chlorophenyl)-8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.4 g, crude, HCl) was obtained as a yellow solid. LCMS: m/z 291.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.18 (s, 1H), 8.08 (s, 1H), 7.58-7.50 (m, 2H), 7.37-7.27 (m, 2H), 7.40-7.32 (m, 2H), 4.78-4.76 (m, 1H), 4.64-4.63 (m, 1H), 4.44-4.41 (m, 3H), 3.78-3.75 (m, 1H), 3.55-3.54 (m, 1H), 1.70 (d, J = 6.8 Hz, 3H).

Example 165: Synthesis of *N*-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-phenylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.1 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-phenylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

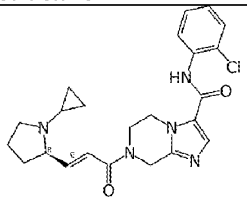
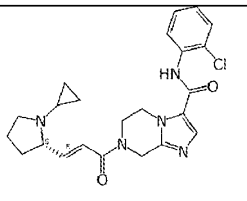


[01062] To a solution of N-(2-chlorophenyl)-7-[rac-(E)-3-[rac-(2S)-pyrrolidin-2-yl]prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (300.00 mg, 750.24 μmol, 1 eq) in DCM (3 mL) was added phenylboronic acid (228.69 mg, 1.88 mmol, 2.5 eq), TEA (189.79 mg, 1.88 mmol, 261.06 μL, 2.5 eq) and $Cu(OAc)_2$ (272.53 mg, 1.50 mmol, 2 eq) in one portion at 20°C. The reaction mixture was warmed to 30°C and stirred at 30°C for 5 hr. LCMS showed N-(2-chlorophenyl)-7-[rac-(E)-3-[rac-(2S)-pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was consumed completely and desired MS was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C_{18} 150 * 40 mm *10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 40%-70% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-phenylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (24.4 mg, 50.01 μmol, 6.67% yield, 97.56% purity) as a yellow solid.

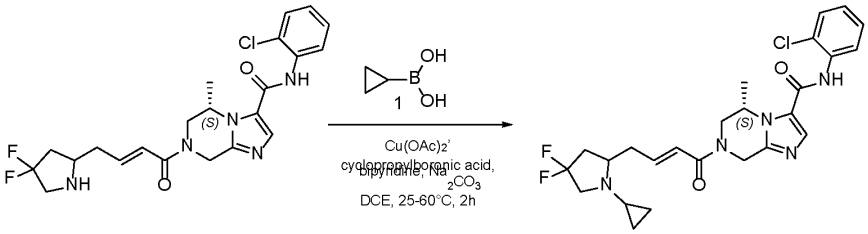
[01063] LCMS: m/z 476.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.86 (s, 1H), 7.53 (t, J = 8.8 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 2H), 6.64-6.60 (m, 3H), 6.58-6.55 (m, 2H), 4.85-4.72 (m, 2H), 4.38-4.36 (m, 1H), 4.27 (s, 2H), 3.92 (s, 2H), 3.52-3.50 (m, 1H), 3.20 (q, J = 8 Hz, 1H), 2.16-2.13 (m, 1H), 1.99-1.96 (m, 2H), 1.86-1.83 (m, 1H).

[01064] Compounds in Table J were synthesized following the procedure for *N*-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-phenylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table J

Name	Structure	NMR	LCMS
N-(2-chlorophenyl)-7-[(E)-3-[(2R)-1-cyclopropylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.86 (s, 1H), 7.55-7.53 (m, 2H), 7.36 (td, *J* = 7.6 Hz, 1.6Hz, 1H), 7.27 (td, *J* = 7.6 Hz, 1.6Hz, 1H), 6.60-6.54 (m, 2H), 4.91-4.75 (m, 2H), 4.32 (s, 2H), 4.00-3.91 (m, 2H), 3.28-3.21 (m, 1H), 3.03-2.98 (m, 1H), 2.48-2.46 (m, 1H), 1.99-1.95 (m, 1H), 1.72-1.65 (m, 3H), 1.55-1.52 (m, 1H), 0.36-0.32 (m, 2H), 0.25-0.23 (m, 2H).	LCMS: m/z 440.2 $[M+H]^+$
N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-cyclopropylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.53 (s, 2H), 7.37-7.28 (m, 2H), 6.70-6.54 (m, 2H), 4.90-4.74 (m, 2H), 4.31-4.26 (m, 2H), 4.01-3.93 (m, 2H), 3.25-3.24 (m, 2H), 3.00 (s, 1H), 1.96-1.92 (m, 1H), 1.70-1.66 (m, 3H), 1.54-1.52 (m, 1H), 0.35-0.34 (m, 2H), 0.24-0.23 (m, 2H).	LCMS: m/z 440.2 $[M+H]^+$

Example 166: Synthesis of (5S)-*N*-(2-chlorophenyl)-7-[(E)-4-(1-cyclopropyl-4,4-difluoro-pyrrolidin -2-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

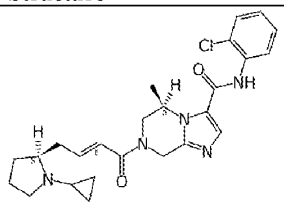


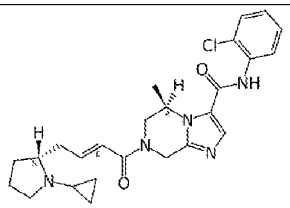
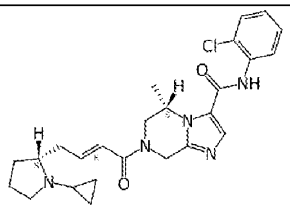
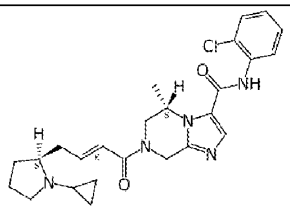
[01065] To a solution of (5S)-N-(2-chlorophenyl)-7-[(E)-4-(4,4-difluoropyrrolidin-2-yl)but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (280 mg, 603.57

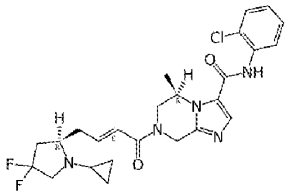
μmol, 1 eq) in DCE (3 mL) were added $Cu(OAc)_2$ (109.63 mg, 603.57 μmol, 1 eq), cyclopropylboronic acid (77.77 mg, 905.35 μmol, 1.5 eq), bipyridine (94.27 mg, 603.57 μmol, 1 eq) and Na_2CO_3 (127.94 mg, 1.21 mmol, 2 eq) in one portion at 25°C. The reaction mixture was warmed to 60°C and stirred at 60°C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Genimi NX C_{18} 150 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 30%- 55% B over 8.0 min) to give (5S)-N-(2-chlorophenyl)-7-[(E)-4-(1-cyclopropyl -4,4-difluoro-pyrrolidin-2-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (5.2 mg, 10.32 μmol, 1.71% yield, 99.75% purity) as a pale white solid. LCMS: m/z 504.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.74-6.68 (m, 2H), 5.27-5.28 (m, 1H), 5.05 (s, 1H), 4.68-4.56 (m, 1H), 4.35-4.25 (m, 1H), 3.71-3.68 (m, 0.5H), 3.30 (s, 1H), 3.25-3.21 (m, 0.5H), 3.05-3.01 (m, 1H), 2.91-2.82 (m, 1H), 2.79-2.74 (m, 1H), 2.38-2.33 (m, 2H), 2.02-1.91 (m, 1H), 1.73-1.72 (m, 1H), 1.30-1.25 (m, 3H), 0.56-0.52 (m, 1H), 0.45-0.37 (m, 2H), 0.30-0.26 (m, 1H).

[01066] Compounds in Table K were synthesized following the procedure for (5S)-*N*-(2-chlorophenyl)-7-[(E)-4-(1-cyclopropyl-4,4-difluoro-pyrrolidin -2-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

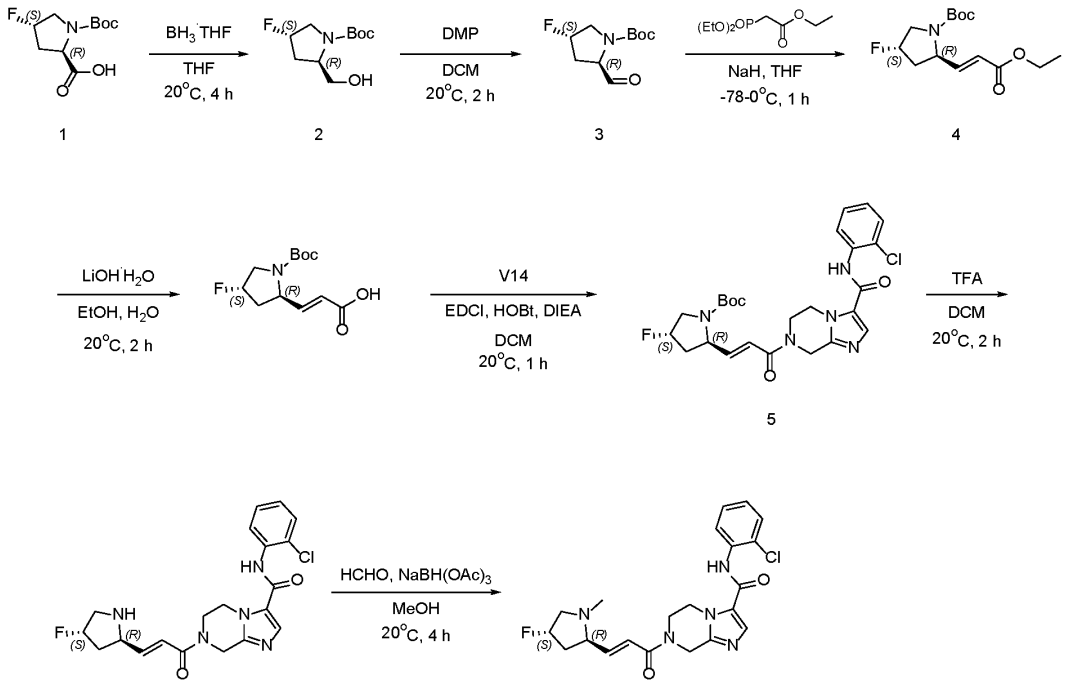
Table K

Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 8.0 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.84-6.58 (m, 2H), 5.24 (d, J = 17.6 Hz, 1H), 5.10-4.98 (m, 1H), 4.74-4.47 (m, 1H), 4.40-4.18 (m, 1H), 3.76-3.57 (m, 0.5H), 3.29-3.19 (m, 0.5H), 3.00-2.92 (m, 1H), 2.72-2.59 (m, 2H), 2.43-2.35 (m, 1H), 2.30-2.21 (m, 1H), 1.91-1.75 (m, 1H), 1.69-1.49 (m, 3H), 1.47-1.35 (m, 1H), 1.33-1.19 (m, 3H), 0.54-0.45 (m, 1H), 0.43-0.30 (m, 2H), 0.29-0.17 (m, 1H).	LCMS: m/z 468.2 $[M+H]^+$

Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.85-6.60 (m, 2H), 5.31-5.17 (m, 1H), 5.10-4.98 (m, 1H), 4.70-4.51 (m, 1H), 4.39-4.22 (m, 1H), 3.73-3.63 (m, 0.6H), 3.26-3.16 (m, 0.4H), 3.01-2.89 (m, 1H), 2.71-2.58 (m, 2H), 2.43-2.33 (m, 1H), 2.30-2.20 (m, 1H), 1.91-1.72 (m, 1H), 1.66-1.51 (m, 3H), 1.47-1.35 (m, 1H), 1.31-1.20 (m, 3H), 0.54-0.18 (m, 4H).	LCMS: m/z 468.2 $[M+H]^+$
(S)-N-(2-chlorophenyl)-7-((E)-4-((R)-1-cyclopropylpyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.90 (br.s, 1H), 7.54 (td, J = 7.6 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.81-6.75 (m, 1H), 6.69-6.62 (m, 1H), 5.26-5.22 (m, 1H), 5.05-5.04 (m, 1H), 4.68-4.56 (m, 1H), 4.35-4.22 (m, 1H), 3.70-3.64 (m, 0.5H), 3.26-3.18 (m, 0.5H), 2.98-2.93 (m, 1H), 2.68-2.63 (m, 2H), 2.39 (q, J = 8.8 Hz, 1H), 2.29-2.22 (m, 1H), 1.85-1.81 (m, 1H), 1.64-1.53 (m, 3H), 1.43-1.39 (m, 1H), 1.30-1.25 (m, 3H), 0.51-0.46 (m, 1H), 0.41-0.32 (m, 2H), 0.25-0.21 (m, 1H).	LCMS: m/z 468.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-1-cyclopropylpyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.84 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 8.0, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.80-6.62 (m, 2H), 5.27-5.19 (m, 1H), 5.04 (s, 1H), 4.67-4.55 (m, 1H), 4.35-4.23 (m, 1H), 3.70-3.64 (m, 0.6H), 3.15-3.10 (m, 0.4H), 2.98-2.92 (m, 1H), 2.69-2.60 (m, 2H), 2.42-2.35 (m, 1H), 2.28-2.21 (m, 1H), 1.82 (s, 1H), 1.62-1.57 (m, 3H), 1.45-1.36 (m, 1H), 1.32-1.23 (m, 3H), 0.52-0.45 (m, 1H), 0.42-0.32 (m, 2H), 0.26-0.20 (m, 1H).	LCMS: m/z 468.2 $[M+H]^+$

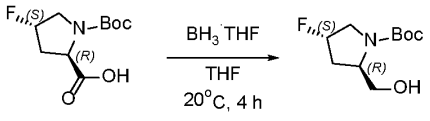
Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-1-cyclopropyl-4,4-difluoro-pyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.78-6.72 (m, 2H), 5.28-5.21 (m, 1H), 5.12-5.02 (m, 1H), 4.71-4.53 (m, 1H), 4.35-4.24 (m, 1H), 3.71-3.67 (m, 0.5H), 3.41-3.37 (m, 1H), 3.28-3.19 (m, 0.5H), 3.10-3.00 (m, 1H), 2.92-2.74 (m, 2H), 2.39-2.33 (m, 2H), 2.03-1.90 (m, 1H), 1.74-1.71 (m, 1H), 1.30-1.23 (m, 3H), 0.56-0.28 (m, 4H).	LCMS: m/z 504.1 [M+H]

Example 167: Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



1 2 3 4 5

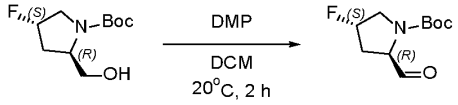
Step 1.1 Synthesis of tert-butyl (2R,4S)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate



1 2

[01067] To a solution of (2R,4S)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidine-2-carboxylic acid (2 g, 8.58 mmol, 1 eq) in THF (20 mL) was added BH_3·THF (1 M, 17.15 mL, 2 eq) dropwise at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at 0°C for 0.5 hours. The reaction mixture was warmed to 20°C and stirred at 20°C for 4 hours. The reaction mixture was cooled to 0°C and quenched with MeOH (3 mL) at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed to 20°C. To the reaction mixture was added water (40 mL) and extracted with EtOAc (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl (2R,4S)-4-fluoro-2-(hydroxymethyl) pyrrolidine-1-carboxylate (1.9 g, crude) as pale-yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.75 (s, 1H), 3.84-3.65 (m, 2H), 3.54-3.47 (m, 2H), 3.44-3.33 (m, 2H), 2.19-2.06 (m, 2H), 1.40 (s, 9H).

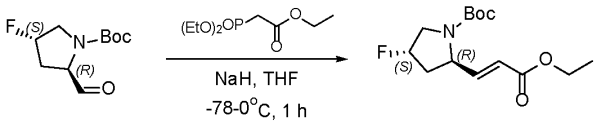
Step 1.2 Synthesis of tert-butyl (2R,4S)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate



2 3

[01068] To a solution of tert-butyl (2R,4S)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.9 g, 8.67 mmol, 1 eq) in DCM (20 mL) was added DMP (4.41 g, 10.40 mmol, 3.22 mL, 1.2 eq) at 0°C. The reaction mixture was warmed to 20°C and stirred at 20°C for 2 hours. The reaction mixture was cooled to 0°C and to the reaction mixture was added $NaHCO_3$ (10 mL) at 0°C. The reaction mixture was warmed to 20°C and filtered. To the filtrate was added water (40 mL) and extracted with DCM (20 mL x 3), the combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~70% Petroleum ether: Ethyl acetate gradient @ 45 mL/min). The eluent was removed under reduced pressure to give tert-butyl (2R,4S)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate (0.9 g, 4.14 mmol, 47.81% yield) as pale-yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42-9.39 (m, 1H), 5.39-5.24 (m, 1H), 4.15-4.10 (m, 1H), 3.70-3.67 (m, 1H), 3.60-3.50 (m, 1H), 2.36-2.20 (m, 2H), 1.42-1.40 (m, 9H).

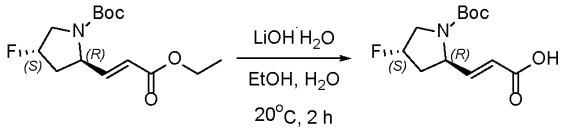
Step 1.3 Synthesis of tert-butyl (2R,4S)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate.



3 4

[01069] To a solution of NaH (198.86 mg, 4.97 mmol, 60% purity, 1.2 eq) in THF (10 mL) was added ethyl 2-diethoxyphosphorylacetate (1.11 g, 4.97 mmol, 986.35 µL, 1.2 eq) dropwise at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 mins. Then a solution of tert-butyl (2R,4S)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate (900.00 mg, 4.14 mmol, 1 eq) in THF (10 mL) was added to the above reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 hour. The reaction mixture was quenched with sat. aq. NH_4Cl (15 mL) at 0°C, and then the reaction mixture was warmed to 20°C. To the reaction mixture was added water (30 mL). The reaction mixture was extracted with EtOAc (15 mL x 3). The combined organic phase was washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~40% Petroleum ether: Ethyl acetate gradient @ 40 mL/min). The eluent was removed under reduced pressure to give tert-butyl (2R,4S)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (0.63 g, 2.08 mmol, 50.15% yield, 94.76% purity) as pale-yellow oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.79-6.74 (m, 1H), 5.94 (d, J = 7.6 Hz, 1H), 5.30-5.17 (m, 1H), 4.44-4.42 (m, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.73-3.70 (m, 1H), 3.68-3.46 (m, 1H), 2.40-2.32 (m, 1H), 2.04-1.99 (m, 1H), 1.40-1.34 (m, 9H), 1.21 (t, J = 6.8 Hz, 3H).

Step 1.4 Synthesis of (E)-3-[(2R,4S)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidin-2-yl]prop- 2-enoic acid.

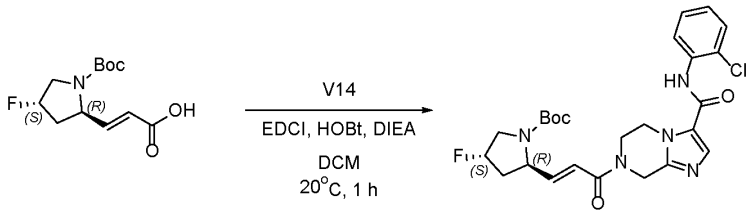


4

[01070] To a solution of tert-butyl (2R,4S)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine -1-carboxylate (0.6 g, 2.09 mmol, 1 *eq*) in EtOH (3 mL) and H_2O (3 mL) was added $LiOH{\cdot}H_2O$ (262.86 mg, 6.26 mmol, 3 *eq*) in portions at 20°C. The reaction mixture was stirred at 20°C for 2 hours. The reaction mixture was concentrated under reduced pressure and cooled to 0°C and adjusted pH = 3 with 1 M HCl at 0°C. The reaction mixture was warmed up to 20°C and to the reaction mixture was added water (20 mL). The reaction mixture was extracted with

EtOAc (7 mL x 3), the combined organic phase was washed with brine (7 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (E)-3-[(2R,4S)-1-tert-butoxycarbonyl-4-fluoro- pyrrolidin-2-yl]prop-2-enoic acid (0.5 g, 1.90 mmol, 91.18% yield, 98.73% purity) as a pale yellow solid. LCMS: m/z 258.1 $[M-H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.32 (s, 1H), 6.71-6.68 (m, 1H), 5.84 (d, J = 7.6 Hz, 1H), 5.30-5.17 (m, 1H), 4.41-4.40 (m, 1H), 3.74-3.65 (m, 1H), 3.54-3.42 (m, 1H), 2.40-2.38 (m, 1H), 1.99-1.91 (m, 1H), 1.48-1.34 (m, 9H).

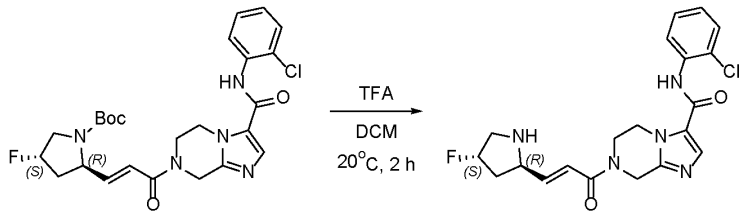
Step 1.5 Synthesis of tert-butyl (2R,4S)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate.



5

[01071] To the reaction mixture of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine- 3-carboxamide (250 mg, 798.26 μmol, 1 eq, HCl) in DCM (3 mL) were added (E)-3-[(2R,4S)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidin-2-yl]prop-2-enoic acid (248.36 mg, 957.91 μmol, 1.2 eq), DIEA (309.50 mg, 2.39 mmol, 417.12 μL, 3 eq) at 20°C. And then HOBt (215.72 mg, 1.60 mmol, 2 eq) and EDCI (229.54 mg, 1.20 mmol, 1.5 eq) were added to the reaction mixture at 20°C. The reaction mixture was stirred at 20°C for 1 hour. To the mixture was added water (20 mL) at 20°C. The reaction mixture was extracted with DCM (7 mL x 3), the combined organic phase was washed with brine (7 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~70% Petroleum ether: Ethyl acetate gradient @ 30 mL/min). The eluent was removed under reduced pressure to give tert-butyl (2R,4S)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (0.35 g, crude) as a pale yellow solid. LCMS: m/z 518.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.56-7.51 (m, 2H), 7.40-7.28 (m, 2H), 6.65-6.60 (m, 2H), 5.31-5.18 (m, 1H), 4.92-4.76 (m, 2H), 4.46-4.30 (m, 3H), 4.00-3.66 (m, 2H), 2.44-2.38 (m, 2H), 2.10-1.98 (m, 1H), 1.45-1.34 (m, 10H).

Step 1.6 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



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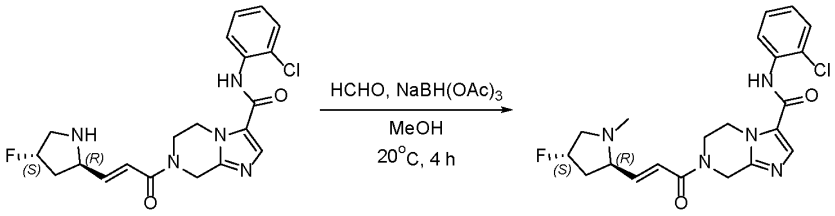
[01072] To a solution of tert-butyl (2R,4S)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (0.35 g, 675.70 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 20°C. The reaction mixture was stirred at 20°C for 2 h. The reaction mixture was concentrated under reduced pressure to give N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.9 g, 646.14 μmol, 95.63% yield, 30% purity) as yellow oil. The part (150 mg) of crude product was adjusted pH = 7 with sat. aq. Na_2CO_3 at 0°C. The crude product was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 25 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; gradient: 10%-40% B over 8.0 min). The residue was dried over lyophilization to give N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (10 mg, 23.50 μmol, 3.48% yield, 98.18% purity) as a white solid. LCMS: m/z 418.2 $[M+H]^+$. HPLC: 98.18% purity. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.2 Hz, 0.8 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.2 Hz, 1H), 6.74-6.69 (m, 2H), 5.32-5.30 (m, 1H), 5.18-5.17 (m, 2H), 4.90-4.75 (m, 2H), 4.31-3.90 (m, 3H), 3.16-3.07 (m, 1H), 3.03-2.96 (m, 1H), 2.90-2.80 (m, 1H), 2.17-2.10 (m, 1H), 1.68-1.55 (m, 1H).

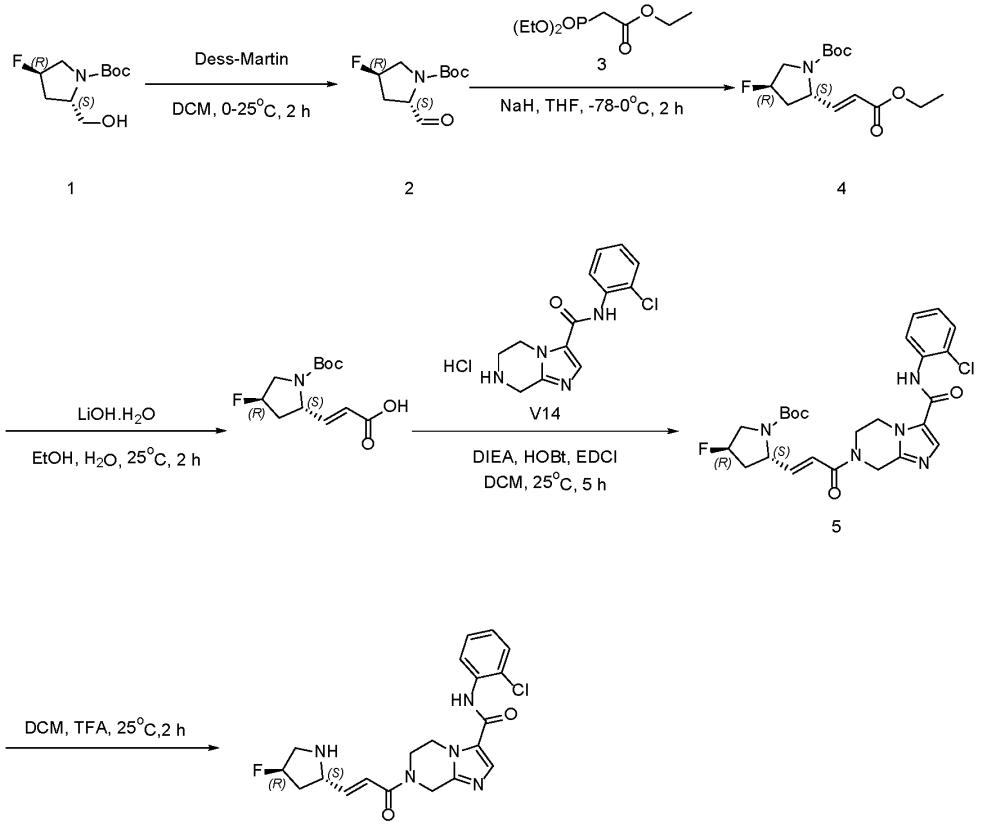
Step 1.7 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



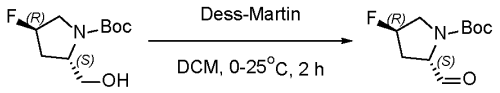
[01073] To a solution of N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (750.00 mg, 538.45 μmol, 1 eq) in MeOH (4 mL) was added formaldehyde (244.70 mg, 3.02 mmol, 224.49 μL, 37% purity, 5.6 eq) in one portion at 20°C and stirred at 20°C for 20 mins. Then $NaBH(OAc)_3$ (399.42 mg,

1.88 mmol, 3.5 eq) was added into the reaction mixture in portions at 20°C. The reaction mixture was stirred at 20°C for 4 hours. To the reaction mixture was added water (0.1 mL) at 20°C. The crude product was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; gradient: 20%-50% B over 8.0 min). The residue was dried over lyophilization to give N-(2-chlorophenyl)-7-[(E)-3-[(2R,4S)-4-fluoro-1-methyl-pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (61 mg, 138.77 μmol, 25.77% yield, 98.25% purity) as a white solid. LCMS: m/z 432.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (td, J = 8.0 Hz, 0.8 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.83 (d, J = 15.2 Hz, 1H), 6.53-6.47 (m, 1H), 5.27-5.13 (m, 1H), 4.93-4.75 (m, 2H), 4.33-4.28 (m, 2H), 4.03-3.96 (m, 2H), 3.53-3.49 (m, 1H), 3.18-3.17 (m, 1H), 2.48-2.47 (m, 1H), 2.39 (s, 3H), 2.35-2.22 (m, 1H), 2.06-1.90 (m, 1H).

Example 168: Synthesis of *N*-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoropyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



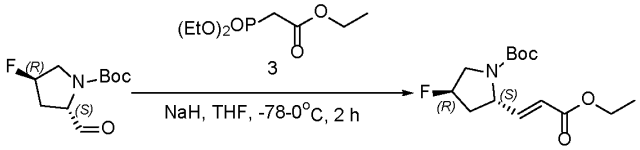
Step 1.1 Synthesis of tert-butyl (2S,4R)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate



1 2

[01074] To a solution of tert-butyl (2S,4R)-4-fluoro-2-(hydroxymethyl)pyrrolidine-1-carboxylate (1 g, 4.56 mmol, 1 eq) in DCM (10 mL) was added Dess-Martin (2.32 g, 5.47 mmol, 1.70 mL, 1.2 eq) in portions at 0°C. The reaction mixture was slowly warmed to 25°C and stirred at 25°C for 2 h. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (20 mL) at 0°C, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 70 mL/min) to give tert-butyl (2S,4R)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate (600 mg, 2.76 mmol, 60.56% yield) as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.41- 9.39 (m, 1H), 3.70-3.47 (m, 3H), 2.36-2.04 (m, 3H), 1.42-1.40 (m, 9H).

Step 1.2 Synthesis of tert-butyl (2S,4R)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate

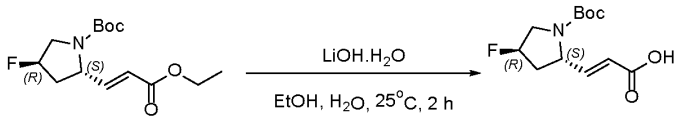


2 4

[01075] To a solution of NaH (132.57 mg, 3.31 mmol, 60% purity, 1.2 eq) in THF (6 mL) was added ethyl 2-diethoxyphosphorylacetate (743.05 mg, 3.31 mmol, 657.56 µL, 1.2 eq) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl (2S,4R)-4-fluoro-2-formyl-pyrrolidine-1-carboxylate (600 mg, 2.76 mmol, 1 eq) in THF (6 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) at 0°C, and then diluted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl (2S,4R)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (600 mg, 2.09 mmol, 75.61% yield) as yellow oil. LCMS: m/z 188.1 $[M+H-100]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.80-

6.74 (m, 1H), 5.94-5.91 (m, 1H), 5.30-5.17 (m, 1H), 4.44-4.40 (m, 1H), 4.15-4.10 (m, 2H), 3.74-3.64 (m, 1H), 3.55-3.42 (m, 1H), 2.43-2.33 (m, 1H), 2.05-1.99 (m, 1H), 1.40-1.34 (m, 9H), 1.21 (t, J = 6.8 Hz, 3H).

Step 1.3 Synthesis of (E)-3-[(2S,4R)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidin-2-yl] prop-2-enoic acid



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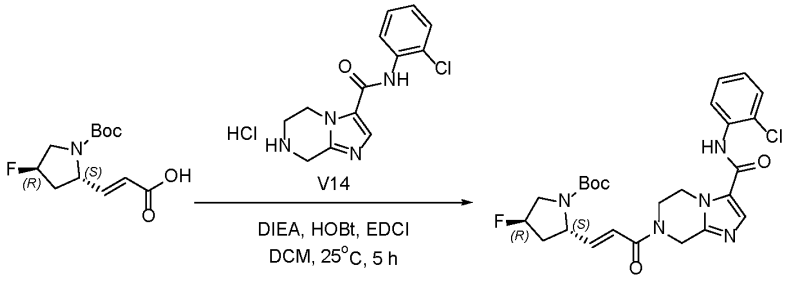
[01076] To a solution of tert-butyl (2S,4R)-2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine -1-carboxylate (0.6 g, 2.09 mmol, 1 eq) in EtOH (3 mL) was added dropwise a solution of LiOH.H_2O (262.86 mg, 6.26 mmol, 3 eq) in H_2O (3 mL) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was cooled to 0°C, and adjusted pH to 4 with HCl (1M) at 0°C. The reaction mixture was diluted with EtOAc (20 mL x 5). The combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (E)-3-[(2S,4R)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidin-2-yl] prop-2-enoic acid (500 mg, crude) as yellow oil. LCMS: m/z 258.1 $[M-H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.30 (s, 1H), 6.71-6.66 (m, 1H), 5.84-5.81 (m, 1H), 5.30-5.17 (m, 1H), 4.42-4.38 (m, 1H), 3.74-3.64 (m, 1H), 3.54-3.41 (m, 1H), 2.44-2.33 (m, 1H), 2.02-1.95 (m, 1H), 1.40-1.34 (m, 9H).

Step 1.4 Synthesis of tert-butyl (2S,4R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate



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[01077] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (251.65 mg, 803.53 μmol, 1 eq, HCl) in DCM (5 mL) were added (E)-3-[(2S,4R)-1-tert- butoxycarbonyl-4-fluoro-pyrrolidin-2-yl]prop-2-enoic acid (250 mg, 964.23 μmol, 1.2 eq), DIEA (311.54 mg, 2.41 mmol, 419.87 μL, 3 eq), HOBt (217.15 mg, 1.61 mmol, 2 eq) and EDCI (231.05 mg, 1.21 mmol, 1.5 eq) in one portion at 25°C. The reaction mixture was stirred

at 25°C for 5 h. The reaction mixture was poured into water (10 mL) and stirred for 2 min at 25°C. The mixture was extracted with DCM (5 mL x 5). The combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl (2S,4R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (300 mg, 579.17 μmol, 72.08% yield) as a yellow solid. LCMS: m/z 518.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.81 (s, 1H), 7.87 (s, 1H), 7.56-7.52 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 8 Hz, 1.6 Hz, 1H), 6.66-6.64 (m, 2H), 5.31-5.10 (m, 1H), 4.91-4.75 (m, 2H), 4.47 (s, 1H), 4.30-4.27 (m, 2H), 4.02-3.97 (m, 2H), 3.75-3.66 (m, 1H), 3.58-3.42 (m, 1H), 2.45-2.35 (m, 1H), 2.05-1.99 (m, 1H), 1.40-1.34 (m, 9H).

Step 1.5 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



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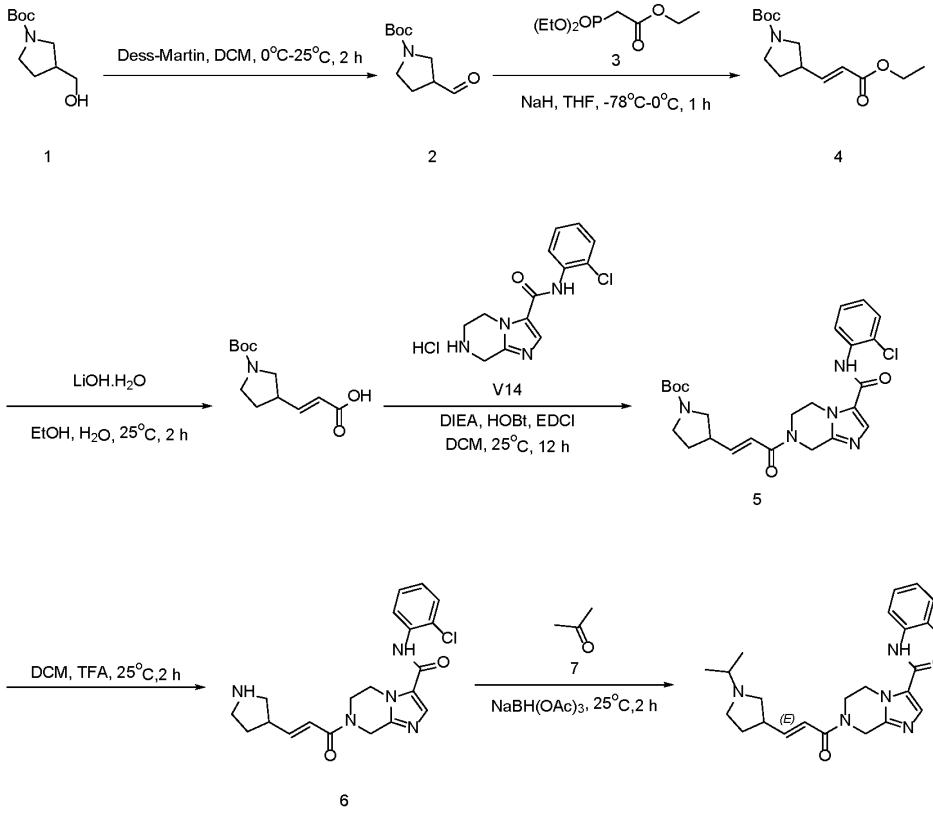
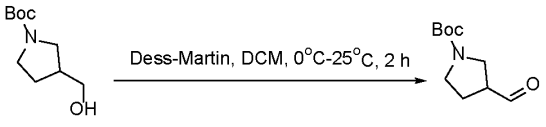
[01078] To a solution of tert-butyl (2S,4R)-2-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H- imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]-4-fluoro-pyrrolidine-1-carboxylate (50 mg, 96.53 μmol, 1 eq) in DCM (0.5 mL) was added dropwise TFA (767.50 mg, 6.73 mmol, 0.5 mL, 69.73 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150*40 mm*10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:15%-45% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoropyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (10.1 mg, 23.87 μmol, 24.73% yield, 98.77% purity) as a white solid. LCMS: m/z 418.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 8 Hz, 1.6 Hz, 1H), 6.70-6.69 (m, 2H), 5.32-5.16 (m, 1H), 4.91-4.75 (m, 2H), 4.31-4.28 (m, 2H),

4.01-3.89 (m, 3H), 3.19-3.06 (m, 1H), 3.03-2.93 (m, 1H), 2.80 (s, 1H), 2.21-2.10 (m, 1H), 1.70-1.57 (m, 1H).

Example 169: *N*-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



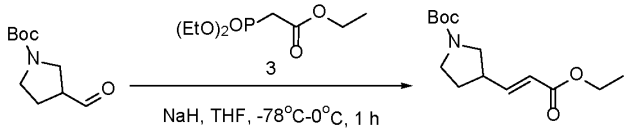
Step 1.1 Synthesis of tert-butyl 3-formylpyrrolidine-1-carboxylate



[01079] To a solution of tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (25.00 g, 124.22 mmol, 1 eq) in DCM (250 mL) was added Dess-Martin (63.22 g, 149.06 mmol, 46.18 mL, 1.2 eq) in portions at 0°C. The reaction mixture was slowly warmed to 25°C and stirred at 25°C for 2 h. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (500 mL) at 0°C, and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue.

The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~28% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give tert-butyl 3-formylpyrrolidine-1-carboxylate (15.5 g, 77.79 mmol, 62.63% yield) as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.61-9.60 (m, 1H), 3.56-3.53 (m, 1H), 3.28-3.24 (m, 2H), 3.15-3.12 (m, 2H), 2.06-2.02 (m, 2H), 1.39 (m, 9H).

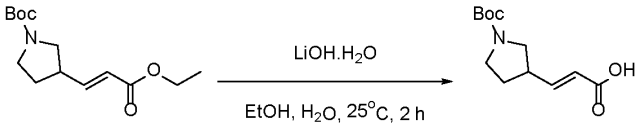
Step 1.2 Synthesis of tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate



2 4

[01080] To a solution of NaH (3.73 g, 93.35 mmol, 60% purity, 1.2 eq) in THF (150 mL) was added ethyl 2-diethoxyphosphorylacetate (20.93 g, 93.35 mmol, 18.52 mL, 1.2 eq) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl 3-formylpyrrolidine-1-carboxylate (15.5 g, 77.79 mmol, 1 eq) in THF (150 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (500 mL) at 0°C, and then diluted with EtOAc (300 mL x 3). The combined organic phase was washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~32% Ethyl acetate/Petroleum ether gradient @ 120 mL/min) to give tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (16.5 g, 61.26 mmol, 78.75% yield) was obtained as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.88-6.82 (m, 1H), 5.93 (d, J = 15.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.47-3.43 (m, 1H), 3.32-3.31 (m, 1H), 3.23-3.18 (m, 1H), 3.01-2.98 (m, 2H), 2.01-1.98 (m, 1H), 1.76-1.74 (m, 1H), 1.39 (m, 9H), 1.20 (t, J = 7.2 Hz, 3H).

Step 1.3 Synthesis of (E)-3-(1-tert-butoxycarbonylpyrrolidin-3-yl)prop-2-enoic acid



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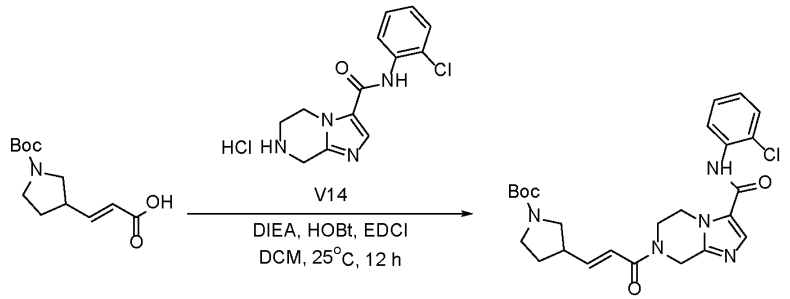
[01081] To a solution of tert-butyl 3-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (16.5 g, 61.26 mmol, 1 eq) in EtOH (165 mL) was added dropwise a solution of $LiOH.H_2O$ (7.71 g, 183.79 mmol, 3 eq) in H_2O (80 mL) at 25°C. The reaction mixture was

stirred at 25°C for 2 h. The reaction mixture was cooled to 0°C, and adjusted pH to 4 with HCl (1M) at 0°C. The reaction mixture was diluted with EtOAc (200 mL x 5). The combined organic phase was washed with brine (200 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (E)-3-(1-tert-butoxycarbonylpyrrolidin-3-yl)prop-2-enoic acid (14 g, 58.02 mmol, 94.71% yield) as yellow oil. LCMS: m/z 186.1 $[M+H-55]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.80-6.74 (m, 1H), 5.85-5.81 (m, 1H), 3.37-3.31 (m, 2H), 3.22-3.18 (m, 1H), 3.04-2.95 (m, 2H), 1.98 (s, 1H), 1.74-1.72 (m, 1H), 1.39 (s, 9H).

Step 1.4 Synthesis of tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate



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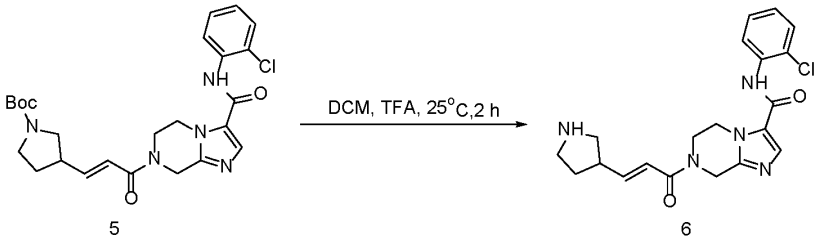
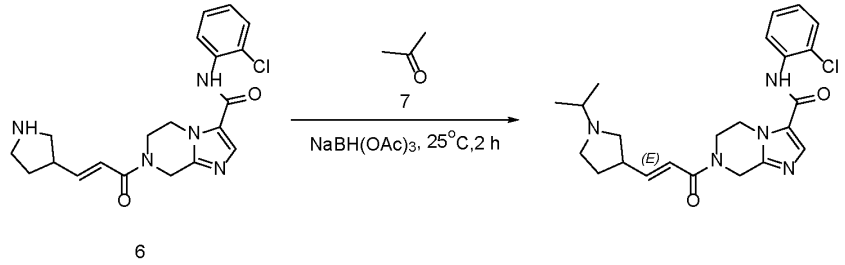
[01082] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1 g, 3.19 mmol, 1 eq, HCl) in MeCN (10 mL) were added (E)-3-(1-tert-butoxycarbonylpyrrolidin-3-yl)prop-2-enoic acid (924.51 mg, 3.83 mmol, 1.2 eq), DIEA (1.24 g, 9.58 mmol, 1.67 mL, 3 eq), HOBt (862.89 mg, 6.39 mmol, 2 eq) and EDCI (918.16 mg, 4.79 mmol, 1.5 eq) in one portion at 25°C. The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into water (6 mL) and stirred for 2 min at 25°C. The mixture was extracted with ethyl acetate (3 mL x 5). The combined organic phase was washed with brine (3 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (1.4 g, 2.80 mmol, 87.69% yield) as a yellow solid. LCMS: m/z 500.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.87 (s, 1H), 7.56-7.51 (m, 2H), 7.37-7.36 (m, 1H), 7.28 (td, J = 4.6 Hz, 1.6 Hz, 1H), 6.70-6.66 (m, 2H), 4.93-4.74 (m, 2H), 4.32-4.28 (m, 2H), 3.95-3.92 (m, 1H), 3.50-3.45 (m, 2H), 3.24-3.22 (m, 2H), 3.08-3.04 (m, 2H), 2.01 (s, 1H), 1.78-1.76 (m, 1H), 1.40 (s, 9H).

Step 1.5 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-pyrrolidin-3-ylprop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01083] To a solution of tert-butyl 3-[(E)-3-[3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (400 mg, 800.02 μmol, 1 eq) in DCM (3 mL) was added dropwise TFA (2.18 g, 21.54 mmol, 3 mL, 26.93 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give N-(2-chlorophenyl)-7-[(E)-3-pyrrolidin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (400 mg, crude) as yellow oil. LCMS: m/z 400.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.35 (s, 1H), 8.27 (s, 1H), 7.59-7.57 (m, 1H), 7.52-7.50 (m, 1H), 7.41-7.39 (m, 1H), 7.35-7.31 (m, 1H), 6.76-6.72 (m, 2H), 4.96-4.94 (m, 2H), 4.44-4.43 (m, 2H), 4.10-4.09 (m, 2H), 3.38-3.35 (m, 1H), 3.28-3.24 (m, 2H), 3.19-3.16 (m, 2H), 2.16-2.14 (m, 1H), 1.83-1.78 (m, 1H).

Step 1.6 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

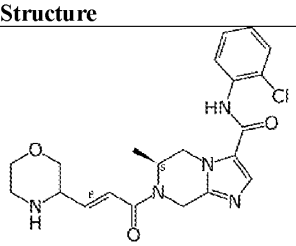
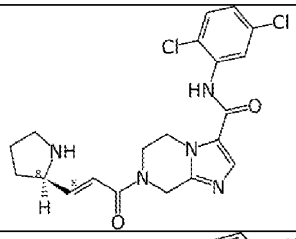
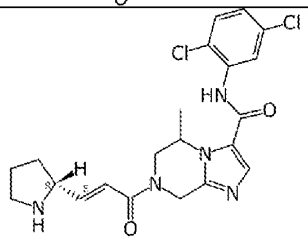


[01084] To a solution of N-(2-chlorophenyl)-7-[(E)-3-pyrrolidin-3-ylprop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide (380.00 mg, 950.30 μmol, 1 eq) in ACETONE (2 mL) was added $NaBH(OAc)_3$ (402.81 mg, 1.90 mmol, 2 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was cooled to 0°C. The reaction mixture was poured into ice-water (1 mL) and stirred for 2 min, and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75*40mm*3um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-40% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-(1-

isopropylpyrrolidin-3-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (5.1 mg, 11.54 μmol, 1.21% yield, 97.52% purity) as a white solid. LCMS: m/z 442.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.76-6.57 (m, 2H), 4.91-4.73 (m, 2H), 4.30-4.29 (m, 2H), 4.00-3.98 (m, 2H), 2.94-2.89 (m, 1H), 2.78 (t, J = 7.6 Hz, 1H), 2.65-2.59 (m, 1H), 2.54-2.53 (m, 1H), 2.36-2.26 (m, 2H), 2.03-1.94 (m, 1H), 1.60-1.52 (m, 1H), 1.02-1.00 (m, 6H).

[01085] Compounds in Table L were synthesized following the procedure for N-(2-chlorophenyl)-7-[(E)-3-pyrrolidin-3-ylprop-2-enoyl]-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3-carboxamide.

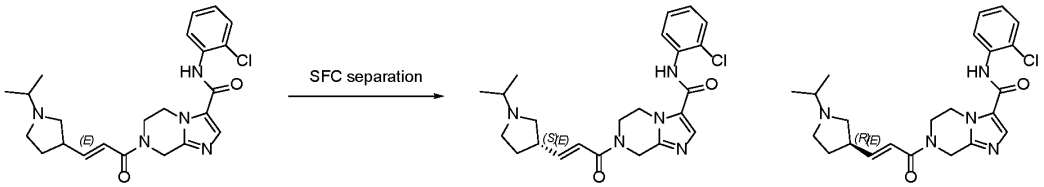
Table L

Name	Structure	NMR	LCMS
(6S)-N-(2-chlorophenyl)-6-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.91 (s, 1H), 7.56-7.54 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.68-6.58 (m, 2H), 5.11-4.85 (m, 2H), 4.63-4.60 (m, 2H), 4.20-4.09 (m, 1H), 3.78-3.65 (m, 2H), 3.44-3.42 (m, 2H), 3.07 (t, J = 10.0 Hz, 1H), 2.79-2.76 (m, 2H), 1.09 (s, 3H).	LCMS: m/z 430.2 $[M+H]^+$
N-(2,5-dichlorophenyl)-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.91 (s, 1H), 7.88 (s, 1H), 7.55 (s, 1H), 7.09 (s, 1H), 6.86 (s, 1H), 4.65-4.57 (m, 2H), 4.29-4.22 (m, 2H), 3.77-3.76 (m, 2H), 1.44 (s, 9H).	LCMS: m/z 434.1 $[M+H]^+$
N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 8.8 Hz, 2.8 Hz, 1H), 6.77-6.61 (m, 2H), 5.27-5.04 (m, 2H), 4.69-4.61 (m, 1H), 4.31-4.29 (m, 1H), 3.70-3.65 (m, 1H), 3.33-3.20 (m, 1H), 2.89-2.77 (m, 2H), 1.89-1.80 (m, 1H), 1.70-1.64 (m, 2H), 1.39-1.30 (m, 1H), 1.29-1.25 (m, 3H).	LCMS: m/z 448.2 $[M+H]^+$

Example 170: Synthesis of *N*-(2-chlorophenyl)-7-[(E)-3-[(3S)-1-isopropylpyrrolidin-3-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-

chlorophenyl)-7- [(E)-3-[(3R)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(3S)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7-[(E)-3-[(3R)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



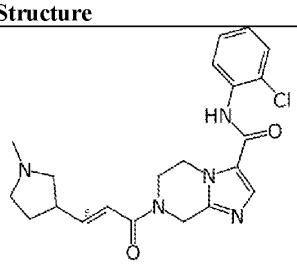
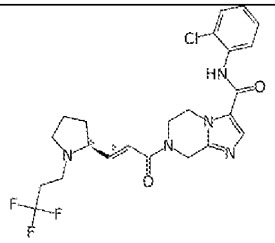
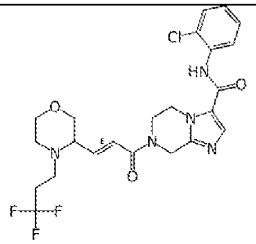
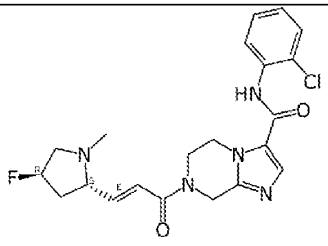
[01086] *N*-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (115 mg, 260.21 μmol, 27.38% yield) was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 3 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-40% B over 8.0 min) to give N-(2-chlorophenyl)-7-[(E)-3-[(3S)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (40.2 mg, 89.13 μmol, 39.39% yield, 97.99% purity) as a white solid and N-(2-chlorophenyl)-7-[(E)-3-[(3R)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (38.3 mg, 84.61 μmol, 37.39% yield, 97.63% purity) as a white solid.

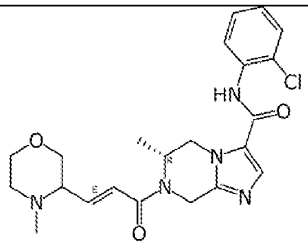
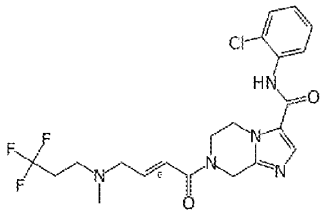
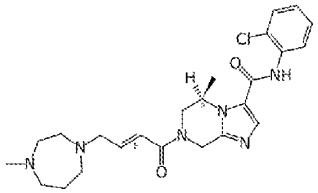
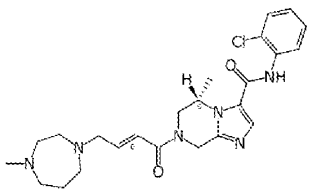
[01087] LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.57 (m, 2H), 4.92-4.73 (m, 2H), 4.30-4.27 (m, 2H), 4.00-3.96 (m, 2H), 2.95-2.91 (m, 1H), 2.78 (t, J = 8 Hz, 1H), 2.65-2.59 (m, 1H), 2.55-2.53 (m, 1H), 2.34-2.28 (m, 2H), 2.01-1.97 (m, 1H), 1.57-1.55 (m, 1H), 1.01 (t, J = 4.8 Hz, 6H).

[01088] LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.57 (m, 2H), 4.91-4.74 (m, 2H), 4.30 (s, 2H), 4.00-3.96 (m, 2H), 2.95-2.89 (m, 1H), 2.79 (t, J = 8 Hz, 1H), 2.66-2.60 (m, 1H), 2.55-2.53 (m, 1H), 2.35-2.29 (m, 2H), 2.00-1.96 (m, 1H), 1.61-1.54 (m, 1H), 1.01 (t, J = 4.8 Hz, 6H).

[01089] Compounds in Table M were synthesized following the procedure for *N-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.*

Table M

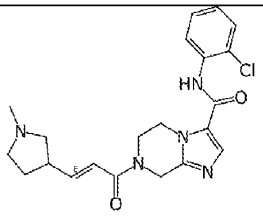
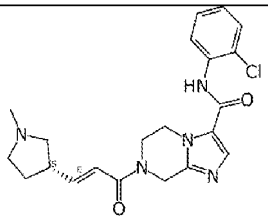
Name	Structure	NMR	LCMS
N-(2-chlorophenyl)-7-[(E)-3-(1-methylpyrrolidin-3-yl)prop-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.76-6.56 (m, 2H), 4.91-4.73 (m, 2H), 4.30 (s, 2H), 4.00-3.93 (m, 2H), 3.00-2.94 (m, 1H), 2.66 (t, J = 8.8 Hz, 1H), 2.54-2.53 (m, 1H), 2.45-2.43 (m, 1H), 2.25 (s, 3H), 2.23-2.21 (m, 1H), 2.02-1.99 (m, 1H), 1.59-1.57 (m, 1H).	LCMS: m/z 414.2 $[M+H]^+$
N-(2-chlorophenyl)-7-[(E)-3-[(2S)-1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.77-6.53 (m, 2H), 4.92-4.75 (m, 2H), 4.32-4.29 (m, 2H), 4.01-3.95 (m, 2H), 3.14-3.03 (m, 2H), 2.83-2.78 (m, 1H), 2.74-2.32 (m, 3H), 2.20 (q, J = 8.8 Hz, 1H), 1.98-1.93 (m, 1H), 1.78-1.71 (m, 2H), 1.55-1.50 (m, 1H).	LCMS: m/z 496.2 $[M+H]^+$
N-(2-chlorophenyl)-7-[(E)-3-[4-(3,3,3-trifluoropropyl)morpholin-3-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.94-12.72 (m, 1H), 10.65-10.52 (m, 1H), 8.49-8.42 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.36-7.15 (m, 2H), 6.98-6.79 (m, 1H), 5.14-5.02 (m, 2H), 4.48-4.39 (m, 2H), 4.18-4.12 (m, 2H), 4.00-3.90 (m, 4H), 3.83-3.81 (m, 1H), 3.60-3.50 (m, 1H), 3.28-3.24 (m, 3H), 3.06-2.98 (m, 2H).	LCMS: m/z 512.2 $[M+H]^+$
N-(2-chlorophenyl)-7-[(E)-3-[(2S,4R)-4-fluoro-1-methyl-pyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.87 (s, 1H), 7.54 (t, J = 8 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 8 Hz, 1.6 Hz, 1H), 6.84-6.80 (m, 1H), 6.52-6.47 (m, 1H), 5.33-5.13 (m, 1H), 4.94-4.75 (m, 2H), 4.33-4.28 (m, 2H), 4.03-	LCMS: m/z 432.1 $[M+H]^+$

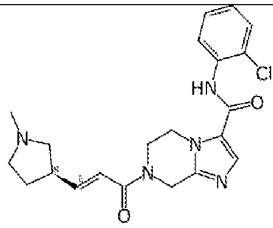
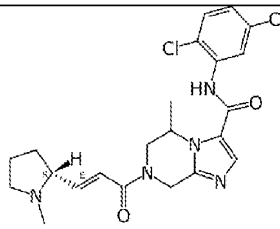
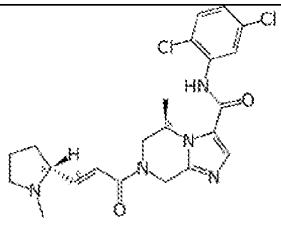
Name	Structure	NMR	LCMS
		3.95 (m, 2H), 3.58-3.47 (m, 1H), 3.17-3.16 (m, 1H), 2.47-2.35 (m, 1H), 2.22 (s, 3H), 2.16-2.05 (m, 1H), 1.94-1.78 (m, 1H).	
(6R)-N-(2-chlorophenyl)-6-methyl-7-[(E)-3-(4-methylmorpholin-3-yl) prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.91 (s, 1H), 7.56-7.54 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.6Hz, 1H), 7.28 (td, J = 8 Hz, 1.6Hz, 1H), 6.87-6.83 (m, 1H), 6.51-6.45 (m, 1H), 5.10-4.85 (m, 2H), 4.64-4.30 (m, 2H), 4.18-4.07 (m, 1H), 3.75-3.72 (m, 1H), 3.62-3.59 (m, 1H), 3.51 (t, J = 10 Hz, 1H), 3.23-3.17 (m, 1H), 2.80-2.76 (m, 1H), 2.71-2.68 (m, 1H), 2.18-2.14 (m, 1H), 2.12-2.11 (m, 3H), 1.08 (s, 3H).	LCMS: m/z 444.2 $[M+H]^+$
N-(2-chlorophenyl)-7-[(E)-4-[methyl(3,3,3-trifluoropropyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.78-6.65 (m, 2H), 4.91-4.76 (m, 2H), 4.32 (s, 2H), 4.01-3.96 (m, 2H), 3.18 (d, J = 5.6 Hz, 2H), 2.58-2.54 (m, 2H), 2.47-2.43 (m, 2H), 2.20 (s, 3H).	LCMS: m/z 470.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(4-methyl-1,4-diazepan-1-yl) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.4 Hz, 2H), 7.34 (dt, J = 6.8 Hz, 2H), 6.27-6.26 (m, 2H), 5.28-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.30-4.25 (m, 1H), 3.69 (d, J = 12.8 Hz, 1H), 3.27 (s, 3H), 2.64-2.54 (m, 7H), 2.25 (s, 3H), 1.71 (s, 2H), 1.28-1.26 (m, 3H).	LCMS: m/z 471.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(4-methyl-1,4-diazepan-1-yl)-but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 7.6 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.72 (m, 2H), 5.28-5.17 (m, 1H), 5.07 (s, 1H), 4.70-4.58 (m, 1H), 4.30-4.25 (m, 1H), 3.70 (d, J = 12.4 Hz, 1H),	LCMS: m/z 471.2 $[M+H]^+$

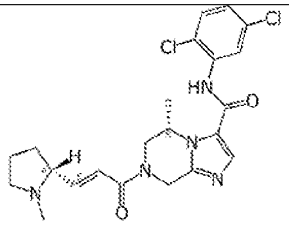
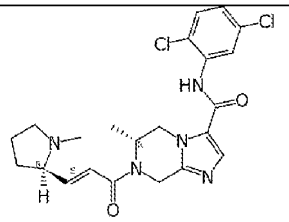
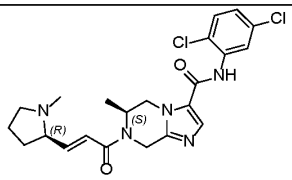
Name	Structure	NMR	LCMS
		3.29-3.22 (m, 3H), 2.65-2.53 (m, 7H), 2.23 (s, 3H), 1.72-1.69 (m, 2H), 1.29-1.26 (m, 3H).	

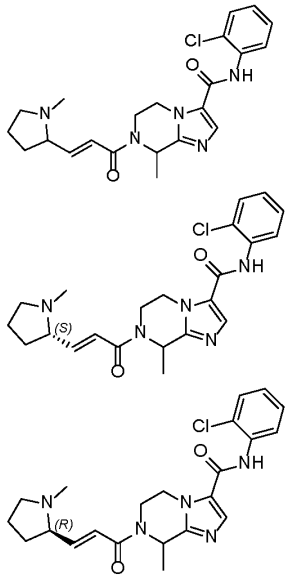
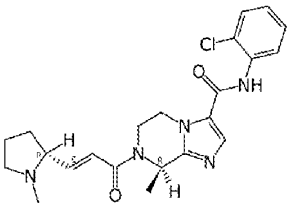
[01090] Compounds in Table N were synthesized following the procedure for *N*-(2-chlorophenyl)-7-[(E)-3-(1-isopropylpyrrolidin-3-yl)prop-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide followed by the procedure for *N*-(2-chlorophenyl)-7-[(E)-3-[(3S)-1-isopropylpyrrolidin-3-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7- [(E)-3-[(3R)-1-isopropylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table N

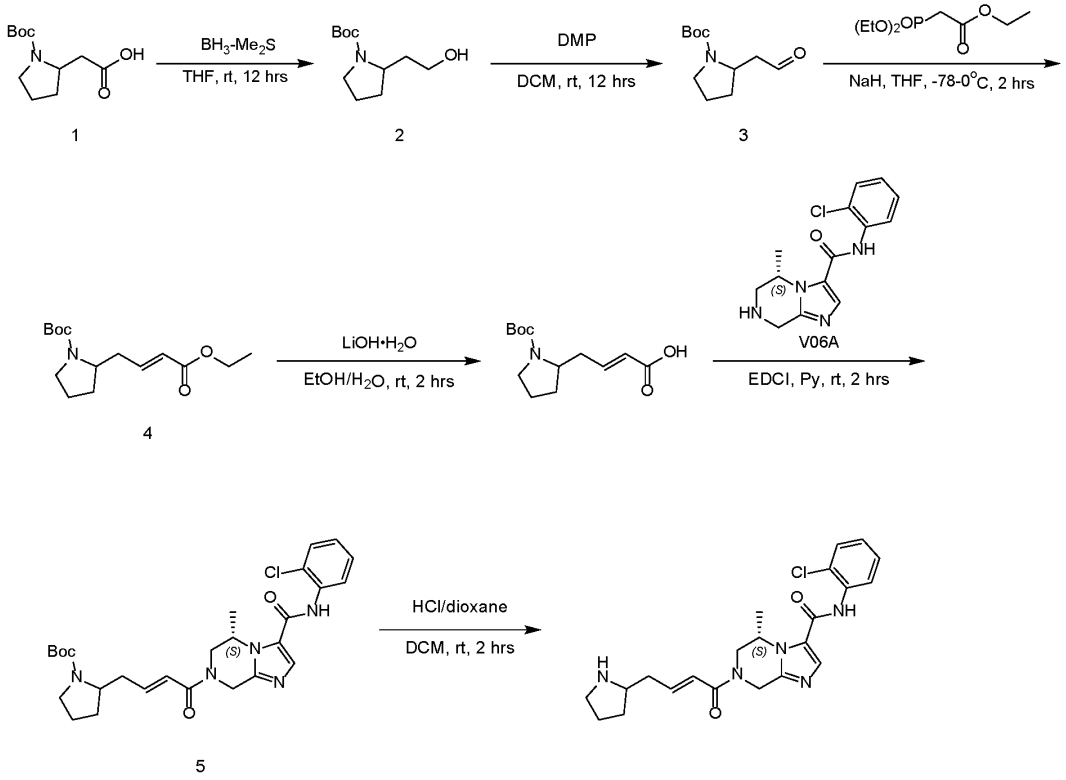
Name	Structure	NMR	LCMS	SFC conditions
N-(2-chlorophenyl)-7-[(E)-3-(1-methylpyrrolidin-3-yl)prop-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.76-6.56 (m, 2H), 4.91-4.73 (m, 2H), 4.30 (s, 2H), 4.00-3.93 (m, 2H), 3.00-2.94 (m, 1H), 2.66 (t, J = 8.8 Hz, 1H), 2.54-2.53 (m, 1H), 2.45-2.43 (m, 1H), 2.25 (s, 3H), 2.23-2.21 (m, 1H), 2.02-1.99 (m, 1H), 1.59-1.57 (m, 1H).	LCMS: m/z 414.2 $[M+H]^+$	
(R,E)-N-(2-chlorophenyl)-7-(3-(1-methylpyrrolidin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.87 (s, 1H), 7.53 (td, J = 8 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.76-6.56 (m, 2H), 4.91-4.74 (m, 2H), 4.30 (s, 2H), 4.00-3.95 (m, 2H), 3.01-2.92 (m, 1H), 2.66 (t, J = 8.8 Hz, 1H), 2.54-2.52 (m, 1H), 2.46-2.41 (m, 1H), 2.25-2.21 (m, 4H), 2.03-2.00 (m, 1H), 1.58-1.57 (m, 1H).	LCMS: m/z 414.2 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (NH_3H_2O 0.1%)]; B%: 50%, isocratic elution mode)

Name	Structure	NMR	LCMS	SFC conditions
N-(2-chlorophenyl) -7-[(E)-3-[(3R)-1-methylpyrrolidin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.77-6.56 (m, 2H), 4.91-4.74 (m, 2H), 4.30 (s, 2H), 4.00-3.94 (m, 2H), 3.00-2.94 (m, 1H), 2.66 (t, J = 8.4 Hz, 1H), 2.54-2.52 (m, 1H), 2.45-2.41 (m, 1H), 2.25-2.21 (m, 4H), 2.04-1.99 (m, 1H), 1.59-1.57 (m, 1H).	LCMS: m/z 414.2 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 2.4 Hz,, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 7.6 Hz, 2.4 Hz, 1H), 6.72-6.60 (m, 1H), 6.59-6.55 (m, 1H), 5.27-5.20 (m, 1H), 5.04 (s, 1H), 4.71-4.67 (m, 1H), 4.34-4.26 (m, 1H), 3.71-3.25 (m, 0.6H), 3.03-2.99 (m, 0.4H), 3.00-2.99 (m, 1H), 2.78-2.77 (m, 1H), 2.17-2.14 (m, 4H), 1.97-1.96 (m, 1H), 1.75-1.71 (m, 2H), 1.56-1.55 (m, 1H), 1.30-1.26 (m, 3H).	LCMS: m/z 462.1 $[M+H]^+$	
(5R)-N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin -2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 6.77-6.60 (m, 2H), 5.27-5.23 (m, 1H), 5.04 (s, 1H), 4.71-4.67 (m, 1H), 4.34-4.26 (m, 1H), 3.71-3.25 (m, 0.5H), 3.33-3.25 (m, 0.5H), 3.03-2.96 (m, 1H), 2.79-2.77 (m, 1H), 2.17-2.00 (m, 4H), 1.97-1.96 (m, 1H), 1.73-1.71 (m, 2H), 1.56-1.55 (m, 1H), 1.29-1.22 (m, 3H).	LCMS: m/z 462.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm* 30 mm,10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode).

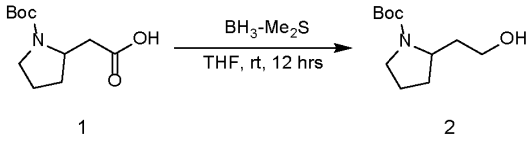
Name	Structure	NMR	LCMS	SFC conditions
(5S)-N-(2,5-dichlorophenyl)-5-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.72-6.55 (m, 2H), 5.29-5.20 (m, 1H), 5.04 (s, 1H), 4.71-4.67 (m, 1H), 4.33-4.26 (m, 1H), 3.71-3.25 (m, 0.5H), 3.03-2.96 (m, 0.5H), 3.00-2.99 (m, 1H), 2.78-2.76 (m, 1H), 2.18-2.15 (m, 4H), 1.98-1.95 (m, 1H), 1.73-1.71 (m, 2H), 1.57-1.55 (m, 1H), 1.29-1.26 (m, 3H).	LCMS: m/z 462.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm* 30 mm,10 um); mobile phase: [CO_2-EtOH (0.1% $NH_3·H_2O$)]; B%: 50%, isocratic elution mode).
(6R)-N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin -2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.91 (s, 1H), 7.73-7.72 (m, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.36-7.33 (m, 1H), 6.70-6.53 (m, 2H), 5.11-4.85 (m, 2H), 4.71-4.33 (m, 2H), 4.19-4.15 (m, 1H), 3.03-2.99 (m, 1H), 2.76 (q, J = 8.0 Hz, 1H), 2.18 (s, 3H), 2.16-2.14 (m, 1H), 2.02-1.91 (m, 1H), 1.77-1.68 (m, 2H), 1.59-1.52 (m, 1H), 1.08 (s, 3H).	LCMS: m/z 462.1 $[M+H]^+$	SFC (column: REGIS (s,s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
(6S)-N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.93 (s, 1H), 7.71-7.70 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.37-7.35 (m, 1H), 6.70-6.52 (m, 2H), 5.11-4.85 (m, 2H), 4.63-4.32 (m, 2H), 4.20-4.02 (m, 1H), 3.03-2.99 (m, 1H), 2.76 (q, J = 8.0 Hz, 1H), 2.17 (s, 3H), 2.14-2.12 (m, 1H), 2.01-1.92 (m, 1H), 1.75-1.68 (m, 2H), 1.58-1.50 (m, 1H), 1.08 (s, 3H).	LCMS: m/z 462.1 $[M+H]^+$	SFC (column: REGIS (s,s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic

Name	Structure	NMR	LCMS	SFC conditions
				elution mode)
N-(2-chlorophenyl)-8-methyl-7-[(E)-3-(1-methylpyrrolidin-2-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide; N-(2-chlorophenyl)-8-methyl-7-((E)-3-((S)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide; N-(2-chlorophenyl)-8-methyl-7-((E)-3-((R)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.89 (s, 1H), 7.55-7.51 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 6.8 Hz, 1H), 6.72-6.56 (m, 2H), 5.55-5.45 (m, 1H), 4.60-4.36 (m, 2H), 4.01-3.62 (m, 1.5H), 3.24-3.20 (m, 0.5H), 3.03-2.99 (m, 1H), 2.77-2.76 (m, 1H), 2.17 (s, 3H), 2.14-2.12 (m, 1H), 2.00-1.91 (m, 1H), 1.74-1.69 (m, 2H), 1.54-1.46 (m, 4H).	LCMS: m/z 428.2 $[M+H]^+$	
(R)-N-(2-chlorophenyl)-8-methyl-7-((E)-3-((S)-1-methylpyrrolidin-2-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.73-6.52 (m, 2H), 5.55-5.47 (m, 1H), 4.60-4.57 (m, 2H), 4.03-3.62 (s, 1.6H), 3.27-3.19 (m, 0.4H), 3.03-2.98 (m, 1H), 2.77-2.75 (m, 1H), 2.17 (s, 3H), 2.16-2.11 (m, 1H), 1.99-1.91 (m, 1H), 1.75-1.68 (m, 2H), 1.56-1.46 (m, 4H).	LCMS: m/z 428.2 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK IC (250 mm *3 0 mm, 10 um); mobile phase: [CO_2-MeOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)

Example 171: Synthesis of (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

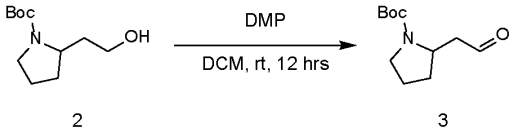


Step 1.1 Synthesis of tert-butyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate



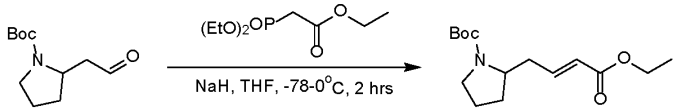
[01091] To a solution of 2-(1-tert-butoxycarbonylpyrrolidin-2-yl)acetic acid (5 g, 21.81 mmol, 1 *eq*) in THF (60 mL) was added BH_3-Me_2S (10 M, 6.54 mL, 3 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 12 hrs. The reaction mixture was quenched by addition methanol (100 mL) at 25°C, and then diluted with water (100 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layers were washed with brine (80 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (4.5 g, 20.90 mmol, 95.85% yield) as colorless oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 4.37 (t, J = 5.2 Hz, 1H), 3.73 (s, 1H), 3.42-3.37 (m, 2H), 3.23-3.19 (m, 2H), 1.87-1.65 (m, 5H), 1.39 (s, 9H).

Step 1.2 Synthesis of tert-butyl 2-(2-oxoethyl)pyrrolidine-1-carboxylate



[01092] To a solution of tert-butyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (4.5 g, 20.90 mmol, 1 *eq*) in DCM (60 mL) was added DMP (10.64 g, 25.08 mmol, 7.77 mL, 1.2 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 12 hrs. The reaction mixture was quenched with aq. $NaHCO_3$ and filtered. Then the filtrate was extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl 2-(2-oxoethyl)pyrrolidine-1-carboxylate (3.6 g, 16.88 mmol, 80.76% yield) was obtained as colorless gum. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.64 (s, 1H), 4.14-4.10 (m, 1H), 3.25-3.23 (m, 2H), 2.68-2.54 (m, 2H), 1.91 (s, 1H), 1.82-1.70 (m, 2H), 1.59-1.53 (m, 1H), 1.37 (s, 9H).

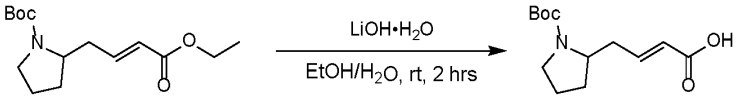
Step 1.3 Synthesis of tert-butyl 2-[(E)-4-ethoxy-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate



3 4

[01093] To a solution of NaH (810.23 mg, 20.26 mmol, 60% purity, 1.2 *eq*) in THF (40 mL) was added ethyl 2-diethoxyphosphorylacetate (4.54 g, 20.26 mmol, 4.02 mL, 1.2 *eq*) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl 2-(2-oxoethyl)pyrrolidine-1-carboxylate (3.6 g, 16.88 mmol, 1 *eq*) in THF (40 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 hr. The reaction mixture was quenched with sat. aq. NH_4Cl (100 mL) at 0°C, and then diluted with EtOAc (100 mL x 3). The combined organic phase was washed with brine (80 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl 2-[(E)-4-ethoxy-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate (2.6 g, 9.18 mmol, 54.36% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.82 (dd, J = 14.8 Hz, 7.2 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.86-3.80 (m, 1H), 3.26-3.22 (m, 2H), 2.35-2.27 (m, 2H), 1.90-1.73 (m, 3H), 1.60-1.59 (m, 1H), 1.38 (s, 9H), 1.20 (t, J = 6.8 Hz, 3H).

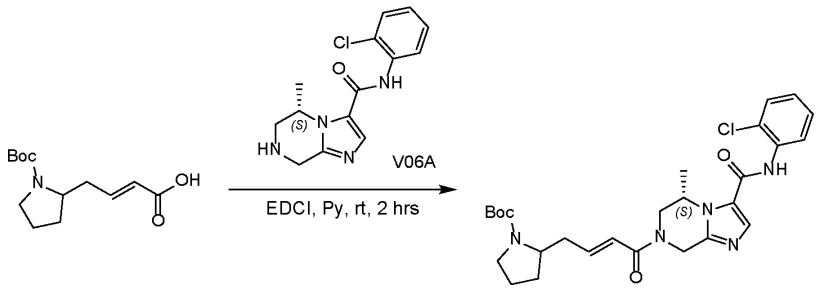
Step 1.4 Synthesis of (E)-4-(1-tert-butoxycarbonylpyrrolidin-2-yl)but-2-enoic acid



4

[01094] To a solution of tert-butyl 2-[(E)-4-ethoxy-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate (2.6 g, 9.18 mmol, 1 *eq*) in EtOH (30 mL) and H_2O (15 mL) was added LiOH•H_2O (962.60 mg, 22.94 mmol, 2.5 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. Then the reaction mixture was extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (80 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound (E)-4-(1-tert-butoxycarbonylpyrrolidin-2-yl)but-2-enoic acid (2.3 g, 9.01 mmol, 98.18% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.17 (s, 1H), 6.77-6.73 (m, 1H), 5.78 (d, J = 15.6 Hz, 1H), 3.82-3.80 (m, 1H), 3.28-3.20 (m, 2H), 2.33-2.26 (m, 1H), 1.91-1.70 (m, 3H), 1.60-1.55 (m, 1H), 1.39 (s, 9H), 1.17 (t, J = 7.2 Hz, 1H).

Step 1.5 Synthesis of tert-butyl 2-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate



5

[01095] To a solution of (E)-4-(1-tert-butoxycarbonylpyrrolidin-2-yl)but-2-enoic acid (105.37 mg, 412.73 μmol, 1.2 *eq*) and (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.1 g, 343.94 μmol, 1 *eq*) in pyridine (5 mL) was added EDCI (131.87 mg, 687.88 μmol, 2 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Genimi NX C_{18} 150 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 30%-60% B over 8.0 min). Compound tert-butyl 2-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate (0.13 g, 239.52 μmol, 69.64% yield, 97.291% purity) was obtained as a white solid. LCMS: m/z 528.3 $[M+H]^+$.

Step 1.6 Synthesis of (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

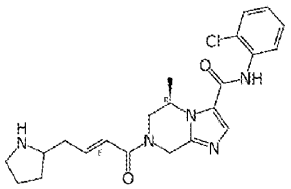


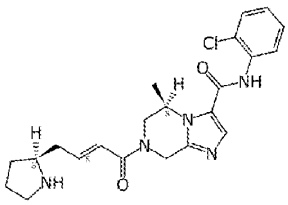
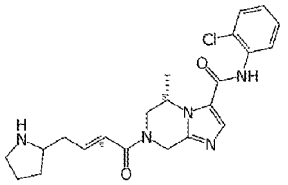
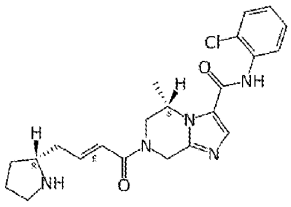
5

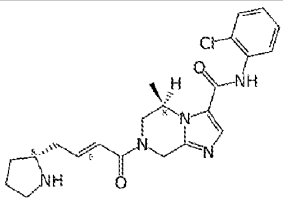
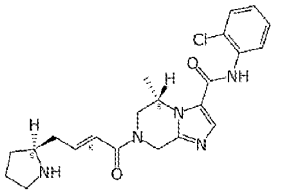
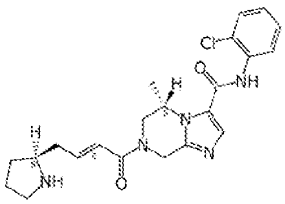
[01096] To a solution of tert-butyl 2-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]pyrrolidine-1-carboxylate (0.12 g, 227.25 µmol, 1 *eq*) in DCM (2 mL) was added HCl/dioxane (4 M, 56.81 µL, 1 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. Compound (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.0062 g, 14.07 µmol, 60.22% yield, 97.137% purity) was obtained as a white solid. LCMS: m/z 428.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.55-10.45 (m, 1H), 9.59-9.55 (m, 1H), 9.14-9.13 (m, 1H), 8.44-8.36 (m, 1H), 7.60-7.58 (m, 1H), 7.54-7.53 (m, 1H), 7.52-7.35 (m, 2H), 6.86-6.78 (m, 2H), 5.52-5.47 (m, 1H), 5.21-5.19 (m, 1H), 4.56-4.48 (m, 3H), 3.83-3.80 (m, 1H), 3.79-3.77 (m, 1H), 3.16-3.13 (m, 3H), 2.73-2.65 (m, 3H), 1.96-1.87 (m, 3H), 1.60-1.33 (m, 4H).

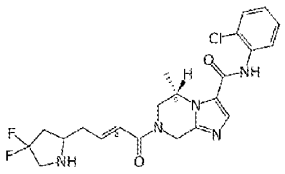
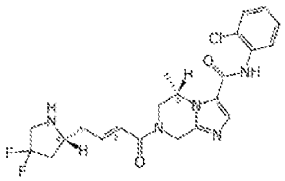
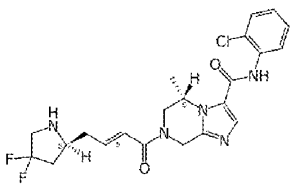
[01097] Compounds in Table O were synthesized following the procedure for *N*-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

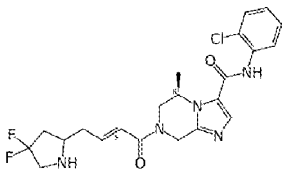
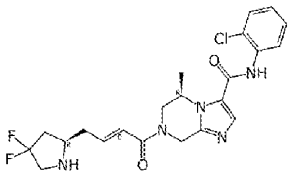
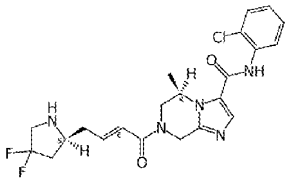
Table O

Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.87 (br.s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.37 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 0.08 Hz, 1H), 6.82-6.59 (m, 2H), 5.27-5.22 (m, 1H), 5.04 (s, 1H), 4.67-4.57 (m, 1H), 4.34-4.23 (m, 1H), 3.70-3.66 (m, 1H), 3.29-3.21 (m, 1H), 3.05-3.02 (m, 1H), 2.83-2.80 (m, 1H), 2.72-2.66 (m, 1H), 2.35-2.30 (m, 2H), 1.77-1.70 (m, 1H), 1.63-	LCMS: m/z 428.2 $[M+H]^+$	

Name	Structure	NMR	LCMS	SFC conditions
		1.58 (m, 2H), 1.28-1.25 (m, 4H).		
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-pyrrolidin-2-yl]but- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6+D2O, 400 MHz) δ 7.85 (s, 1H), 7.58-7.45 (m, 2H), 7.41-7.33 (m, 1H), 7.32-7.25 (m, 1H), 6.85-6.67 (m, 1H), 6.60 (d, *J* = 15.2 Hz, 1H), 5.32-5.12 (m, 1H), 5.03 (s, 1H), 4.72-4.46 (m, 1H), 4.36-4.18 (m, 1H), 3.71-3.58 (m, 1H), 3.27-3.20 (m, 0.5H), 3.19-3.05 (m, 1H), 2.90-2.80 (m, 1H), 2.79-2.69 (m, 1H), 2.63-2.52 (m, 0.5H), 2.36-2.33 (m, 2H), 1.85-1.80 (m, 1H), 1.68-1.64 (m, 2H), 1.27-1.23 (m, 4H)	LCMS: m/z 428.2 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.55-10.45 (m, 1H), 8.44-8.36 (m, 1H), 7.60-7.58 (m, 1H), 7.54-7.53 (m, 1H), 7.52-7.35 (m, 2H), 6.86-6.78 (m, 2H), 5.52-5.47 (m, 1H), 5.21-5.19 (m, 1H), 4.56-4.48 (m, 2H), 3.83-3.80 (m, 1H), 3.79-3.77 (m, 1H), 3.16-3.13 (m, 2H), 2.73-2.65 (m, 3H), 1.96-1.87 (m, 3H), 1.60-1.33 (m, 4H).	LCMS: m/z 428.2 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.85-6.78 (m, 1H), 6.63-6.59 (m, 1H), 5.24 (d, *J* = 18.4 Hz, 1H), 5.04 (br.s, 1H), 4.68-4.56 (m, 1H), 4.36-4.24 (m, 1H), 3.68 (d, *J* = 11.6 Hz, 1H), 3.21 (s, 1H), 3.03 (q, *J* = 6.4 Hz, 1H), 2.85-2.79 (m, 1H), 2.72-2.66 (m, 1H), 2.33-2.28 (m, 2H), 1.77-1.55 (m, 3H), 1.29-1.21 (m, 4H).	LCMS: m/z 428.2 $[M+H]^+$	

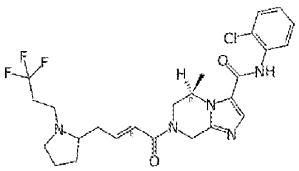
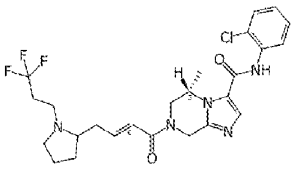
Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2R)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (br.s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.87-6.73 (m, 1H), 6.68-6.56 (m, 1H), 5.27-5.20 (m, 1H), 5.04 (s, 1H), 4.72-4.50 (m, 1H), 4.40-4.19 (m, 1H), 3.73-3.62 (m, 0.5H), 3.03-3.00 (m, 1H), 2.81-2.80 (m, 1H), 2.69-2.67 (m, 1H), 2.48-2.44 (m, 0.5H), 2.29 (t, *J* = 6.4 Hz, 2H), 1.63-1.59 (m, 3H), 1.28-1.23 (m, 4H).	LCMS: m/z 428.1 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (br.s, 1H), 7.88 (s, 1H), 7.54 (td, *J* = 7.6 Hz, 1.2 Hz, 2H), 7.37 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.82-6.59 (m, 2H), 5.27-5.20 (m, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 4.68-4.49 (m, 1H), 4.34-4.23 (m, 1H), 3.69 (d, *J* = 14.0 Hz, 1H), 3.07-3.02 (m, 1H), 2.85-2.80 (m, 1H), 2.73-2.66 (m, 1H), 2.62-2.56 (m, 1H), 2.38-2.26 (m, 2H), 1.93-1.75 (m, 2H), 1.69-1.59 (m, 2H), 1.33-1.24 (m, 3H).	LCMS: m/z 428.1 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[(2S)-pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br.s, 1H), 7.88 (s, 1H), 7.54 (td, *J* = 7.6 Hz, 1.2 Hz, 2H), 7.37 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.82-6.59 (m, 2H), 5.27-5.20 (m, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 4.68-4.49 (m, 1H), 4.34-4.23 (m, 1H), 3.69 (d, *J* = 14.0 Hz, 1H), 3.07-3.02 (m, 1H), 2.85-2.80 (m, 1H), 2.73-2.66 (m, 1H), 2.62-2.56 (m, 1H), 2.38-2.26 (m, 2H), 1.93-	LCMS: m/z 428.1 $[M+H]^+$	

Name	Structure	NMR	LCMS	SFC conditions
		1.75 (m, 2H), 1.69-1.59 (m, 2H), 1.33-1.24 (m, 3H).		
(5S)-N-(2-chlorophenyl)-7-((E)-4-(4,4-difluoropyrrolidin-2-yl)but-2-enoyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.80-6.63 (m, 2H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.05 (s, 1H), 4.70-4.51 (m, 1H), 4.34-4.24 (m, 1H), 3.70-3.67 (m, 1H), 3.23-3.14 (m, 2H), 3.06-2.95 (m, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 2.33-2.26 (m, 1H), 1.89-1.78 (m, 1H), 1.30-1.23 (m, 3H).	LCMS: m/z 464.1 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-4,4-difluoropyrrolidin-2-yl] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.89 (s, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.80-6.63 (m, 2H), 5.25 (d, *J* = 18.0 Hz, 1H), 5.05 (s, 1H), 4.69-4.54 (m, 1H), 4.34-4.24 (m, 1H), 3.69 (d, *J* = 12.4 Hz, 0.5H), 3.30-3.28 (m, 1H), 3.25-3.23 (m, 0.5H), 3.20-3.17 (m, 1H), 3.06-2.95 (m, 1H), 2.85-2.83 (m, 1H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.34-2.26 (m, 1H), 1.89-1.75 (m, 1H), 1.30-1.24 (m, 3H).	LCMS: m/z 464.1 $[M+H]^+$	SFC (column: Waters Xbridge BEH C_{18} 100 * 30 mm * 10um; mobile phase: [H_2O(10 mM NH_4HCO_3)-ACN];gradient:15%-55% B over 8.0 min
(5S)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 6.8 Hz, 1H), 6.80-6.63 (m, 2H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.05 (s, 1H), 4.68-4.51 (m, 1H), 4.34-4.20 (m, 1H), 3.71-3.67 (m, 0.5H), 3.30-3.28 (m, 1H), 3.25-3.22 (m, 0.5H), 3.20-3.14 (m, 1H), 3.06-2.96 (m, 1H), 2.85-2.84 (m, 1H), 2.39	LCMS: m/z 464.1 $[M+H]^+$	SFC (column: Waters Xbridge BEH C_{18} 100 * 30 mm * 10um; mobile phase: [H_2O(10 mM NH_4HCO_3)-ACN];gradient:15%-55% B over 8.0 min

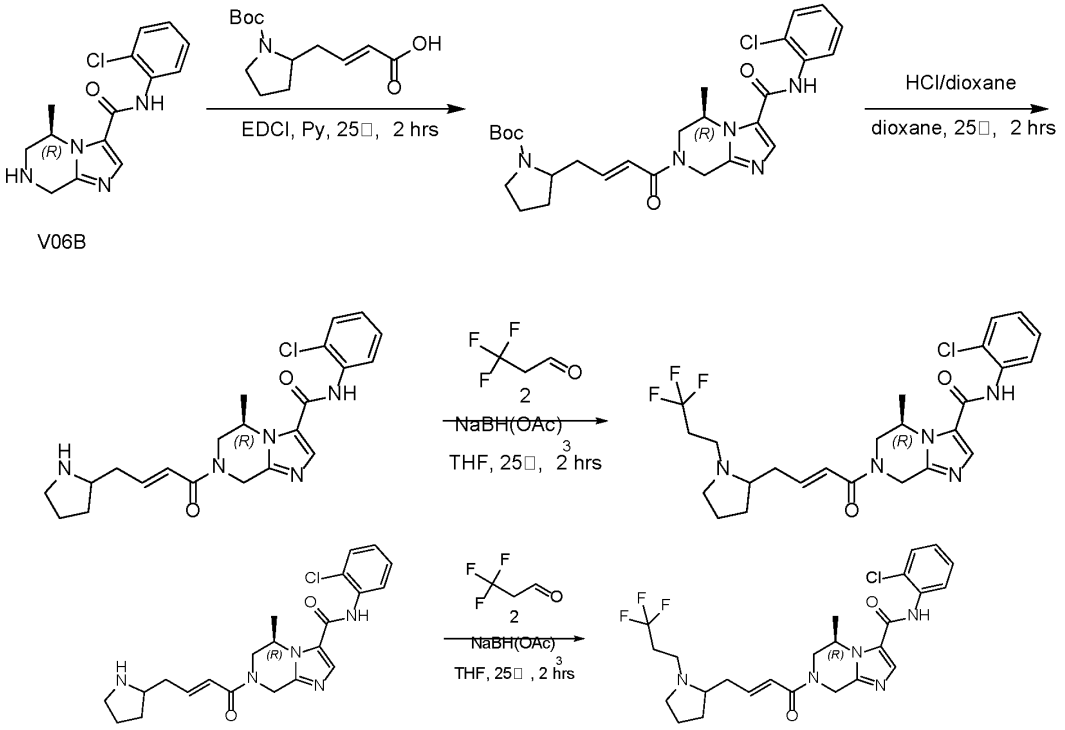
Name	Structure	NMR	LCMS	SFC conditions
		(t, *J* = 6.8 Hz, 2H), 2.33-2.27 (m, 1H), 1.90-1.75 (m, 1H), 1.32-1.23 (m, 3H).		
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(4,4-difluoropyrrolidin-2-yl)but-2- enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 6.80-6.63 (m, 2H), 5.27-5.04 (m, 2H), 4.69-4.20 (m, 2H), 3.70-3.64 (m, 1H), 3.25-3.14 (m, 2H), 3.06-2.95 (m, 1H), 2.89-2.84 (m, 1H), 2.39 (t, *J* = 6.4 Hz, 2H), 2.33-2.28 (m, 1H), 1.92-1.75 (m, 1H), 1.33-1.23 (m, 3H).	LCMS: m/z 464.1 $[M+H]^+$	
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2R)-4,4-difluoropyrrolidin-2-yl] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.80-6.63 (m, 2H), 5.27-5.05 (m, 2H), 4.68-4.51 (m, 1H), 4.36-4.20 (m, 1H), 3.73-3.64 (m, 0.4H), 3.37-3.35 (m, 0.6H), 3.28-3.14 (m, 2H), 3.06-2.86 (m, 2H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.34-2.26 (m, 1H), 1.89-1.75 (m, 1H), 1.33-1.24 (m, 3H).	LCMS: m/z 464.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK ID (250 mm * 30 mm, 10 um); mobile phase: [CO_2-IPA (0.1% NH_3H_2O)]; B%: 56%, isocratic elution mode)
(5R)-N-(2-chlorophenyl)-7-[(E)-4-[(2S)-4,4-difluoropyrrolidin-2-yl]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.80-6.63 (m, 2H), 5.27-5.25 (m, 1H), 5.09-5.05 (m, 1H), 4.68-4.55 (m, 1H), 4.35-4.24 (m, 1H), 3.69 (d, *J* = 12.8 Hz, 0.5H), 3.41-3.38 (m, 0.5H), 3.26-3.14 (m, 2H), 3.06-2.91 (m, 2H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.33-2.27 (m, 1H), 1.91-1.75 (m, 1H), 1.30-1.25 (m, 3H).	LLCMS: m/z 464.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK ID (250 mm * 30 mm, 10 um); mobile phase: [CO_2-IPA (0.1% NH_3H_2O)]; B%: 56%, isocratic elution mode)

[01098] Compounds in Table P were synthesized following the procedure for *N*-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table P

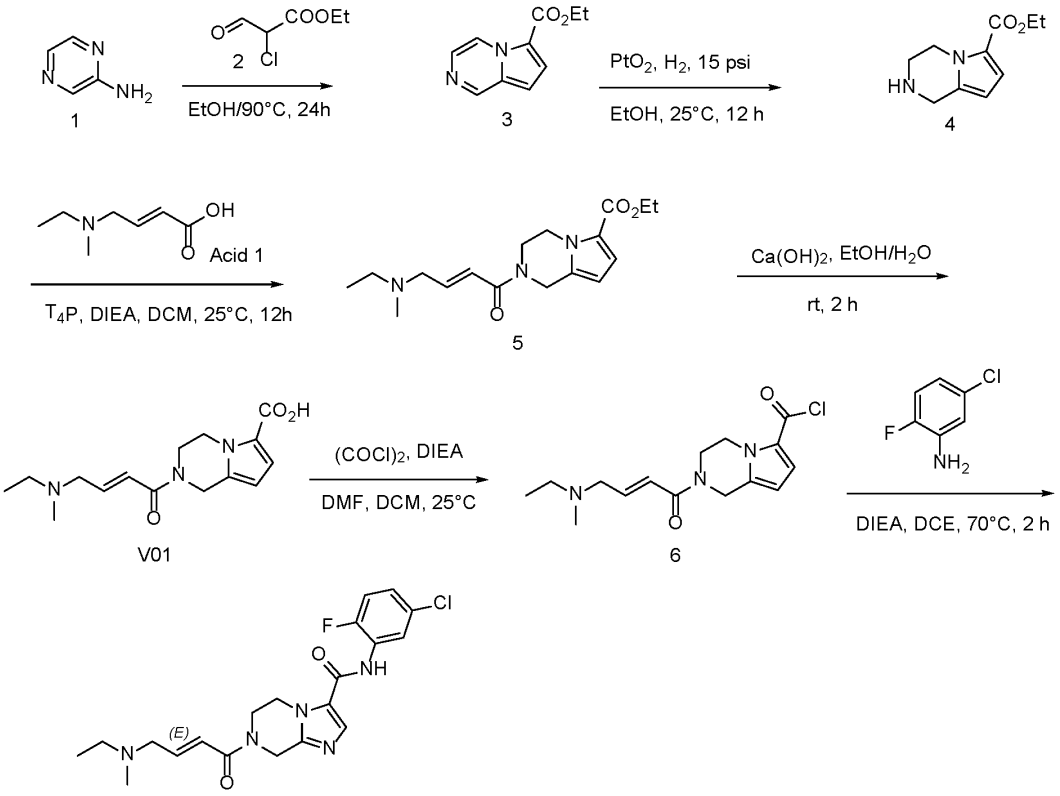
Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (br.s, 1H), 7.88 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 6.76-6.64 (m, 2H), 5.27-5.23 (m, 1H), 5.04 (s, 1H), 4.67-4.56 (m, 1H), 4.34-4.23 (m, 1H), 3.70-3.66 (m, 1H), 3.24 (s, 1H), 3.05-2.98 (m, 2H), 2.40-2.38 (m, 2H), 2.35-2.34 (m, 2H), 2.23-2.20 (m, 1H), 2.13-2.07 (m, 1H), 1.81 (s, 1H), 1.63 (d, *J* = 2.4 Hz, 2H), 1.45-1.44 (m, 1H), 1.28-1.25 (m, 3H).	LCMS: m/z 524.2 [M+H]+
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl) pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.80-6.64 (m, 2H), 5.28-5.21 (m, 1H), 5.04 (s, 1H), 4.68-4.57 (m, 1H), 4.35-4.24 (m, 1H), 3.70-3.66 (m, 0.5H), 3.28-3.21 (m, 0.5H), 3.08-2.97 (m, 2H), 2.43-2.31 (m, 4H), 2.26-2.19 (m, 1H), 2.14-2.08 (m, 1H), 1.84-1.77 (m, 1H), 1.65-1.61 (m, 2H), 1.47-1.40 (m, 1H), 1.29-1.23 (m, 3H).	LCMS: m/z 524.2 [M+H]+

Example 172: Synthesis of (5R)-*N*-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

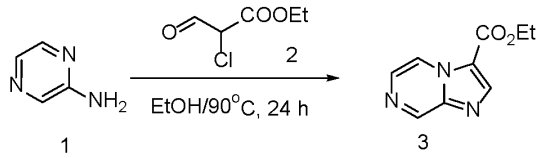


[01099] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-pyrrolidin-2-ylbut-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (60 mg, 140.21 μmol, 1 eq) in tetrahydrofuran (1.5 mL) was added 3,3,3-trifluoropropanal (18.85 mg, 168.25 μmol, 1.2 eq) at 25°C, and the mixture was stirred at 25°C for 20 mins, then $NaBH(OAc)_3$ (89.15 mg, 420.63 μmol, 3 eq) was added to the mixture. The mixture was stirred at 25°C for 2 hrs. The reaction mixture was poured into water (0.5 mL) and stirred for 2 mins, concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 100 × 30 mm × 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20% - 65% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[1-(3,3,3-trifluoropropyl)pyrrolidin-2-yl]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (42.2 mg, 80.21 μmol, 57.20% yield) was obtained as a white solid. LCMS: m/z 524.2 $[M+H]^+$.

Example 173: Synthesis of N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



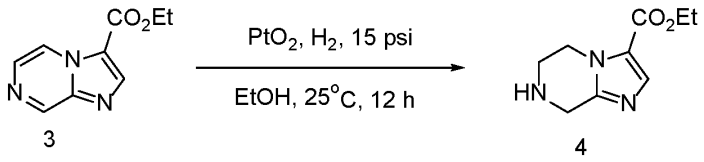
Step 1.1 Synthesis of ethyl imidazo[1,2-a]pyrazine-3-carboxylate-



[01100] To a solution of pyrazin-2-amine (20 g, 210.30 mmol, 1 eq) in EtOH (20 mL) was added ethyl 2-chloro-3-oxo-propanoate (38.00 g, 252.36 mmol, 1.2 eq) at 25°C. The mixture was heated to 90°C and was stirred at 90°C for 24 hr. The reaction mixture was cooled to 25°C and the reaction mixture was concentrated under reduced pressure to give a residue, the residue was diluted with H_2O (50 mL) and adjusted pH = 7 by aq. $NaHCO_3$, then the reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 150 mL/min). Compound ethyl imidazo[1,2-a]pyrazine-3-carboxylate (19 g, 99.38 mmol, 47.26% yield) was obtained as a yellow solid. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.30 (d, J =

1.6 Hz, 1H), 9.11 (d, *J* = 4.4 Hz, 1H), 8.43 (s, 1H), 8.23 (d, *J* = 4.4 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 1H), 1.36 (t, *J* = 6.8 Hz, 1H).

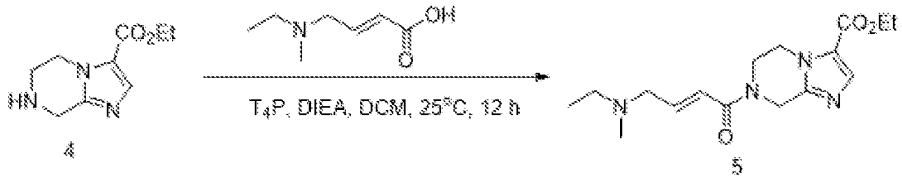
Step 1.2 Synthesis of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxylate -



3 4

[01101] The PtO_2 (7.50 g, 33.03 mmol, 0.42 eq) was added into flask stand-up bottom under Ar atmosphere at 25°C, then EtOH (300 mL) was added into flask stand-up bottom, then reaction mixture was added ethyl imidazo[1,2-a]pyrazine-3-carboxylate (15 g, 78.46 mmol, 1 eq) and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 25°C for 12 hr under H_2 atmosphere. The reaction solution was filtered and the filtration was concentrated to give yellow oil. Without purification. Compound ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (15 g, 76.84 mmol, 97.93% yield) was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.56 (s, 1H), 4.23 (q, *J* = 6.8 Hz, 2H), 4.09 (t, *J* = 5.6 Hz, 1H), 3.88 (s, 2H), 3.05 (q, *J* = 5.6 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

Step 1.3 Synthesis of ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylate

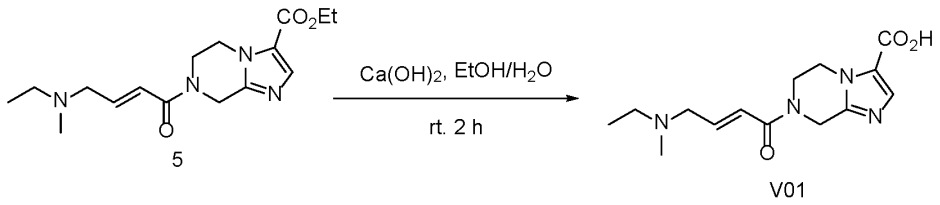


4 5

[01102] To a solution of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (818.22 mg, 4.19 mmol, 1 eq) in DCM (10 mL) were added (E)-4-[ethyl(methyl)amino]but-2-enoic acid (1.28 g, 7.13 mmol, 1.7 eq, HCl), T_4P (6.64 g, 9.22 mmol, 50% purity, 2.2 eq) and DIEA (2.17 g, 16.77 mmol, 2.92 mL, 4 eq) at 25°C. The reaction mixture was stirred at 25°C for 1hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% DCM/MeOH gradient @ 100 mL/min). Compound ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate (3 g, crude) was obtained as a black oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.70 (s, 1H), 7.05-6.92

(m, 2H), 4.63 (s, 1H), 4.33-4.28 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 3.76-3.71 (m, 2H), 3.65-3.59 (m, 2H), 3.09-3.03 (m, 2H), 2.58-2.51 (m, 2H), 1.36-1.32 (m, 3H), 1.25-1.20 (m, 3H).

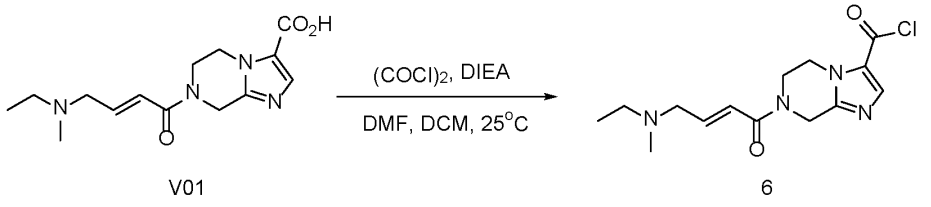
Step 1.4 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid (V01)



5 V01

[01103] To a solution of ethyl 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylate (5 g, 15.61 mmol, 1 eq) in H_2O (20 mL) and EtOH(40 ml) was added $Ca(OH)_2$ (4.63 g, 62.42 mmol, 2.06 mL, 4 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hr. The reaction mixture was concentrated to remove the EtOH, then the reaction mixture was filtered and filtration was adjusted pH = 5 by 2N HCl, then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250*70mm,15 um); mobile phase: [H_2O (0.04% HCl)-ACN]; B%:0%, isocratic elution mode). Compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (V01) (1.5 g, 5.13 mmol, 32.88% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.20-11.12 (m, 1H), 8.87-7.96 (m, 1H), 7.14-6.99 (m, 1H), 6.80-6.73 (m, 1H), 5.05-4.93 (m, 2H), 4.41-4.31 (m, 1H), 4.11-4.05 (m, 2H), 4.40-3.93 (m, 2H), 3.87-3.78 (m, 2H), 3.19-3.00 (m, 2H), 2.68 (d, *J* = 4.4 Hz, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

Step 1.5 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride

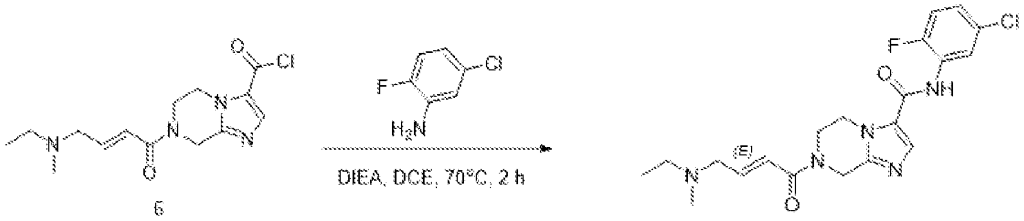


V01 6

[01104] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (400 mg, 1.22 mmol, 1 eq, HCl) in DCM (4 mL) were added DIEA (314.47 mg, 2.43 mmol, 423.81 µL, 2 eq), $(COCl)_2$ (435.00 mg, 3.43 mmol, 0.3 mL, 2.82 eq) and DMF (8.89 mg, 121.66 µmol, 9.36 µL, 0.1 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hr. The reaction mixture was concentrated under reduced pressure to give

a residue. Without purification. Compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro- 5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (400 mg, crude) was obtained as a black oil.

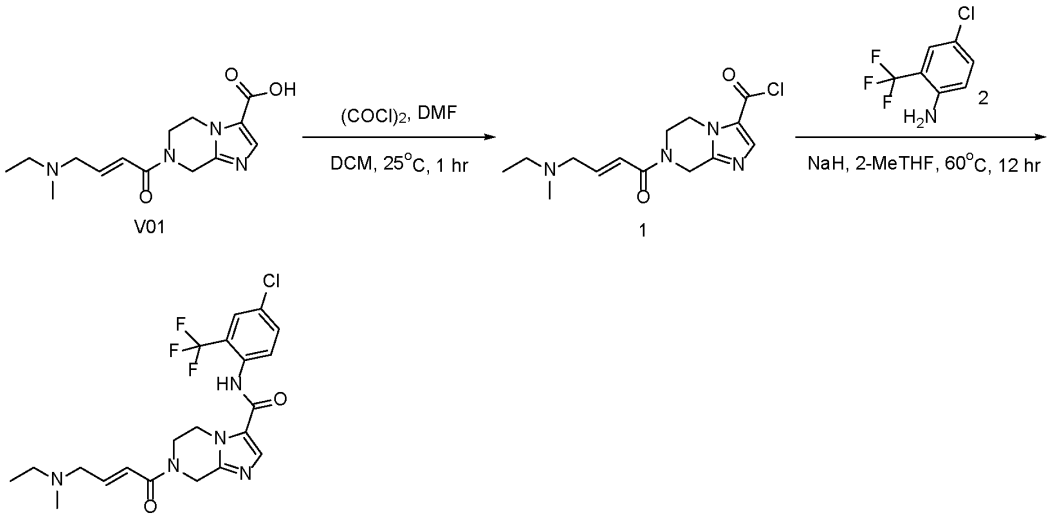
Steo 1.6 Synthesis of N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



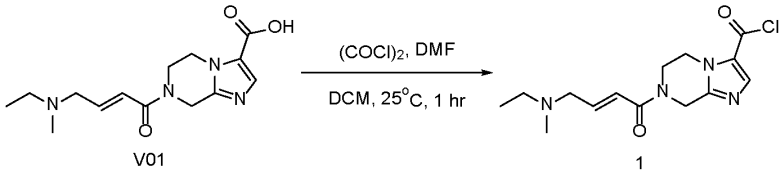
6

[01105] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride (200 mg, 643.55 μmol, 1 eq) in DCE (2 mL) were added DIEA (83.17 mg, 643.55 μmol, 112.09 μL, 1 eq) and 5-chloro-2-fluoro-aniline (140.51 mg, 965.32 μmol, 1.5 eq) at 25°C. The mixture was heated to 70°C and was stirred at 70 °C for 12hr. LC-MS showed 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride consumed and ~60% of desired compound was detected. The reaction mixture was cooled to 25°C and was quenched by addition H_2O (0.5 mL) at 25°C, and then the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 100*30mm*10um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 10%-40% B over 8.0 min). Compound N-(5-chloro-2-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (55.4 mg, 131.94 μmol, 20.50% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.87 (s, 1H), 7.73-7.72 (m, 1H), 7.36-7.30 (m, 2H), 6.72-6.70 (m, 2H), 4.91-4.75 (m, 2H), 4.32 (s, 2H), 4.01-3.96 (m, 2H), 3.13 (d, J = 4.4 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).

Example 174: Synthesis of N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

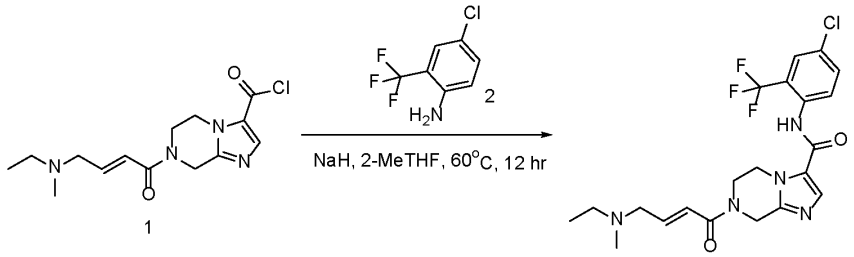


Step 1.1 Synthesis of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carbonyl chloride -



[01106] To a solution of 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid (0.45 g, 1.54 mmol, 1 eq) in DCM (6 mL) was added $(COCl)_2$ (586.17 mg, 4.62 mmol, 404.25 µL, 3 eq) and a drop of DMF at 25°C. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give compound 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (0.45 g, crude) as a black oil. LCMS: m/z 307.1 $[M+H]^+$.

Step 1.2 Synthesis of N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

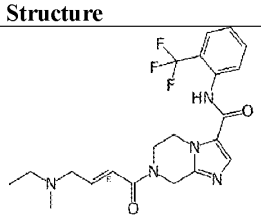
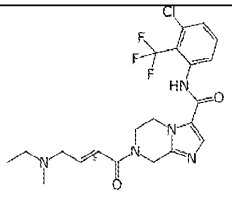


[01107] To a solution of 4-chloro-2-(trifluoromethyl)aniline (141.59 mg, 723.99 µmol, 102.16 µL, 1.5 eq) in 2-MeTHF (2 mL) was added NaH (38.61 mg, 965.32 µmol, 60% purity, 2 eq) at

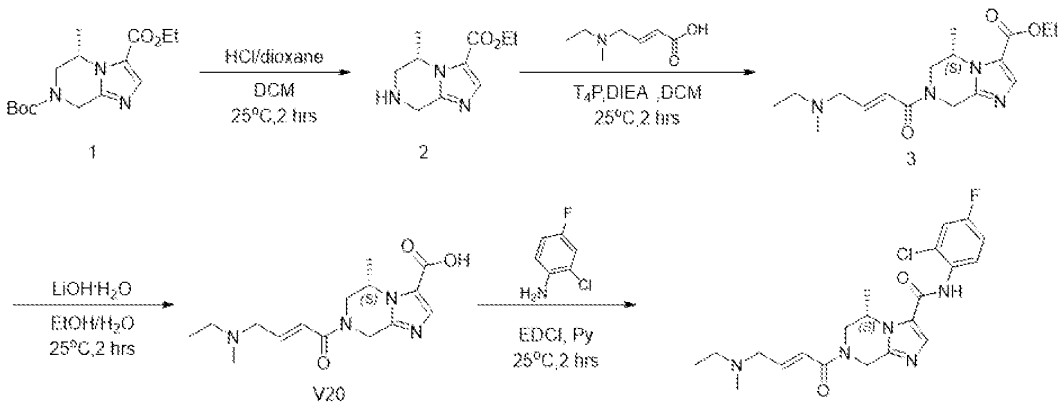
0°C then the reaction mixture was heated to 60°C and was stirred at 60°C for 12 hr under N_2 atmosphere, then the reaction mixture was cooled to 25°C and the reaction mixture was added 7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carbonyl chloride (150 mg, 482.66 μmol, 1 eq) at 25°C and then the reaction mixture was stirred at 60°C for 12 hr under N_2 atmosphere. The reaction mixture was cooled to 0°C and was quenched by addition aq. NH_4Cl (1 mL) at 0°C, and extracted with EtOAc (3 mL x 2). The combined organic layers were washed with brine (5 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 25% - 55% B over 8.0 min). Compound N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (21 mg, 44.69 μmol, 9.26% yield) was obtained as a yellow solid. LCMS: m/z 470.2 $[M+H]^+$. ^1H NMR (DMSO-*d*6, 400 MHz) δ 9.97 (s, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.83-7.81 (m, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 6.72-6.69 (m, 2H), 4.91-4.75 (m, 2H), 4.29-4.25 (m, 2H), 4.00-3.94 (m, 2H), 3.11 (d, *J* = 4.4 Hz, 2H), 2.35 (q, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

[01108] Compounds in Table Q were synthesized following the procedure for N-[4-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

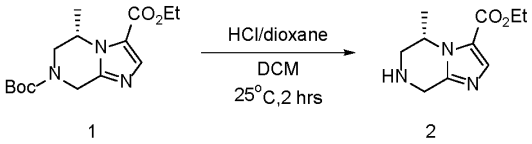
Table Q

Name	Structure	NMR	LCMS
7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-N-[2-(trifluoromethyl)phenyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.91(s, 1H), 7.81-7.78 (m, 2H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.53-7.49 (m, 2H), 6.71-6.69 (m, 2H), 4.91-4.75 (m, 2H), 4.29-4.28 (m, 2H), 4.01-3.95 (m, 2H), 3.11 (d, *J* = 4.4 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 436.2 $[M+H]^+$
N-[3-chloro-2-(trifluoromethyl)phenyl]-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 10.22 (s, 1H), 7.81 (s, 1H), 7.71-7.64 (m, 2H), 7.43-7.41 (m, 1H), 6.75-6.67 (m, 2H), 4.91-4.75 (m, 2H), 4.29-4.27 (m, 2H), 4.01-3.95 (m, 2H), 3.12 (d, *J* = 4.8 Hz, 2H), 2.35 (q, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 470.2 $[M+H]^+$

Example 175: Synthesis of (5S)-*N*-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

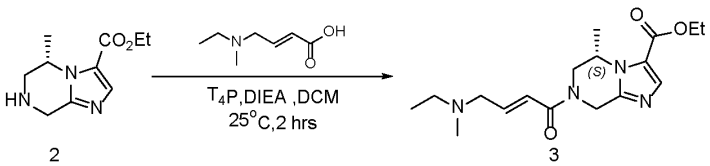


Step 1.1 Synthesis of ethyl (5S)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate.



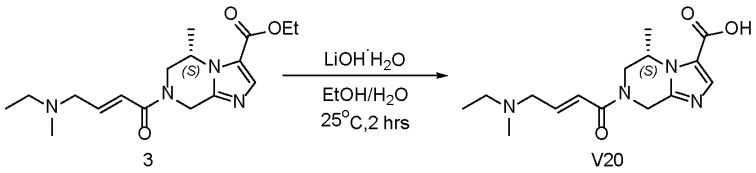
[01109] To a solution of O7-tert-butyl O3-ethyl (5S)-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3,7-dicarboxylate (12 g, 38.79 mmol, 1 eq) in DCM (60 mL) was added HCl/dioxane (4 M, 50.00 mL) at 25°C. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound ethyl (5S)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxylate (12 g, crude, HCl) was obtained as a pink solid. LCMS: m/z 210.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 8.15 (s, 1H), 5.14-5.10 (m, 1H), 4.53 (q, J = 16.4 Hz, 2H), 4.37-4.27 (m, 2H), 3.64-3.59 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H).

Step 1.2 Synthesis of ethyl (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate.



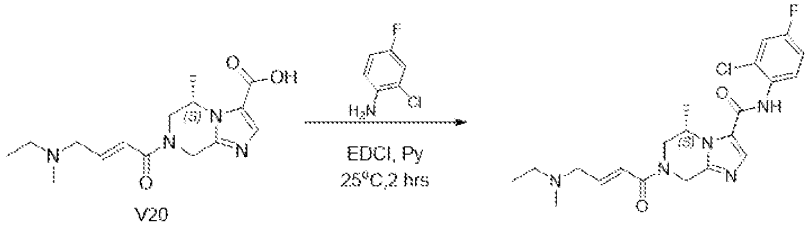
[01110] To a solution of ethyl (5S)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (3 g, 12.21 mmol, 1 eq, HCl) and (E)-4-[ethyl(methyl)amino]but-2-enoic acid (2.97 g, 20.76 mmol, 1.7 eq) in DCM (30 mL) were added T_4P (8.80 g, 24.42 mmol, 2 *eq*) and DIEA (6.31 g, 48.84 mmol, 8.51 mL, 4 eq) at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound ethyl (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylate (1.96 g, 5.86 mmol, 48.00% yield) was obtained as yellow oil. LCMS: m/z 335.4 $[M+H]^+$.

Step 1.3 Synthesis of (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (V20).



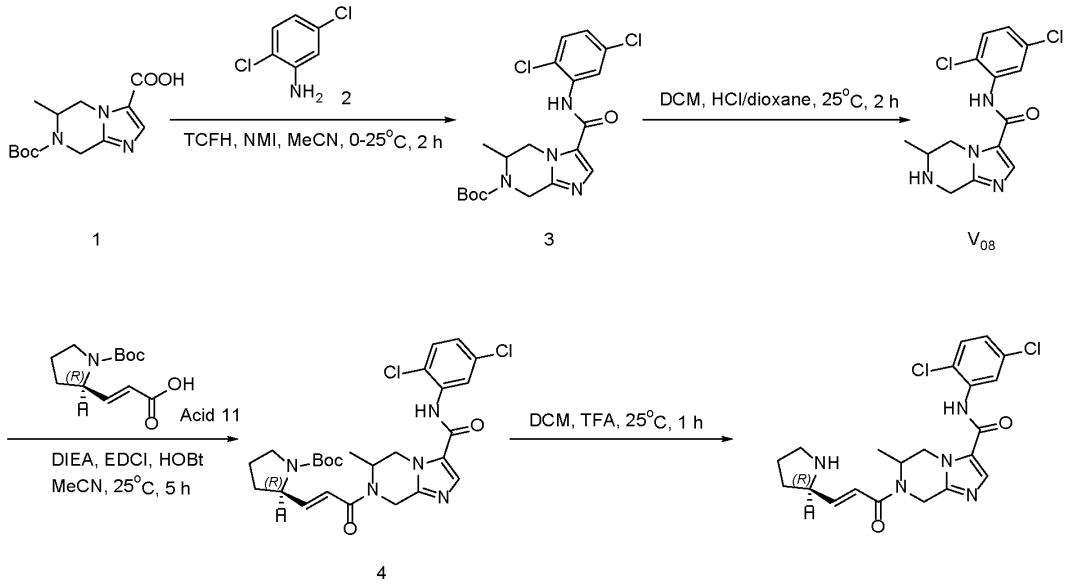
[01111] To a solution of ethyl (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate (1.86 g, 5.56 mmol, 1 eq) in EtOH (15 mL) and H_2O (5 mL) was added $LiOH{\cdot}H_2O$ (700.14 mg, 16.69 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was added HCl (3 M) to adjust pH = 3 at 0°C. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1%- 15% B over 8.0 min). The residue was dried over lyophilization. Compound (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (V20) (150 mg, 489.62 μmol, 8.80% yield) was obtained as a white solid. LCMS: m/z 307.1 $[M+H]^+$.

Step 1.4 Synthesis of (5S)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4- [ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

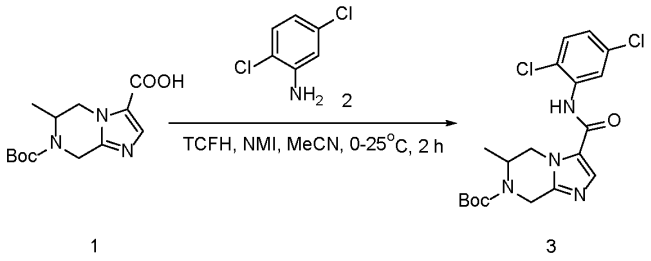


[01112] To a solution of 2-chloro-4-fluoro-aniline (23.76 mg, 163.21 μmol, 1 eq) and (5S)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (50 mg, 163.21 μmol, 1 eq) in Pyridine (0.1 mL) was added EDCI (62.57 mg, 326.41 μmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Phenomenex Luna C_{18} 100 * 30 mm * 5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%- 20% B over 8.0 min). The residue was dried over lyophilization. Compound (5S)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (20.6 mg, 45.54 μmol, 27.91% yield, 95.93% purity) was obtained as a white solid. LCMS: m/z 434.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 10.72-10.55 (m, 1H), 10.34-10.20 (m, 1H), 8.23-8.05 (m, 1H), 7.59-7.51 (m, 2H), 7.31-7.27 (m, 1H), 7.11-7.02 (m, 1H), 6.82-6.79 (m, 1H), 5.44-5.34 (m, 1H), 5.15 (s, 1H), 4.84-4.56 (m, 1H), 4.41 (dd, J = 50.0 Hz, 17.6 Hz, 1H), 4.00-3.94 (m, 1H), 3.89-3.84 (m, 1H), 3.87-3.85 (m, 1H), 3.19-3.14 (m, 2H), 3.07-3.06 (m, 1H), 2.77-2.71 (m, 3H), 1.38-1.24 (m, 6H).

Example 176: Synthesis of *N*-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



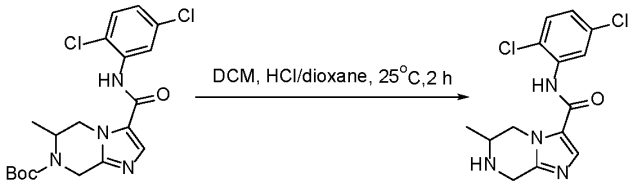
Step 1.1 Synthesis of tert-butyl 3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



[01113] To a solution of 7-tert-butoxycarbonyl-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (1 g, 3.55 mmol, 1 eq) in MeCN (10 mL) were added NMI (875.56 mg, 10.66 mmol, 850.05 μL, 3 eq), 2,5-dichloroaniline (1.15 g, 7.11 mmol, 2 eq) and TCFH (1.99 g, 7.11 mmol, 2 eq) in one portion at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 h. The mixture was poured into ice-water (20 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~56% Ethyl acetate/Petroleum ether gradient @ 45 mL/min) to give tert-butyl 3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-7-carboxylate (400 mg, 940.49 μmol, 26.46% yield) as yellow oil. LCMS: m/z 425.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.91 (s, 1H), 7.91

(s, 1H), 7.71-7.70 (m, 1H), 7.60-7.58 (m, 1H), 7.37-7.34 (m, 1H), 4.80-4.76 (m, 1H), 4.65-4.54 (m, 1H), 4.17-4.09 (m, 2H), 1.45 (s, 9H), 1.05 (d, J = 7.2 Hz, 3H).

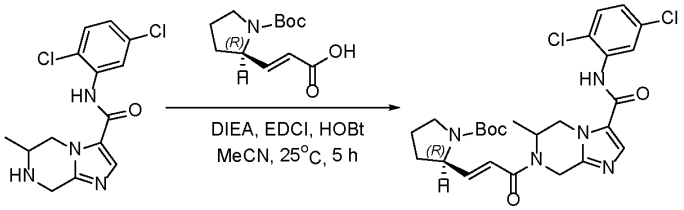
Step 1.2 Synthesis of N-(2,5-dichlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V08)



3 V08

[01114] To a solution of tert-butyl 3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-7-carboxylate (0.4 g, 940.49 μmol, 1 eq) in DCM (4 mL) was added HCl/dioxane (4 M, 4 mL, 17.01 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated in vacuum to give N-(2,5-dichlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V08) (500 mg, crude) as yellow oil. LCMS: m/z 325.0 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.22 (s, 1H), 8.03 (s, 1H), 7.68-7.67 (m, 1H), 7.62-7.60 (m, 1H), 7.40-7.38 (m, 1H), 4.78-4.74 (m, 1H), 4.59-4.45 (m, 2H), 4.13-4.07 (m, 1H), 3.88-3.78 (m, 1H), 1.43 (d, J = 7.8 Hz, 3H).

Step 1.3 Synthesis of tert-butyl (2R)-2-[(E)-3-[3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate

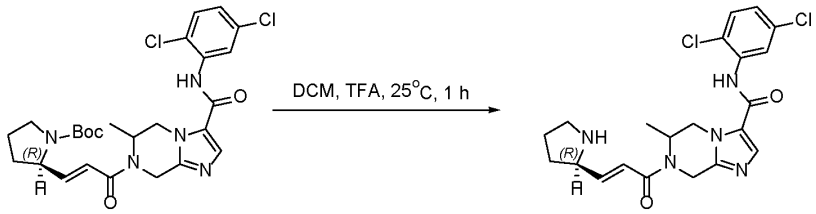


V08 4

[01115] To a solution of N-(2,5-dichlorophenyl)-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide (500 mg, 1.54 mmol, 1 eq) in MeCN (4 mL) were added DIEA (993.57 mg, 7.69 mmol, 1.34 mL, 5 eq), EDCI (736.87 mg, 3.84 mmol, 2.5 eq), HOBt (457.06 mg, 3.38 mmol, 2.2 eq) and (E)-3-[(2R)-1-tert-butoxycarbonylpyrrolidin-2-yl]prop-2-enoic acid (445.18 mg, 1.85 mmol, 1.2 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 5 h. The reaction mixture was poured into water (1 mL) and stirred for 2 min at 25°C. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give tert-butyl (2R)-

2-[(E)-3-[3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (0.4 g, crude) as a yellow solid. LCMS: m/z 548.2 $[M-H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.93 (s, 1H), 7.71-7.70 (m, 1H), 7.60-7.58 (m, 1H), 7.37-7.35 (m, 1H), 6.66-6.46 (m, 1H), 6.73 - 6.40 (m, 1H), 5.12-4.71 (m, 2H), 4.63-4.59 (m, 1H), 4.43-4.27 (m, 2H), 4.21-4.09 (m, 1H), 2.06-2.04 (m, 2H), 1.80-1.71 (m, 4H), 1.37-1.34 (m, 9H), 1.17 (t, J = 7.2 Hz, 3H).

Step 1.4 Synthesis of N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

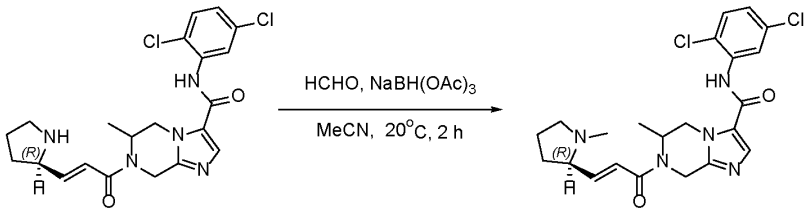


4

[01116] To a solution of tert-butyl (2R)-2-[(E)-3-[3-[(2,5-dichlorophenyl)carbamoyl]-6-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (400 mg, 729.31 μmol, 1 eq) in DCM (4 mL) was added TFA (6.14 g, 53.85 mmol, 4 mL, 73.83 eq)in one portion at 25°C. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C_{18} 150*40 mm*10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:20%-50% B over 8.0 min) to give N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (23. mg, 50.03 μmol, 6.86% yield, 97.52% purity) was obtained as a white solid. LCMS: m/z 448.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.93 (s, 1H), 7.92 (s, 1H), 7.71 (d, J = 2.8 Hz, 1H), 7.60-7.58 (m, 1H), 7.37-7.34 (m, 1H), 6.76-6.60 (m, 2H), 5.11-4.84 (m, 2H), 4.63-4.39 (m, 2H), 4.15-4.12 (m, 1H), 3.66 (q, J = 6.8 Hz, 1H), 2.91-2.76 (m, 2H), 1.92-1.86 (m, 1H), 1.74-1.63 (m, 2H), 1.44-1.37 (m, 1H), 1.08 (s, 3H).

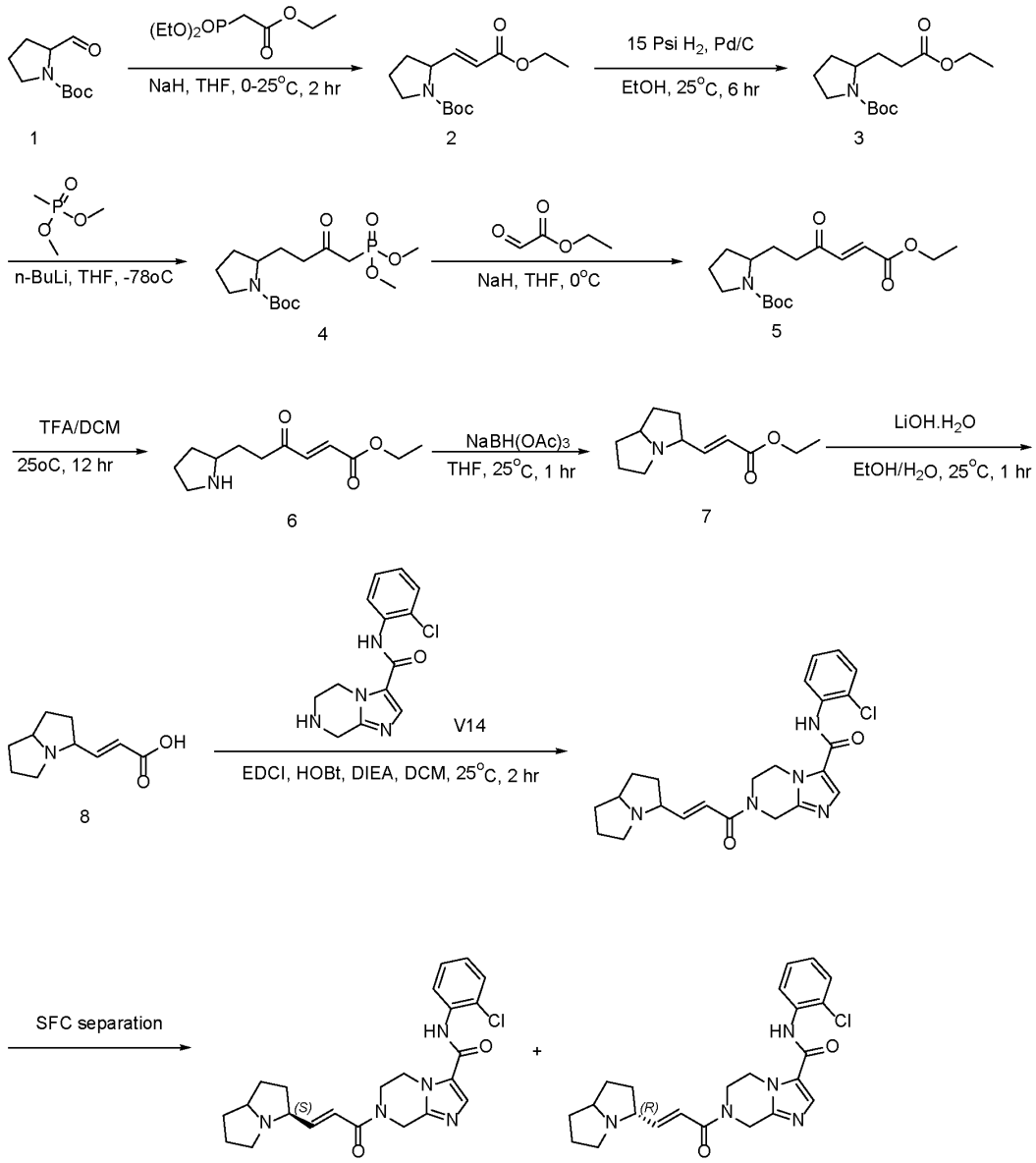
Example 177: Synthesis of N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl] prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

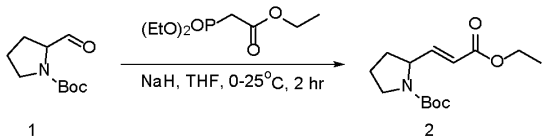


[01117] To a solution of N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-pyrrolidin-2-yl]prop-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (250 mg, 557.61 μmol, 1 eq) in MeOH (6 mL) was added formaldehyde (708.33 mg, 8.73 mmol, 649.85 μL, 37% purity, 15.65 eq) in one portion at 25°C and stirred at 25°C for 20 min. Then $NaBH(OAc)_3$ (354.54 mg, 1.67 mmol, 3 eq) was added into the reaction mixture in portions at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:15%-45% B over 8.0 min), which was further separated by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-65% B over 8.0 min) to give N-(2,5-dichlorophenyl)-6-methyl-7-[(E)-3-[(2R)-1-methylpyrrolidin-2-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (5.1 mg, 10.28 μmol, 1.84% yield, 95.03% purity) as a white solid. LCMS: m/z 462.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.93 (s, 1H), 7.93 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.37-7.35 (m, 1H), 6.69-6.52 (m, 2H), 5.12-4.86 (m, 2H), 4.63-4.34 (m, 2H), 4.16-4.11 (m, 1H), 3.03-2.99 (m, 1H), 2.76 (q, J = 8.0 Hz, 1H), 2.18-2.12 (m, 4H), 2.00-1.92 (m, 1H), 1.77-1.68 (m, 2H), 1.58-1.53 (m, 1H), 1.08 (s, 3H).

Example 178: Synthesis of N-(2-chlorophenyl)-7-((E)-3-((3S)-hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7-((E)-3-((3R)-hexahydro-1H-pyrrolizin-3-yl)acryloyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



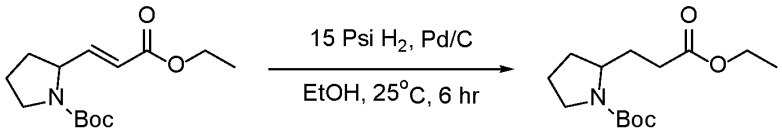
Step 1.1 Synthesis of tert-butyl 2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate



[01118] To a solution of NaH (521.92 mg, 13.05 mmol, 60% purity, 1.3 eq) in THF (20 mL) was added ethyl 2-diethoxyphosphorylacetate (2.70 g, 12.05 mmol, 2.39 mL, 1.2 eq) at 0°C. The reaction mixture was stirred at 0°C for 20 min, then the reaction mixture was added the solution of tert-butyl 2-formylpyrrolidine-1-carboxylate (2 g, 10.04 mmol, 1 eq) in THF (20 mL) at 0°C, then the reaction mixture was warmed to 25°C and was stirred at 25°C for 2 hr.

The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) at 0°C, and then diluted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/ Petroleum ether gradient @ 80 mL/min). Compound tert-butyl 2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (1.8 g, 6.68 mmol, 66.58% yield) was obtained as a colorless oil. LCMS: m/z 170.1 $[M-100+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.84-6.81 (m, 1H), 5.85-5.81 (m, 1H), 4.50-4.37 (m, 1H), 4.22-4.16 (m, 2H), 3.43-3.39 (m, 2H), 2.08-2.05 (m, 1H), 1.89-1.84 (m, 3H), 1.44 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H).

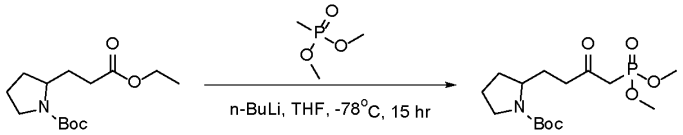
Step 1.2 Synthesis of tert-butyl 2-(3-ethoxy-3-oxo-propyl)pyrrolidine-1-carboxylate



2 3

[01119] To a solution of tert-butyl 2-[(E)-3-ethoxy-3-oxo-prop-1-enyl]pyrrolidine-1-carboxylate (0.2 g, 742.57 μmol, 1 eq) in THF (2 mL), MeOH (2 mL) was added Pd/C (79.02 mg, 74.26 μmol, 10% purity, 0.1 eq) at 25°C, the reaction mixture was degassed and purged with H_2 for 3 times. The reaction mixture was stirred at 25°C for 6 hr under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give tert-butyl 2-(3-ethoxy-3-oxo-propyl)pyrrolidine-1-carboxylate (0.2 g, 737.05 μmol, 99.26% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.12 (q, *J* = 7.2 Hz, 2H), 3.82-3.81 (m, 1H), 3.33-3.28 (m, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.84-1.82 (m, 4H), 1.63-1.62 (m, 2H), 1.47 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H).

Step 1.3 Synthesis of tert-butyl 2-(4-dimethoxyphosphoryl-3-oxo-butyl)pyrrolidine-1-carboxylate

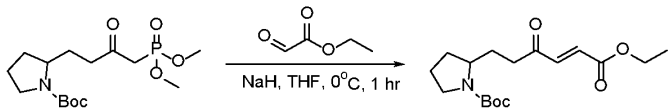


3 4

[01120] To a solution of [methoxy(methyl)phosphoryl]oxymethane (0.91 g, 7.33 mmol, 783.81 μL, 9.95 eq) in THF (6 mL) was degassed and purged with N_2 for 3 times and cooled to -78°C, the solution was added n-BuLi (2.5 M, 2.06 mL, 7 eq) at -78°C, the reaction mixture was stirred at -78°C for 0.5 hr. Then the reaction mixture was added dropwise the solution of

tert-butyl 2-(3-ethoxy-3-oxo-propyl)pyrrolidine-1-carboxylate (0.2 g, 737.05 μmol, 1 eq) in THF (2 mL) at -78°C, the reaction mixture was stirred at -78°C for 1 hr. The reaction mixture was warmed to 0°C and was quenched by addition aq. NH_4Cl (20 mL) at 0°C, and then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 36 mL/min). Compound tert-butyl 2-(4-dimethoxyphosphoryl-3-oxo-butyl)pyrrolidine-1-carboxylate (0.15 g, 429.36 μmol, 58.25% yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.80-3.78 (m, 6H), 3.76-3.73 (m, 1H), 3.37-3.26 (m, 2H), 3.16-3.10 (m, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.95-1.76 (m, 4H), 1.70-1.59 (m, 2H), 1.46 (s, 9H).

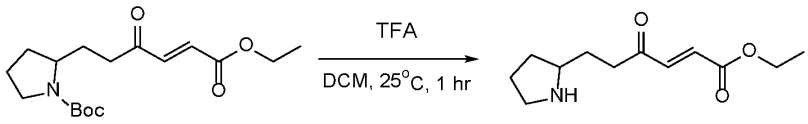
Step 1.4 Synthesis of tert-butyl 2-[(E)-6-ethoxy-3,6-dioxo-hex-4-enyl]pyrrolidine-1-carboxylate



4 5

[01121] To a solution of NaH (302.24 mg, 7.56 mmol, 60% purity, 1.2 eq) in THF (10 mL) was added dropwise the solution of tert-butyl 2-(4-dimethoxyphosphoryl-3-oxo-butyl)pyrrolidine-1- carboxylate (2.2 g, 6.30 mmol, 1 eq) in THF (10 mL) at 0°C. The mixture was stirred at 0°C for 0.5 hr, the reaction mixture was added the solution of ethyl 2-oxoacetate (1.29 g, 6.30 mmol, 1 eq) in THF (10 mL) at 0°C, the reaction mixture was stirred at 0°C for 0.5 hr. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) at 0°C, and then diluted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound tert-butyl 2-[(E)-6-ethoxy-3,6-dioxo-hex-4-enyl]pyrrolidine-1-carboxylate (0.46 g, 1.41 mmol, 22.45% yield) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.08 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.86-3.85 (m, 1H), 3.38-3.28 (m, 2H), 2.68-2.66 (m, 2H), 1.96-1.93 (m, 4H), 1.77-1.61 (m, 2H), 1.46 (m, 9H), 1.33 (t, J = 7.2 Hz, 3H).

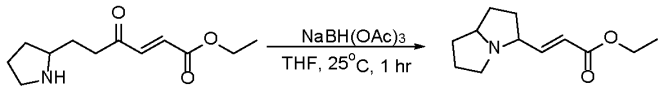
Step 1.5 Synthesis of ethyl (E)-4-oxo-6-pyrrolidin-2-yl-hex-2-enoate



5 6

[01122] To a solution of ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (3.5 g, 14.88 mmol, 1 eq) in DCM (40 mL) were added Boc_2O (3.90 g, 17.85 mmol, 4.10 mL, 1.2 eq) and DIEA (2.88 g, 22.31 mmol, 3.89 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (5 mL) at 25°C, and adjusted the reaction mixture pH = 5 by sat. aq. citric acid and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (5 g, crude) was obtained as a white solid. LCMS: m/z 336.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (s, 1H), 4.85 (d, J = 17.6 Hz, 1H), 4.62 (d, J = 13.6 Hz, 2H), 4.44 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.11 (dd, J = 13.2 Hz, 4.4 Hz, 1H), 3.86-3.83 (m, 1H), 1.43 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 0.91-0.84 (m, 1H), 0.46-0.33 (m, 4H).

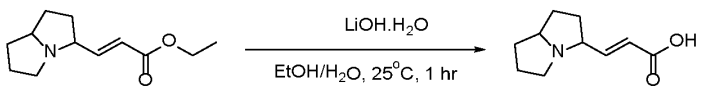
Step 1.6 Synthesis of ethyl (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoate



6 7

[01123] To a solution of ethyl (E)-4-oxo-6-pyrrolidin-2-yl-hex-2-enoate (0.256 g, 1.14 mmol, 1 eq) in THF (5 mL) was added $NaBH(OAc)_3$ (361.26 mg, 1.70 mmol, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 36 mL/min). Compound ethyl (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoate (0.1 g, 477.82 μmol, 42.05% yield) was obtained as a yellow oil. LCMS: m/z 308.0 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.09-7.00 (m, 1H), 6.10-6.07 (m, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.92-2.90 (m, 1H), 2.24-2.20 (m, 1H), 2.22-2.06 (m, 2H), 1.59-1.55 (m, 8H), 1.31 (t, J = 7.2 Hz, 3H).

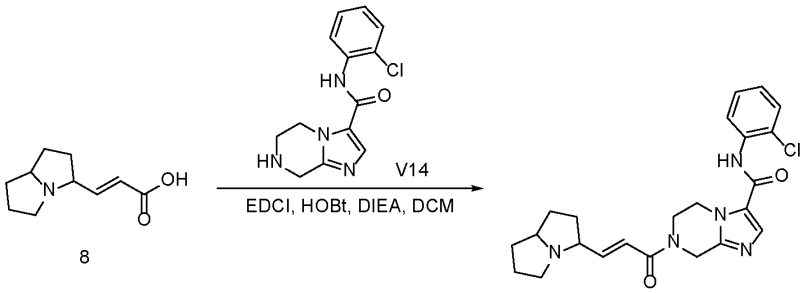
Step 1.7 Synthesis of (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoic acid



7 8

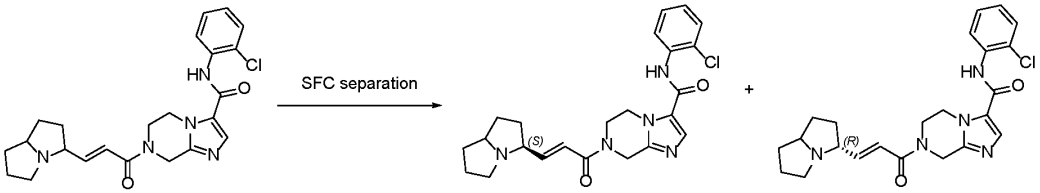
[01124] To a solution of ethyl (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoate (0.075 g, 358.36 μmol, 1 eq) in EtOH (1 mL), H_2O (0.5 mL) was added $LiOH.H_2O$ (45.11 mg, 1.08 mmol, 3 eq). The reaction mixture was stirred at 25°C for 1 hr. TLC indicated the reaction was complete. The reaction mixture was adjusted pH = 3 by 1 N HCl, and then concentrated under reduced pressure to give compound (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoic acid (0.06 g, crude) was obtained as a yellow oil. LCMS: m/z 417.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.23 (s, 1H), 7.03-6.97 (m, 1H), 6.22-6.18 (m, 1H), 4.16-4.14 (m, 1H), 4.08-4.07 (m, 1H), 3.16-3.10 (m, 2H), 2.16-2.01 (m, 2H), 1.98-1.93 (m, 3H), 1.77-1.73 (m, 3H).

Step 1.8 Synthesis of (N-(2-chlorophenyl)-7-[(E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl) prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01125] To a solution of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (138.25 mg, 441.43 μmol, 1 eq, HCl), (E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl) prop-2-enoic acid (0.08 g, 441.43 μmol, 1 eq) in DCM (2 mL) were added EDCI (126.93 mg, 662.14 μmol, 1.5 eq) and HOBt (89.47 mg, 662.14 μmol, 1.5 eq), DIEA (171.15 mg, 1.32 mmol, 230.66 μL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. LC-MS showed the reaction mixture was complete. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl) - ACN]; gradient: 1% - 25% B over 8.0 min) to give compound N-(2-chlorophenyl)-7-[(E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl)prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (54.7 mg, 124.3 μmol, 28.17% yield) as a white solid. 10 mg was delivered, the rest was separation by SFC. LCMS: m/z 440.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.65-10.53 (m, 1H), 8.47-8.41 (m, 1H), 7.99-7.71 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 6.8 Hz, 1H), 7.35 (t, J = 6.8 Hz, 1H), 7.14-7.10 (m, 1H), 6.90-6.85 (m, 1H), 5.20-5.02 (m, 2H), 4.98-4.42 (m, 2H), 4.23-4.00 (m, 4H), 3.30-3.21 (m, 2H), 2.32-2.21 (m, 2H), 2.12-1.78 (m, 6H).

Step 1.9 Synthesis of N-(2-chlorophenyl)-7-[(E)-3-[(3S)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin -3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and N-(2-chlorophenyl)-7-[(E)-3-[(3R)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

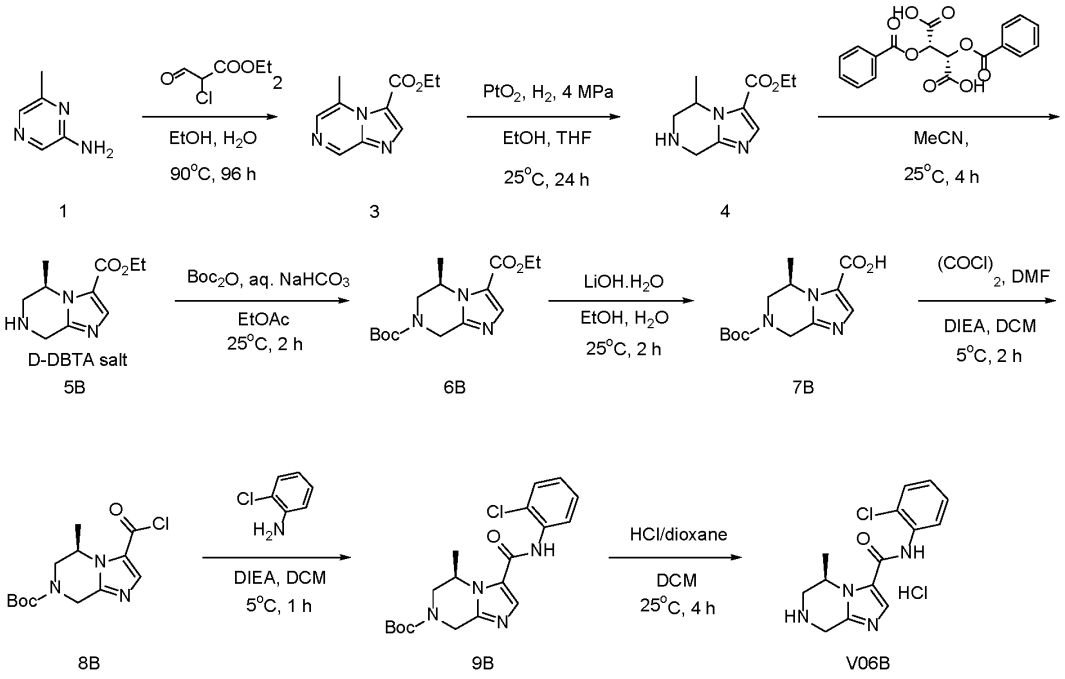


[01126] 44.7 mg of compound N-(2-chlorophenyl)-7-[(E)-3-(2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl) prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide was separation by SFC (column: Chiral Pak IH, 250 * 30 mm, 10 um; mobile phase: [CO_2 – IPA (0.1% NH_3H_2O)]; B%: 45%, isocratic elution mode) to give compound N-(2-chlorophenyl)-7-[(E)-3-[(3S)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (8 mg, 18.18 μmol, 4.12% yield) was obtained as a white solid. And compound N-(2-chlorophenyl)-7-[(E)-3-[(3R)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (12 mg, crude), then compound N-(2-chlorophenyl)-7-[(E)-3-[(3R)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (12 mg, crude) was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl) - ACN]; gradient: 1% - 40% B over 8.0 min) to give compound N-(2-chlorophenyl)-7-[(E)-3-[(3R)-2,3,5,6,7,8-hexahydro-1H-pyrrolizin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (6 mg, 13.64 μmol, 3.09% yield) was obtained as a white solid.

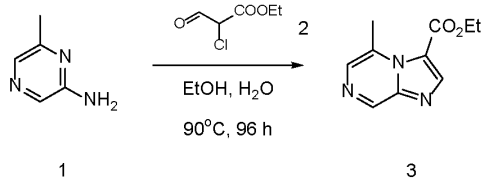
[01127] LCMS: m/z 440.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.88 (s, 1H), 7.56-7.51 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 2.0 Hz, 1H), 6.98-6.72 (m, 2H), 4.98-4.78 (m, 2H), 4.36-4.29 (m, 2H), 4.10-3.85 (m, 4H), 3.18-3.06 (m, 2H), 2.20-2.19 (m, 2H), 2.00-1.95 (m, 2H), 1.93-1.62 (m, 4H).

LCMS: m/z 440.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.28-11.15 (m, 1H), 10.37-10.20 (m, 1H), 8.27-8.16 (m, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 6.8 Hz, 1H), 7.33 (t, J = 6.8 Hz, 1H), 7.12-7.01 (m, 1H), 6.88-6.82 (m, 1H), 5.10-4.95 (m, 2H), 4.46-4.35 (m, 2H), 4.25-4.10 (m, 1H), 4.09-3.87 (m, 3H), 3.29-3.20 (m, 2H), 2.30-2.22 (m, 2H), 2.08-1.68 (m, 6H).

Example 179: Methods of synthesis for (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide.



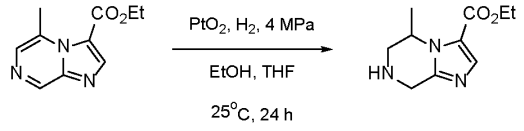
Step 1.1 Synthesis of ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate



[01128] To the reaction mixture of 6-methylpyrazin-2-amine (500 g, 4.58 mol, 1 eq) in EtOH (3.7 L) and H_2O (1.2 L) was added ethyl 2-chloro-3-oxo-propanoate (827.8 g, 5.50 mol, 1.2 eq) at 25°C. The reaction mixture was heated to 90°C and stirred at 90°C for 96 hours. 3 parallel reactions were combined to workup. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. The reaction mixture was diluted with water (7.5 L), adjusted pH = 8 with sat.aq. Na_2CO_3 at 0°C. There was precipitate formed. The reaction mixture was warmed to 25°C and stirred at 25°C for 0.5 hours. The precipitate was collected through filtration and concentrated under reduced pressure. The filtrate was extracted with EtOAc (7 L x 3), the combined organic phase was washed with brine (7 L x 1), dried over Na_2SO_4, and concentrated under reduced pressure. The crude was triturated with MTBE (2 L x 1), filtered and filter cake was concentrated under reduced pressure to give compound ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (1.2 kg, 5.58 mol, 50.82% yield) as a yellow solid. LCMS: m/z 206.0

$[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.11 (s, 1H), 8.41 (s, 1H), 8.00 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 2.76 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).

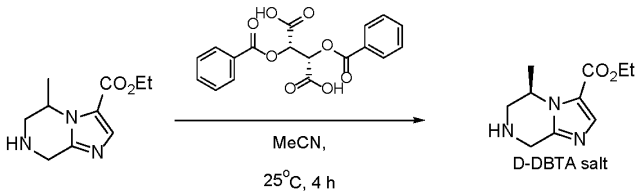
Step 1.2 Synthesis of ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate



3 4

[01129] To the reaction mixture of PtO_2 (6.00 g, 26.43 mmol, 0.009 eq) in EtOH (3 L) and THF (6 L) was added ethyl 5-methylimidazo[1,2-a]pyrazine-3-carboxylate (600 g, 2.92 mol, 1 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 24 hours under H_2 (4 MPa). 2 parallel reactions were combined to workup. The reaction mixture was filtered through a pad of celite. The filter cake was washed with EtOH (6 L x 4). The filtrate was concentrated under reduced pressure to give compound ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxylate (1.2 kg, 5.74 mol, 98.07% yield) as brown oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.58 (s, 1H), 4.65-4.64 (m,1H), 4.26-4.21 (m,2H), 3.98-3.94 (m, 1H), 3.83-3.79 (m, 1H), 3.02-3.00 (m, 1H), 2.96-2.93 (m, 1H), 1.37 (d, J = 6.4 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H).

Step 1.3 Synthesis of (2S,3S)-2,3-dibenzoyloxybutanedioic acid;ethyl (5R)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate and ethyl (5S)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate

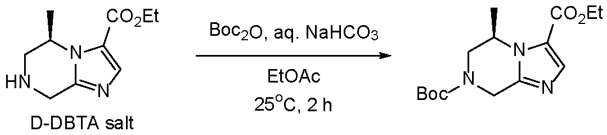


4 5B

[01130] To a solution of ethyl 5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (200 g, 955.82 mmol, 1 eq) in MeCN (2 L) was added (2S,3S)-2,3-dibenzoyloxybutanedioic acid (345.89 g, 965.38 mmol, 1.01 eq) at 25°C. The reaction mixture was stirred at 25°C for 4 hours, solid precipitated. Chiral HPLC showed peak 2 was 98.52% ee (filtrate was peak 2). 5 parallel reactions were combined to workup. The precipitate was collected through filtration and washed with MeCN (200 mL x 2), this part is enriched S-isomer. The filtrate was collected under reduced pressure to give compound (2S,3S)-2,3-dibenzoyloxybutanedioi acid ethyl (5R)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (1.5 kg, 2.63 mol, 45.80% yield, 99.38% purity) as a yellow solid. Chiral HPLC:

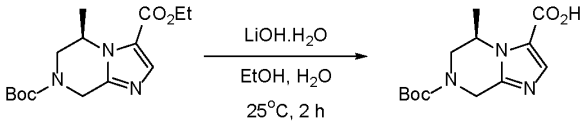
98.72% ee. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.00-7.98 (m, 5H), 7.72-7.70 (m, 2H), 7.68-7.62 (m, 1H), 7.59-7.55 (m, 5H), 5.88 (s, 2H), 4.79-4.77 (m, 1H), 4.26-4.22 (m, 2H), 4.17-4.13 (m, 1H), 4.04-4.00 (m, 1H), 3.26-3.17 (m, 2H), 1.40 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H).

Step 1.4 Synthesis of O7-tert-butyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3,7-dicarboxylate



[01131] To a solution of (2S,3S)-2,3-dibenzoyloxybutanedioic acid ethyl (5R)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (300 g, 528.59 mmol, 1 eq) in EtOAc (400 mL) was added sat. aq. $NaHCO_3$ (1200 mL) at 0°C. The reaction mixture was warmed to 25°C. Then Boc_2O (138.44 g, 634.31 mmol, 145.73 mL, 1.2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hours. 5 parallel reactions were combined to workup. The organic phase was separated, the aqueous phase was extracted with EtOAc (400 mL x 3), the combined organic phase was washed with brine (400 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was diluted with water (300 mL). The reaction mixture was cooled to 0°C and adjusted pH = 3~4 with sat.aq. citric acid at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed up to 25°C and to the reaction mixture was added water (500 mL). The reaction mixture was extracted with EtOAc (300 mL x 3), the combined organic phase was washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound O7-tert-butyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (650 g, 2.09 mol, 73.38% yield) as brown oil. LCMS: m/z 310.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.64 (s, 1H), 4.90-4.88 (m, 2H), 4.29-4.22 (m, 3H), 4.18-4.09 (m, 1H), 3.44-3.41 (m, 1H), 1.44 (s, 9H), 1.30-1.26 (m, 6H).

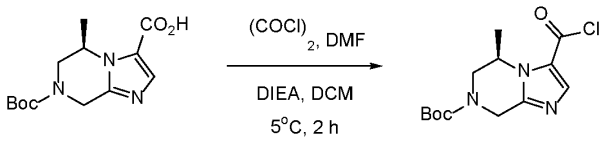
Step 1.5 Synthesis of (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



[01132] To the reaction mixture of O7-tert-butyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (300 g, 969.74 mmol, 1 *eq*) in EtOH (600 mL) and

H_2O (1200 mL) was added $LiOH{\cdot}H_2O$ (81.38 g, 1.94 mol, 2 *eq*) in portions at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hours. 2 parallel reactions were combined to workup. The reaction mixture was concentrated under reduced pressure and then cooled to 0°C and adjusted pH = 5 with 1 M HCl at 0°C. There was precipitate formed. The precipitate was collected through filtration and concentrated under reduced pressure. The filtrate was extracted with DCM: *i*-PrOH (v: v = 3:1, 2 L x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (350 g, 1.24 mol, 61.22% yield) as a white solid. LCMS: m/z 310.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.53 (s, 1H), 4.93-4.90 (m, 2H), 4.38-4.23 (m, 1H), 4.11-4.08 (m, 1H), 3.43-3.66 (m, 1H), 1.44 (s, 9H), 1.28 (d, J = 6.4 Hz, 3H).

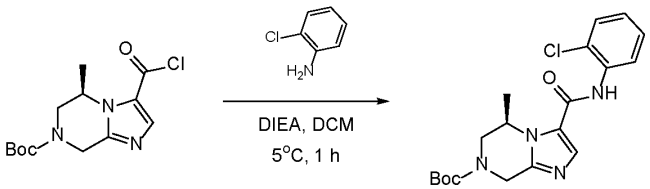
Step 1.6 Synthesis of tert-butyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



7B 8B

[01133] To a solution of (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid (100 g, 414.61 mmol, 1 eq) in DCM (1 L) was added DMF (1.51 g, 19.20 mmol, 1.60 mL, 0.05 eq) and DIEA (53.59 g, 414.63 mmol, 72.22 mL, 1 eq) at 25°C. Then the reaction mixture was added dropwise oxalyl dichloride (131.58 g, 1.04 mol, 90.74 mL, 2.5 eq) at 5°C. The mixture was stirred at 5°C for 2hr. TLC indicated reaction was complete (quenched by MeOH). 3 parallel reactions were combined to workup. The reaction mixture was concentrated under reduced pressure to give tert-butyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (370 g, crude) as a black oil.

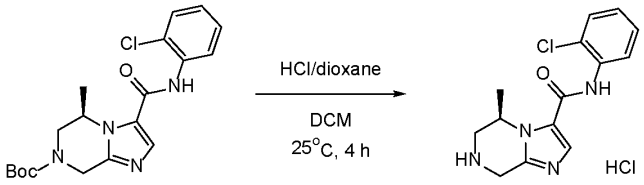
Step 1.7 Synthesis of tert-butyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



8B 9B

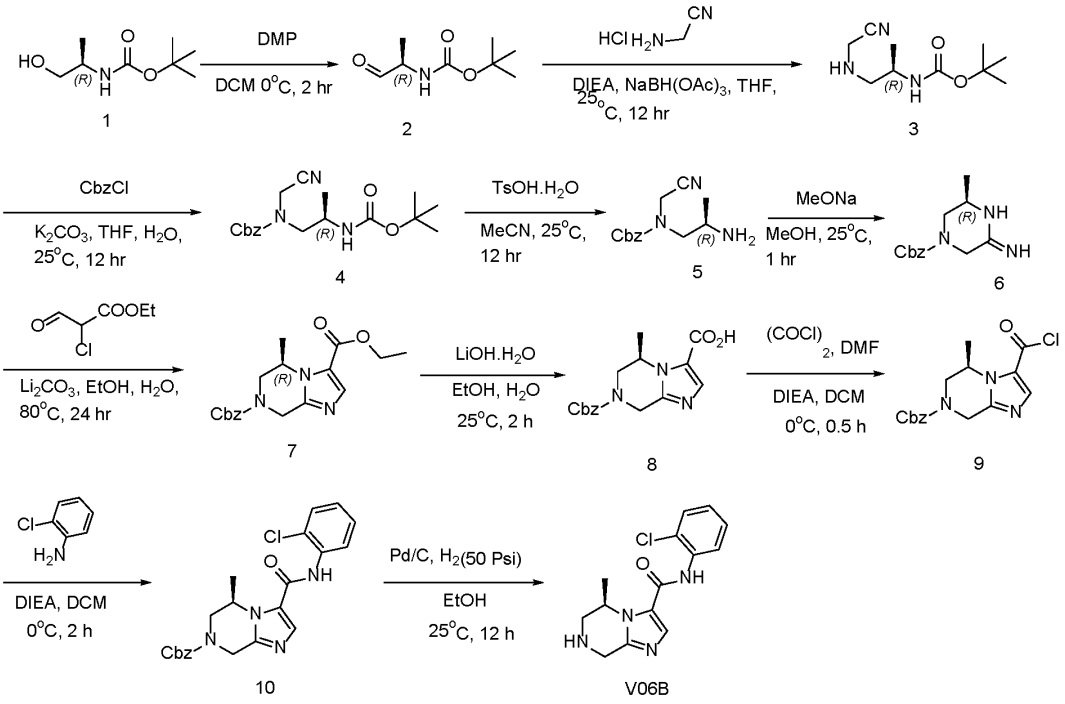
[01134] To a solution of tert-butyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (370 g, 1.23 mol, 1 eq) in DCM (2.7 L) was added dropwise 2-chloroaniline (152.73 g, 1.20 mol, 126.24 mL, 0.97 eq) at 0°C, then the reaction was added dropwise DIEA (398.81 g, 3.09 mol, 537.49 mL, 2.5 eq) at 0°C. The mixture was stirred at 5°C for 1hr. The reaction mixture was poured into water (1.5 L) and extracted with DCM (1 L x 2). The combined organic phase was concentrated in vacuo to give a crude. The crude product was purified by chromatography on a silica gel eluted with Petroleum ether: ethyl acetate (from 10/1 to 1/1) to give tert-butyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (310 g, 793.13 mmol, 64.48% yield) was obtained as a white solid. LCMS: m/z 391.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.83 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 5.01-4.91 (m, 2H), 4.42-4.27 (m, 1H), 4.09-4.04 (m, 1H). 3.46-3.43 (m, 1H), 1.45 (s, 9H), 1.28 (d, J = 6.0 Hz, 3H).

Step 1.8 Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide

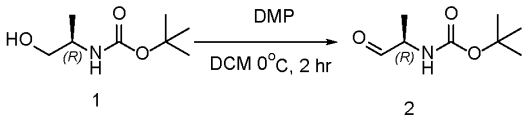


9B V06B

To a solution of tert-butyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H -imidazo[1,2-a]pyrazine-7-carboxylate (310 g, 793.13 mmol, 1 eq) in DCM (1.5 L) was added HCl (gas)/dioxane (4 M, 2 L) at 25°C. The reaction mixture was stirred at 25°C for 4 hours. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with MTBE (600 mL) at 25°C for 2 hours. The precipitate was filtered, washed Petroleum ether (500 mL x 2), collected and concentrated under reduced pressure. Compound (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxamide (240 g, HCl salt) was obtained as an off-white solid. LCMS: m/z 291.1 $[M+H]^+$. HPLC: 97.20% purity. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.37 (s, 1H), 8.17-8.16 (m, 1H), 7.58-7.49 (m, 2H), 7.40-7.38 (m, 1H), 7.33-7.32 (m, 1H), 5.21-5.18 (m, 1H), 4.49 (q, J = 8.0 Hz, 2H), 3.63-3.62 (m, 1H), 3.58-3.57 (m, 1H), 1.56 (d, J = 6.4 Hz, 3H).

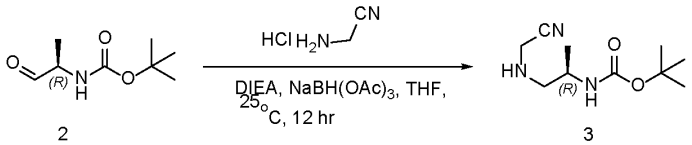


Step 2.1 Synthesis of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate



[01135] To a solution of tert-butyl N-[(1R)-2-hydroxy-1-methyl-ethyl]carbamate (70 g, 399.49 mmol, 1 eq) in DCM (800 mL) was added Dess-Martin (177.91 g, 419.46 mmol, 129.96 mL, 1.05 eq) at 0°C. The reaction mixture was stirred at 0°C for 2hr. The reaction mixture was cooled to 0°C and quenched by aq. K_2CO_3 (100 mL) at 0°C, then diluted with H_2O (200 mL) extracted with DCM (400 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (BIOTAGE ®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~28% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate (60 g, 346.40 mmol, 86.71% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.42 (s, 1H), 7.31 (d, J = 6.0 Hz, 1H), 3.89-3.36 (m, 1H), 1.39 (s, 9H), 1.12 (d, J = 7.2 Hz, 3H).

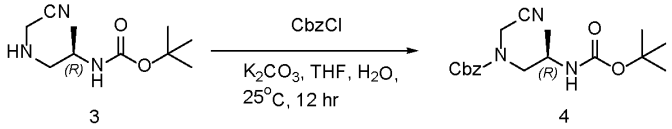
Step 2.2 Synthesis of tert-butyl N-[(1R)-2-(cyanomethylamino)-1-methyl-ethyl]carbamate



2 3

[01136] To a solution of 2-aminoacetonitrile (28.85 g, 311.76 mmol, 2 eq, HCl) in THF (270 mL) was added DIEA (30.22 g, 233.82 mmol, 40.73 mL, 1.5 eq) at 25°C, the reaction mixture was stirred at 25°C for 0.5 hr, then tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate (27 g, 155.88 mmol, 1 eq) and $NaBH(OAc)_3$ (49.56 g, 233.82 mmol, 1.5 eq) was added into the reaction mixture at 25°C. The reaction mixture was added to sat.aq. K_2CO_3 to adjust pH = 8 and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (BIOTAGE ®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl N-[(1R)-2-(cyanomethylamino)-1-methyl-ethyl]carbamate (18 g, 84.40 mmol, 54.14% yield) was obtained as yellow oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.62 (d, J = 7.6 Hz, 1H), 3.59 (d, J = 4.8 Hz, 2H), 3.51 (t, J = 5.6 Hz, 1H), 2.56-2.52 (m, 1H), 2.45-2.42 (m, 1H), 1.37 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H).

Step 2.3 Synthesis of benzyl N-[(2R)-2-(tert-butoxycarbonylamino)propyl]-N-(cyanomethyl)carbamate

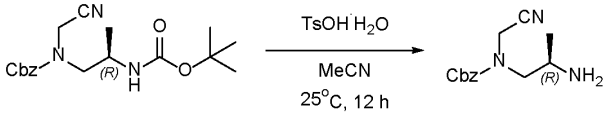


3 4

[01137] To a solution of tert-butyl N-[(1R)-2-(cyanomethylamino)-1-methyl-ethyl]carbamate (13 g, 60.95 mmol, 1 eq) in H_2O (130 mL) was added K_2CO_3 (25.27 g, 182.86 mmol, 3 eq) and the solution of CbzCl (13.52 g, 79.24 mmol, 11.31 mL, 1.3 eq) in THF (130 mL) was added into the reaction mixture at 0°C. The reaction mixture was warmed to 25°C and was stirred at 25°C for 12hr. The reaction mixture was quenched by addition H_2O (30 mL) at 25°C, and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (BIOTAGE ®; 110 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound benzyl N-[(2R)-2-(tert-butoxycarbonylamino)propyl]-N-(cyanomethyl)carbamate (12.29 g, 35.38 mmol, 58.04% yield) was obtained as pale yellow oil. ^1H NMR (DMSO-d_6,

400 MHz) δ 7.39-7.31 (m, 5H), 6.74 (d, *J* = 7.2, 1H), 5.13 (d, *J* = 4.0, 2H), 4.34 (d, *J* = 13.2, 2H), 3.75 (s, 1H), 3.33-3.32 (m, 1H), 3.20-3.14 (m, 1H), 1.35 (s, 9H), 0.98 (d, *J* = 6.4 Hz, 3H).

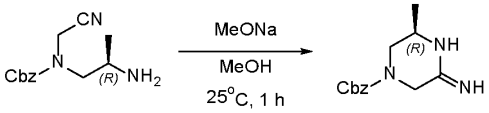
Step 2.4 Synthesis of benzyl N-[(2R)-2-aminopropyl]-N-(cyanomethyl)carbamate



4 5

[01138] To the reaction mixture of benzyl N-[(2R)-2-(tert-butoxycarbonylamino)propyl]-N-(cyanomethyl)carbamate (10 g, 28.78 mmol, 1 eq) in MeCN (100 mL) was added TsOH·H2O (10.95 g, 57.57 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 12 hours. The reaction mixture was concentrated under reduced pressure to give compound benzyl N-[(2R)-2-aminopropyl]-N-(cyanomethyl) carbamate (18.8 g, crude, PTSA salt) was obtained as yellow oil. LCMS: m/z 247.9 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.84 (s, 2H), 7.41-7.31 (m, 5H), 5.18-5.10 (m, 2H), 4.42-4.33 (m, 2H), 3.56-3.35 (m, 3H), 1.16-1.15 (m, 3H).

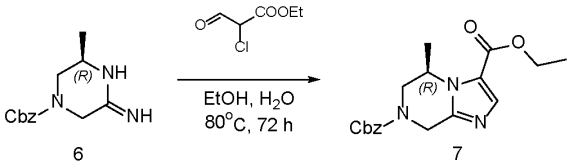
Step 2.5 Synthesis of benzyl (5R)-3-imino-5-methyl-piperazine-1-carboxylate



5 6

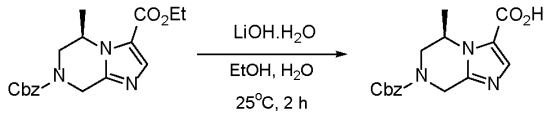
[01139] To the reaction mixture of benzyl *N*-[(2R)-2-aminopropyl]-N-(cyanomethyl)carbamate (18.8 g, 44.82 mmol, 1 eq, p-TSA) in MeOH (188 mL) was added NaOMe (12.11 g, 224.08 mmol, 5 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with MeCN (500 mL) at 25°C for 15 mins. The solid was collected by filtrate and concentrated under reduced to give compound benzyl (5R)-3-imino-5-methyl-piperazine-1-carboxylate (4.5 g, 17.76 mmol, 39.63% yield, 97.6% purity) as a white solid and compound benzyl (5R)-3-imino-5-methyl-piperazine-1- carboxylate (3 g, 8.01 mmol, 17.87% yield, 66% purity) as pale yellow solid. LCMS: m/z 248.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.38-7.31 (m, 5H), 5.56 (s, 2H), 5.09 (s, 2H), 3.83-3.70 (m, 2H), 3.58 (dd, *J* = 10.8 Hz, 2.8 Hz, 1H), 2.67-2.61 (m, 1H), 2.59-2.57 (m, 1H), 1.01 (d, *J* = 6.4, 3H).

Step 2.6 Synthesis of O7-benzyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate



[01140] To the reaction mixture of benzyl (5R)-3-imino-5-methyl-piperazine-1-carboxylate (7.5 g, 30.33 mmol, 1 eq) in H_2O (12 mL) and EtOH (60 mL) were added Li_2CO_3 (2.24 g, 30.33 mmol, 1 eq), ethyl 2-chloro-3-oxo-propanoate (5.02 g, 33.36 mmol, 1.1 eq) at 25°C. The reaction mixture was heated to 80°C and stirred at 80°C for 72 hours. The reaction mixture was cooled to 25°C and concentrated under reduced pressure. The reaction mixture was cooled to 0°C and adjusted pH=7 with sat.aq. $NaHCO_3$ at 0°C. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (50 mL) and then extracted with EtOAc (25 mL x 2). The combined organic layers were washed with brine (25 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 80 g SepaFlash® Silica Flash Column, Eluent of 25~33% Petroleum ether / Ethyl acetate gradient @ 80 mL/min). The eluent was removed under reduced pressure to give compound O7-benzyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine- 3,7-dicarboxylate (3.5 g, 8.71 mmol, 28.74% yield, 85.5% purity) as brown oil. LCMS: m/z 344.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.65 (s, 1H), 7.40-7.31 (m, 5H), 5.20-5.16 (m, 2H), 4.98-4.93 (m, 2H), 4.40-4.35 (m, 1H), 4.28-4.23 (m, 2H), 4.19-4.16 (m, 1H), 3.51-3.40 (m, 1H), 1.30-1.26 (m, 6H).

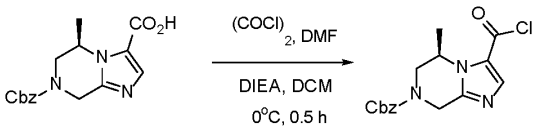
Step 2.7 Synthesis of (5R)-7-benzyloxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid -



[01141] To the reaction mixture of O7-benzyl O3-ethyl (5R)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate (3.5 g, 10.19 mmol, 1 eq) in EtOH (24 mL) and H_2O (12 mL) was added $LiOH{\cdot}H_2O$ (855.39 mg, 20.39 mmol, 2 eq) in portions at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hours. The reaction mixture was concentrated under reduced pressure and then cooled to 0°C and adjusted pH = 5 with 1 M HCl at 0°C. There was precipitate formed. The precipitate was collected through filtration and concentrated under reduced pressure to give compound (5R)-7-benzyloxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (1.8 g, 5.70 mmol, 55.94% yield,

99.89% purity) as a pale yellow solid. LCMS: m/z 316.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.59 (s, 1H), 7.40-7.33 (m, 5H), 5.20-5.13 (m, 2H), 4.96-4.93 (m, 2H), 4.51-4.35 (m, 1H), 4.18-4.15 (m, 1H), 3.51-3.46 (m, 1H), 1.28 (d, J = 6.0 Hz, 3H).

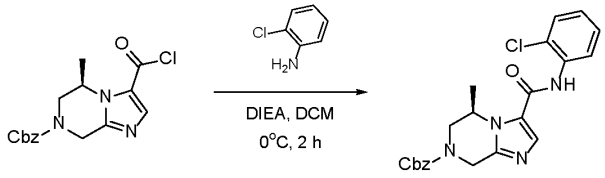
Step 2.8 Synthesis of benzyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate



8 9

[01142] To a solution of (5R)-7-benzyloxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (1.6 g, 5.07 mmol, 1 *eq*) in DCM (16 mL) were added DMF (3.71 mg, 50.74 μmol, 3.90 μL, 0.01 *eq*), DIEA (655.78 mg, 5.07 mmol, 883.81 μL, 1 *eq*) at 25°C. The reaction mixture was cooled to 0°C. And then oxalyl dichloride (1.61 g, 12.69 mmol, 1.11 mL, 2.5 *eq*) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 0.5 hours. LCMS showed the reaction was complete (quenched by EtOH). The reaction mixture was warmed to 25°C and concentrated under reduced pressure to give compound benzyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate (1.6 g, 4.79 mmol, 94.47% yield) as a yellow solid. LCMS: m/z 344.3 $[M+H]^+$.

Step 2.9 Synthesis of benzyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate

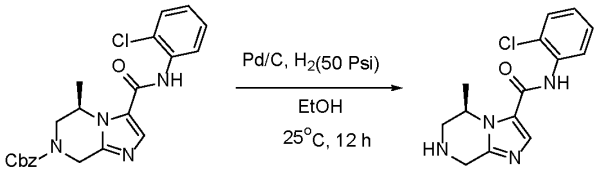


9 10

[01143] To a solution of benzyl (5R)-3-chlorocarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate (1.6 g, 4.79 mmol, 1 eq) in DCM (5 mL) were added 2-chloroaniline (611.54 mg, 4.79 mmol, 505.41 μL, 1 eq), DIEA (1.55 g, 11.98 mmol, 2.09 mL, 2.5 eq) at 0°C. The reaction mixture was stirred at 0°C for 2 hours. The reaction mixture was quenched with water (50 mL) at 0°C and then warmed to 25°C. The organic phase was separated, the aqueous phase was extracted with DCM (20 mL x 3), the combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 20 g Sepa Flash® Silica Flash Column, Eluent of 25~55% Petroleum ether / Ethyl acetate

gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound benzyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (1.4 g, 3.27 mmol, 68.11% yield, 99.09% purity) as a yellow solid. LCMS: m/z 425.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.53 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.40-7.31 (m, 7H), 5.20-5.14 (m, 2H), 5.05-4.94 (m, 2H), 4.54-4.42 (m, 1H), 4.17-4.13 (m, 1H), 3.44-3.40 (m, 1H), 1.29 (d, J = 6.0 Hz, 3H).

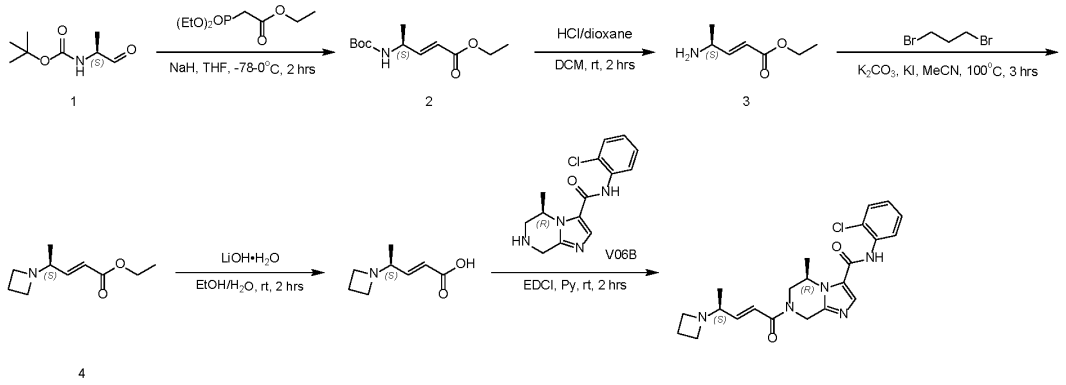
Step 3.0 Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide



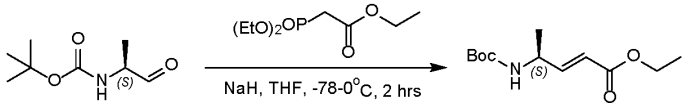
10 V06B

[01144] To a solution of Pd/C (10 mg, 9.40 μmol, 10% purity) in EtOH (10 mL) was added benzyl (5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (0.1 g, 235.36 μmol, 1 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 12 hours under H_2 (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-50% B over 8.0 min). The residue was dried over lyophilization to give compound (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (32 mg, 105.12 μmol, 44.66% yield, 95.51% purity) as a white solid. LCMS: m/z 291.0 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.74 (s, 1H), 7.78 (s, 1H), 7.54 (dt, J = 8.0 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 8.0 Hz, 1.6 Hz, 1H), 4.78-4.75 (m, 1H), 3.98 (d, J = 16.8 Hz, 1H), 3.84 (d, J = 16.8 Hz, 1H), 3.08-3.02 (m, 1H), 2.93 (d, J = 13.2 Hz, 1H), 2.83 (s, 1H), 1.35 (d, J = 6.4 Hz, 3H).

Example 180: Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

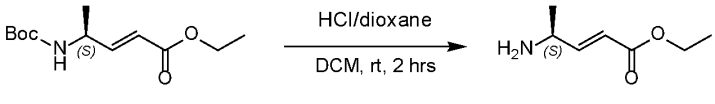


Step 3.1.1 Synthesis of ethyl (E,4S)-4-(tert-butoxycarbonylamino)pent-2-enoate



[01145] To a solution of NaH (2.91 g, 72.74 mmol, 60% purity, 1.2 eq) in THF (150 mL) was added ethyl 2-diethoxyphosphorylacetate (16.31 g, 72.74 mmol, 14.43 mL, 1.2 eq) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl N-[(1S)-1-methyl-2-oxo-ethyl]carbamate (10.5 g, 60.62 mmol, 1 eq) in THF (50 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 hr. The reaction mixture was quenched with sat. aq. NH_4Cl (200 mL) at 0°C, and then extracted with EtOAc (150 mL * 3). The combined organic phase was washed with brine (150 mL * 2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @100 mL/min). Compound ethyl (E,4S)-4-(tert-butoxycarbonylamino)pent-2-enoate (15 g, crude) was obtained as colorless oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.11 (d, J = 7.6 Hz, 1H), 6.80 (dd, J =15.6 Hz, 5.2 Hz, 1H), 5.80 (dd, J =15.6 Hz, 1.6 Hz, 1H), 4.21-4.18 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 1.38 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H).

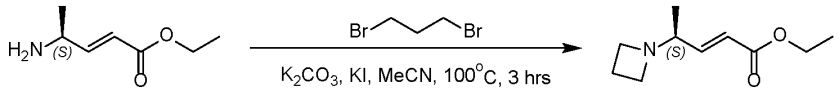
Step 3.1.2 Synthesis of ethyl (E,4S)-4-aminopent-2-enoate



[01146] To a solution of ethyl (E,4S)-4-(tert-butoxycarbonylamino)pent-2-enoate (15 g, 61.65 mmol, 1 eq) in DCM (30 mL) was added HCl/dioxane (4 M, 30 mL, 1.95 eq) at 25°C. The

reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give ethyl (E,4S)-4-aminopent-2-enoate (11.8 g, crude) was obtained as brown oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.59 (br.s, 2H), 6.87 (dd, J=16.0 Hz, 6.0 Hz, 1H), 6.11 (dd, J=16.0 Hz, 1.6 Hz, 1H), 4.15 (q, J= 6.4 Hz, 2H), 4.01 (br.s, 1H), 1.34 (d, J= 6.8 Hz, 3H), 1.22 (t, J= 6.8 Hz, 3H).

Step 3.1.3 Synthesis of ethyl (E,4S)-4-(azetidin-1-yl)pent-2-enoate



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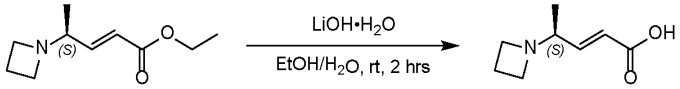
[01147] To a solution of ethyl (E,4S)-4-aminopent-2-enoate (11 g, 76.82 mmol, 1 eq) and 1,3-dibromopropane (23.26 g, 115.24 mmol, 11.75 mL, 1.5 eq) in MeCN (200 mL) were added K_2CO_3 (26.54 g, 192.06 mmol, 2.5 eq) and KI (1.28 g, 7.68 mmol, 0.1 eq) at 25°C. The reaction mixture was heated to 100°C and stirred at 100°C for 3 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound ethyl (E,4S)-4-(azetidin-1-yl)pent-2-enoate (2.6 g, 14.19 mmol, 18.47% yield) was obtained as yellow oil. LCMS: m/z 184.2 $[M+H]^+$.

Step 3.1.4 Synthesis of (E,4S)-4-(azetidin-1-yl)pent-2-enoic acid



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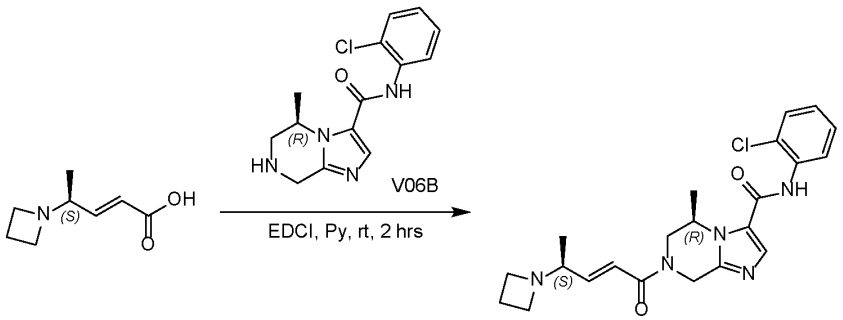
[01148] To a solution of ethyl (E,4S)-4-(azetidin-1-yl)pent-2-enoate (2.60 g, 14.19 mmol, 1 eq) in EtOH (25 mL) and H_2O (4 mL) was added LiOH•H_2O (1.49 g, 35.47 mmol, 2.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 250 * 50 mm * 15 um; mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 1%-5% B over 10.0 min). Compound (E,4S)-4-(azetidin-1-yl)pent-2-enoic acid (850 mg, 5.48 mmol, 38.60% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.53 (dd, J=15.6 Hz, 7.6 Hz, 1H), 5.95 (d, J= 15.6 Hz, 1H), 3.43 (t, J= 7.6 Hz, 4H), 3.38-3.33 (m, 1H), 2.04 (q, J = 8.0 Hz, 2H), 1.05 (d, J= 6.4 Hz, 3H).

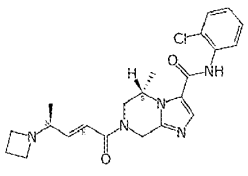
Step 3.1.5 Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

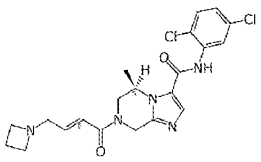
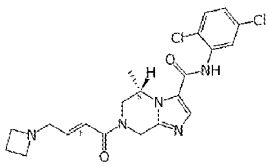
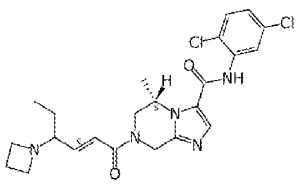
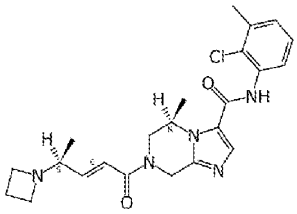
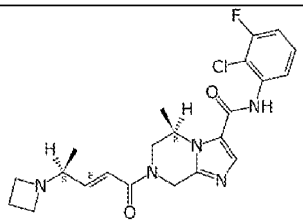


[01149] To a solution of (E,4S)-4-(azetidin-1-yl)pent-2-enoic acid (843.45 mg, 4.40 mmol, 1.2 eq, HCl) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1.2 g, 3.67 mmol, 1 eq, HCl) in pyridine (15 mL) was added EDCI (1.41 g, 7.33 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 250 * 50 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 10.0 min). Compound (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (489.4 mg, 1.13 mmol, 30.75% yield, 98.6% purity) was obtained as a yellow solid. LCMS: m/z 428.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 7.6 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.67-6.61 (m, 1H), 6.55-6.50 (m, 1H), 5.26-5.16 (m, 1H), 5.06 (br.s, 1H), 4.70-4.55 (m, 1H), 4.32-4.25 (m, 1H), 3.68 (d, J = 12.4 Hz, 0.5H), 3.27-3.22 (m, 0.5H), 3.08 (t, J = 7.2 Hz, 4H), 2.93 (q, J = 6.4 Hz, 1H), 1.91 (q, J = 7.2 Hz, 2H), 1.29-1.23 (m, 3H), 0.95 (d, J = 6.0 Hz, 3H).

[01150] Compounds in Table R were synthesized following the procedure for (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

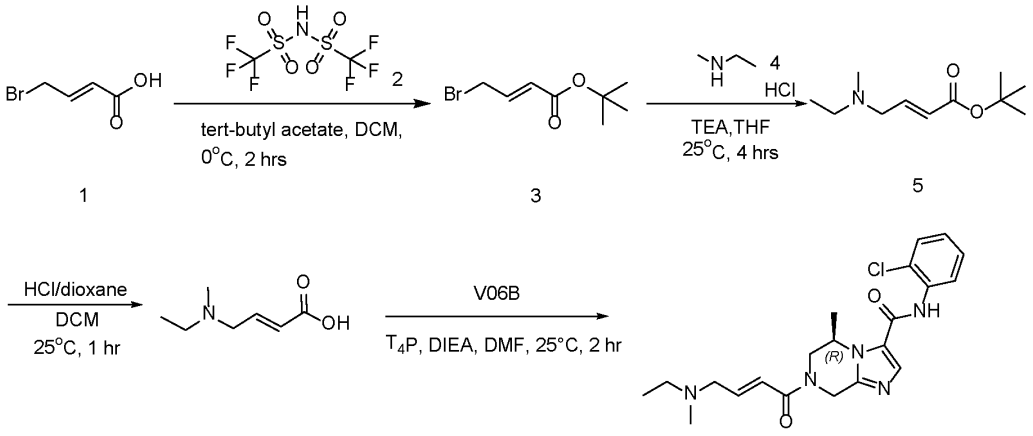
Table R

Name	Structure	NMR	LCMS
(5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.68-6.62 (m, 1H), 6.52-6.47 (m, 1H), 5.28-5.17 (m, 1H), 5.04 (s, 1H), 4.69-4.56 (m, 1H), 4.32-4.24 (m, 1H), 3.69 (d, J = 11.6 Hz, 0.5H), 3.28-3.18 (m, 0.5H), 3.08-3.04 (m, 4H), 2.95-2.89 (m, 1H), 1.92-1.88 (m, 2H), 1.29-	LCMS: m/z 428.2 $[M+H]^+$

Name	Structure	NMR	LCMS
		1.23 (m, 3H), 0.96 (d, *J* = 6.4 Hz, 3H).	
(5R)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2,5dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (br s, 1H), 7.89 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.37-7.34 (m, 1H), 6.62-6.61 (m, 2H), 5.28-5.14 (m, 1H), 5.05-5.04 (m, 1H), 4.70-4.56 (m, 1H), 4.29-4.24 (m, 1H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.15-3.12 (m, 6H), 2.02-1.95 (m, 2H), 1.29-1.95 (m, 3H).	LCMS: m/z 448.1 $[M+H]^+$
(S,E)-7-(4-(azetidin-1-yl)but-2-enoyl)-N-(2,5-dichlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.92 (s, 1H), 7.89 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.63 (d, *J* = 4.0 Hz, 2H), 5.28-5.15 (m, 1H), 5.06 (br.s, 1H), 4.71-4.57 (m, 1H), 4.31-4.25 (m, 1H), 3.69 (d, *J* = 12.8 Hz, 0.5H), 3.30 (s, 0.5H), 3.16-3.12 (m, 6H), 1.99 (q, *J* = 6.8 Hz, 2H), 1.29-1.25 (m, 3H).	LCMS: m/z 448.1 $[M+H]^+$
(5S)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.36 (dd, *J* = 8.8 Hz, 2.8 Hz, 1H), 6.67-6.64 (m, 1H), 6.48-6.38 (m, 1H), 5.28-5.17 (m, 1H), 5.04 (s, 1H), 4.70-4.53 (m, 1H), 4.36-4.25 (m, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.06 (q, *J* = 6.8 Hz, 4H), 2.75 (t, *J* = 4.4 Hz, 1H), 1.95-1.89 (m, 2H), 1.50-1.42 (m, 1H), 1.29-1.19 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 476.1 $[M+H]^+$
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.79 (s, 1H), 7.87 (s, 1H), 7.40-7.35 (m, 1H), 7.30-7.22 (m, 2H), 6.64-6.49 (m, 2H), 5.26-5.16 (m, 1H), 5.04 (s, 1H), 4.69-4.55 (m, 1H), 4.31-4.24 (m, 1H), 3.68 (d, *J* = 12.4 Hz, 0.5H), 3.25-3.19 (m, 0.5H), 3.07 (t, *J* = 6.8 Hz, 4H), 2.92 (q, *J* = 6.4 Hz, 1H), 1.91 (q, *J* = 6.8 Hz, 3H), 1.94-1.87 (m, 2H), 1.29-1.24 (m, 3H), 0.96-0.94 (m, 3H).	LCMS: m/z 442.2 [M+H]
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-fluoro- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.00 (s, 1H), 7.90 (s, 1H), 7.43-7.38 (m, 2H), 7.36-7.31 (m, 1H), 6.66-6.60 (m, 1H), 6.55-6.45 (m, 1H), 5.26-5.16 (m, 1H), 5.03 (s, 1H), 4.66 (dd, *J* = 45.2 Hz, 16.8 Hz, 1H), 4.29 (t, *J* = 13.6 Hz, 1H) 3.68 (d, *J* = 13.6 Hz, 0.5H), 3.26-3.19 (m, 0.5H), 3.07 (t, *J* = 8.0 Hz, 4H), 2.95-2.89 (m, 1H), 1.94-1.87 (m, 2H), 1.29-1.24 (m, 3H), 0.95 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 446.1 $[M+H]^+$

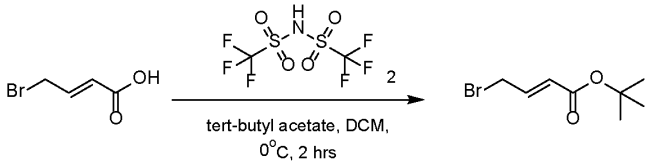
Example 181: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Part 3.2 General procedure for Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



1 3 5

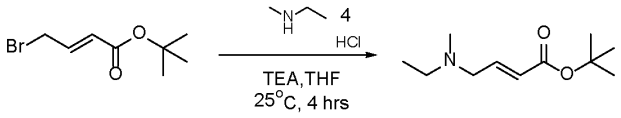
Step 3.2.1 Synthesis of tert-butyl (E)-4-bromobut-2-enoate



1 3

[01151] To a solution of (E)-4-bromobut-2-enoic acid (25 g, 151.53 mmol, 1 eq) in tert-butyl acetate (650 mL) was added a solution of 1,1,1-trifluoro-N-(trifluoromethylsulfonyl) methanesulfonamide (10.65 g, 37.88 mmol, 0.25 eq) in DCM (50 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 hrs. The reaction mixture was quenched by addition of aq. Na_2CO_3 to adjusted pH = 7, and then extracted with EtOAc (100 mL x 1), washed with brine (100 mL x 1), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl (E)-4-bromobut-2-enoate (21 g, 94.98 mmol, 62.68% yield) was obtained as colorless oil. ^{1}H NMR (MeOD, 400 MHz) δ 6.93-6.86 (m, 1H), 5.97 (d, J = 15.2 Hz, 1H), 4.10 (dd, J = 7.6 Hz, 1.2 Hz, 2H), 1.49 (s, 9H).

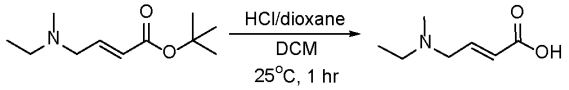
3.2.2 Synthesis of tert-butyl (E)-4-[ethyl(methyl)amino]but-2-enoate



3 5

[01152] To a solution of TEA (25.59 g, 252.85 mmol, 35.19 mL, 3 eq) in THF (200 mL) was added N-methylethanamine (9.67 g, 101.14 mmol, 14.05 mL, 1.20 eq, HCl) at 25°C. Then was added to tert-butyl (E)-4-bromobut-2-enoate (20.5 g, 84.28 mmol, 1 eq) at 25°C. The reaction mixture was stirred at 25°C for 4 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 220 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). The eluent was removed under reduced pressure. Compound tert-butyl (E)-4-[ethyl(methyl)amino]but-2-enoate (10 g, 50.18 mmol, 59.53% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.72 (dt, J = 15.6 Hz, 6.0 Hz, 1H), 5.88 (d, J = 15.6 Hz, 1H), 3.07 (d, J = 6.0 Hz, 2H), 2.34 (q, J = 7.2 Hz, 2H), 2.11 (s, 3H), 1.42 (s, 9H), 0.97 (t, J = 7.2 Hz, 3H).

Step 3.2.3 Synthesis of methyl (E)-4-[ethyl(methyl)amino]but-2-enoic acid



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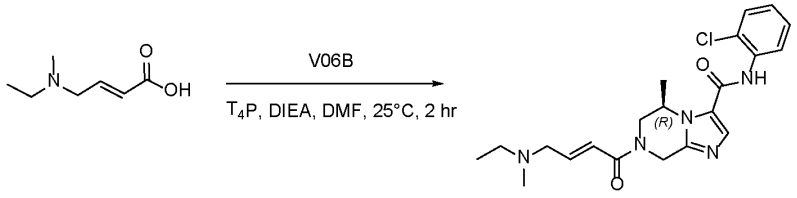
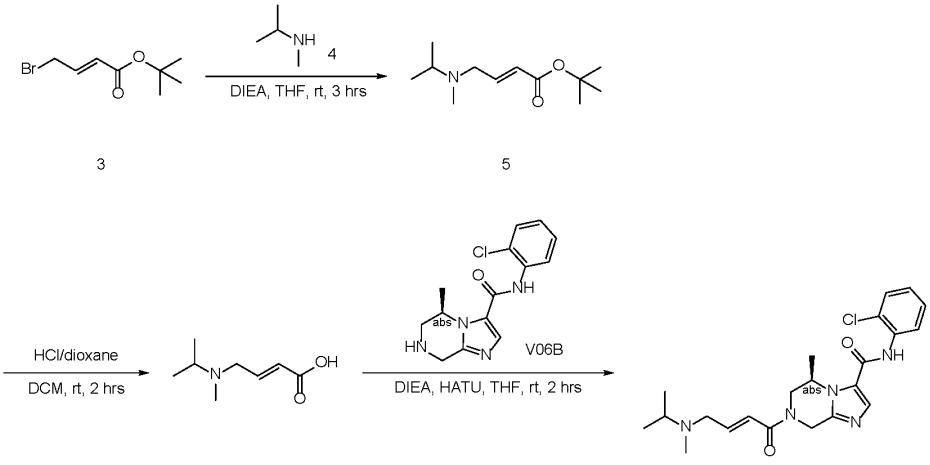
[01153] To a solution of tert-butyl (E)-4-[ethyl(methyl)amino]but-2-enoate (10 g, 50.18 mmol, 1 eq) in DCM (100 mL) was added HCl/dioxane (4 M, 100 mL, 7.97 eq) at 25°C. The reaction mixture was stirred at 25°C for 1hr. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound (E)-4-[ethyl(methyl)amino]but-2-enoic acid (8 g, crude) was obtained as a white solid. LCMS: m/z 144.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.10 (s, 1H), 6.86 (dt, J = 15.6 Hz, 6.8 Hz, 1H), 6.2 (d, J = 16.0 Hz, 1H), 3.95-3.80 (m, 2H), 3.13-3.00 (m, 2H), 2.66 (d, J = 4.0 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H).

3.2.4 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

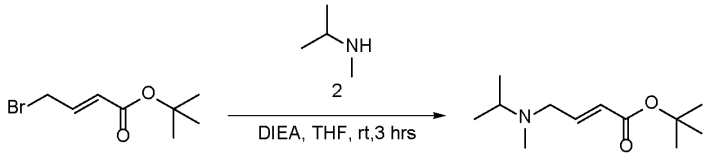


[01154] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (10 g, 30.56 mmol, 1 eq, HCl) in DMF (100 mL) was added T_4P (33.03 g, 45.84 mmol, 50% purity, 1.5 eq) and (E)-4-[ethyl(methyl)amino]but-2-enoic acid (6.31 g, 35.15 mmol, 1.15 eq, HCl) and DIEA (19.75 g, 152.81 mmol, 26.62 mL, 5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2hr. The reaction mixture was quenched by addition H_2O (200 mL) at 25 °C, and then adjusted pH = 9, by aq. $NaHCO_3$ and extracted with DCM (100 mL x 3). The combined organic layers were washed with H_2O (200 mL x 2), and concentrated under reduced pressure to give a residue, the residue was added H_2O (100 mL), and then adjusted pH = 1-2, by 4 M HCl, then extracted with DCM (100 mL x 3), the water layers was adjusted pH = 9-10 by aq. Na_2CO_3, then extracted with DCM (100 mL x 3), The combined organic layers were washed with brine (200 mL x 2), and concentrated under reduced pressure to give a residue .The residue was purified by prep-HPLC (column: Welch Xtimate C_{18} 250*100mm#10um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-55% B over 20.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (10.5 g, 25.24 mmol, 39.34% yield) was obtained as Off-white solid. LCMS: m/z 416.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.58 (m, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.79-6.69 (m, 2H), 5.29-5.18 (m, 1H), 5.05-5.04-4 (m, 1H), 4.70-4.58 (m, 1H), 4.32-4.26 (m, 1H), 3.72 (d, *J* = 13.6 Hz, 0.5H), 3.26 (d, *J* = 13.6 Hz, 0.5H), 3.15-3.13 (m, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.30-1.26 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

Example 182: *Synthesis of* (5R)-N-(2-chlorophenyl)-7-[(E)-4-[isopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.2 Synthesis of tert-butyl (E)-4-[isopropyl(methyl)amino]but-2-enoate



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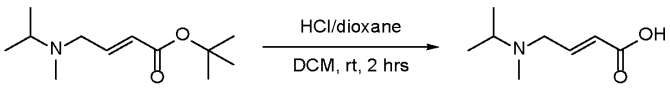
[01155] To a solution of tert-butyl (E)-4-bromobut-2-enoate (3 g, 13.57 mmol, 1 eq) and N-methylpropan-2-amine (992.39 mg, 13.57 mmol, 1.41 mL, 1 eq) in THF (30 mL) was added DIEA (2.63 g, 20.35 mmol, 3.55 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 3 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound tert-butyl (E)-4-[isopropyl(methyl)amino]but-2-enoate (2 g, 9.38 mmol, 69.10% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.70 (dt, J = 15.6 Hz, 5.6 Hz, 1H), 5.87 (dt, J =17.2 Hz, 1.6 Hz, 1H), 3.10 (dd, J =5.6 Hz, 1.6 Hz, 2H), 2.77-2.71 (m, 1H), 2.07 (s, 3H), 1.42 (s, 9H), 0.93 (d, J = 6.4 Hz, 6H).

Step 1.3 Synthesis of (E)-4-[isopropyl(methyl)amino]but-2-enoic acid



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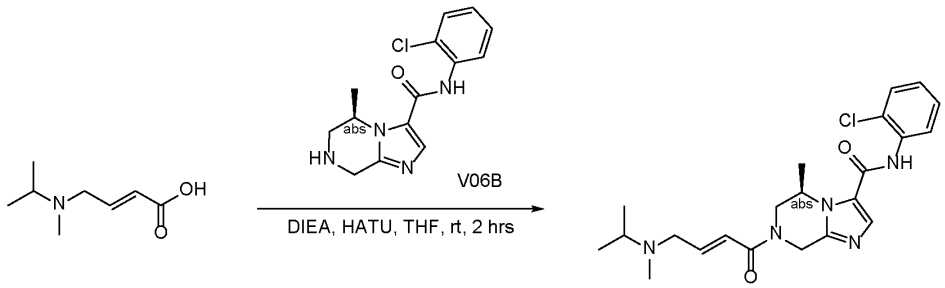
[01156] To a solution of tert-butyl (E)-4-[isopropyl(methyl)amino]but-2-enoate (2 g, 9.38 mmol, 1 eq) in DCM (5 mL) was added HCl/dioxane (4 M, 10 mL, 4.27 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. Compound (E)-4-[isopropyl(methyl)amino]but-2-enoic acid (1.6 g, crude) was obtained as a white solid. LCMS: m/z 158.2 $[M+H]^+$. ^{1}H NMR (MeOD, 400 MHz) δ 6.61-6.54 (m, 1H), 5.97-5.93 (m, 1H), 3.73-3.66 (m, 1H), 3.58-3.53 (m, 1H), 2.97-2.95 (m, 1H), 2.42 (s, 3H), 1.07-1.00 (m, 6H).

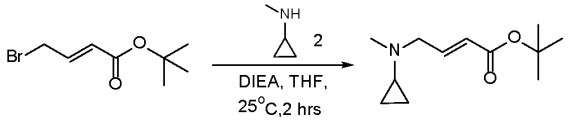
Step 1.4 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[isopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01157] To a solution of (E)-4-[isopropyl(methyl)amino]but-2-enoic acid (86.48 mg, 550.11 µmol, 1.2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxamide (150 mg, 458.42 µmol, 1 eq, HCl) in THF (3 mL) were added DIEA (118.50 mg, 916.85 µmol, 159.70 µL, 2 eq) and HATU (209.17 mg, 550.11 µmol, 1.2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-50% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-[isopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (62.8 mg, 141.01 µmol, 30.76% yield, 96.538% purity) was obtained as a white solid. LCMS: m/z 430.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.55 (td, J = 8.4 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 0.8 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.71 (m, 2H), 5.29-5.16 (m, 1H), 5.06 (br.s, 1H), 4.71-4.55 (m, 1H), 4.34-4.25 (m, 1H), 3.72-3.69 (m, 0.5H), 3.27-3.22 (m, 0.5H), 3.18 (d, J = 3.6 Hz, 2H), 2.83-2.74 (m, 1H), 2.11 (s, 3H), 1.30-1.25 (m, 3H), 0.96 (d, J = 6.4 Hz, 6H).

Example 183: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[cyclopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of tert-butyl (E)-4-[cyclopropyl(methyl)amino]but-2-enoate.

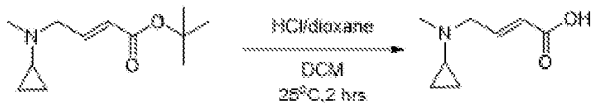


1 3

[01158] To a solution of tert-butyl (E)-4-bromobut-2-enoate (2.77 g, 12.51 mmol, 1 eq) and N-methylcyclopropanamine (0.89 g, 12.51 mmol, 1 eq) in THF (15 mL) was added DIEA (2.43 g, 18.77 mmol, 3.27 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent at 25°C. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). The

eluent was removed under reduced pressure. Compound tert-butyl (E)-4-[cyclopropyl(methyl)amino]but-2-enoate (1.8 g, 8.52 mmol, 68.07% yield) was obtained as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 (dt, J = 12.4 Hz, 6.0 Hz, 1H), 5.85 (dt, J = 15.6 Hz, 1.6 Hz, 1H), 3.24 (dd, J = 6.0 Hz, 1.2 Hz, 2H), 2.21 (s, 3H), 1.73-1.68 (m, 1H), 1.42 (s, 9H), 0.44-0.41 (m, 2H), 0.32-0.29 (m, 2H).

Step 1.2 Synthesis of (E)-4-[cyclopropyl(methyl)amino]but-2-enoic acid.



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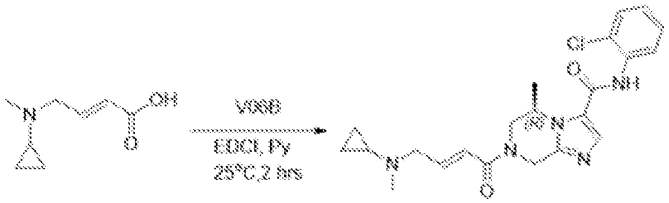
[01159] To a solution of tert-butyl (E)-4-[cyclopropyl(methyl)amino]but-2-enoate (1.8 g, 8.52 mmol, 1 eq) in DCM (18 mL) was added HCl/dioxane (4 M, 18 mL, 8.45 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed tert-butyl (E)-4-[cyclopropyl(methyl)amino]but-2-enoate was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound (E)-4-[cyclopropyl(methyl)amino]but-2-enoic acid (1.1 g, 5.74 mmol, 67.38% yield, HCl)was obtained as yellow oil. LCMS: m/z 156.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 12.75 (s, 1H), 11.31 (s, 1H), 6.93-6.86 (m, 1H), 6.19 (d, J = 15.6 Hz, 1H), 3.99 (t, J = 8.0 Hz, 2H), 2.75 (s, 3H), 1.11-1.07 (m, 2H), 0.79 (s, 2H).

Step 1.3 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-[cyclopropyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

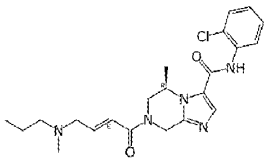


[01160] To a solution of (E)-4-[cyclopropyl(methyl)amino]but-2-enoic acid (142.29 mg, 916.85 μmol, 1.2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxamide (250 mg, 764.04 μmol, 1 eq, HCl) in Pyridine (3 mL) was added EDCI (292.93 mg, 1.53 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxamide was consumed. One new peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5 um; mobile

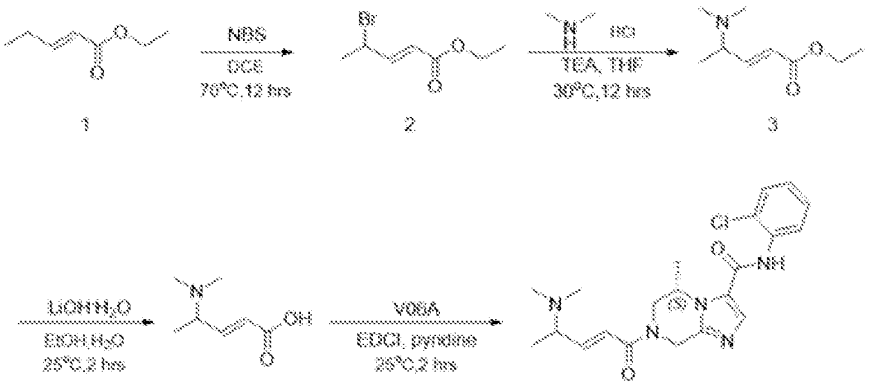
phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 50% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-[cyclopropyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (66.2 mg, 148.91 μmol, 19.49% yield, 96.26% purity) was obtained as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 9.85 (s, 1H), 7.88 (s, 1H), 7.53 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 2.0 Hz, 1H), 6.77-6.68 (m, 2H), 5.28-5.16 (m, 1H), 5.07-5.03 (m, 1H), 4.71-4.53 (m, 1H), 4.35-4.25 (m, 1H), 3.71-3.65 (m, 0.5H), 3.33 (s, 0.5H), 3.29 (d, J = 4.8 Hz, 2H), 2.23 (s, 3H), 1.70-1.69 (m, 1H), 1.28-1.24 (m, 3H), 0.42-0.41 (m, 2H), 0.32-0.31 (m, 2H).

[01161] Compounds in Table RA were synthesized following the procedure for (5R)-N-(2-chlorophenyl)-7-[(E)-4-[cyclopropyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

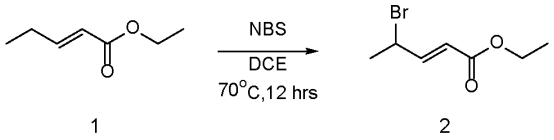
Table RA

Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-[methyl(propyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.71 (m, 2H), 5.28-5.17 (m, 1H), 5.09-4.99 (m, 1H), 4.69-4.57 (m, 1H), 4.34-4.22 (m, 1H), 3.75-3.68 (m, 0.5H), 3.27-3.22 (m, 0.5H), 3.29 (d, J = 4.0 Hz, 2H), 2.30-2.24 (m, 2H), 2.14 (s, 3H), 1.47-1.38 (m, 2H), 1.29-1.25 (m, 3H), 0.84 (t, J = 6.8 Hz, 3H).	LCMS: m/z 430.2 $[M+H]^+$

Example 184: Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

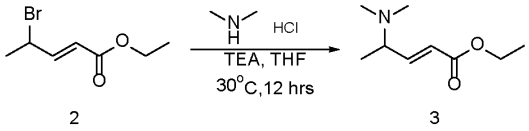


Step 1.1 Synthesis of ethyl (E)-4-bromopent-2-enoate.



[01162] To a solution of ethyl (E)-pent-2-enoate (5 g, 39.01 mmol, 1 eq) in DCM (50 mL) was added NBS (10.41 g, 58.52 mmol, 1.5 eq) in portions at 0°C. The reaction mixture was warmed to 25°C and then heated to 70°C and was stirred at 70°C for 12 hrs. The reaction mixture was cooled to 25°C and then concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). The eluent was removed under reduced pressure. Compound ethyl (E)-4-bromopent-2-enoate (4 g, 19.32 mmol, 49.52% yield) was obtained as white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (dd, J = 15.6 Hz, 8.4 Hz, 1H), 6.09 (d, J = 15.6 Hz, 1H), 5.09-5.02 (m, 1H), 4.03 (q, J = 7.2 Hz, 2H), 1.76 (d, J = 6.8 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H).

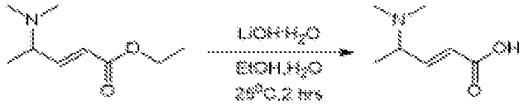
Step 1.2 Synthesis of ethyl (E)-4-(dimethylamino)pent-2-enoate



[01163] To a solution of N-methylmethanamine (2.36 g, 28.98 mmol, 2.65 mL, 1.5 eq, HCl) in THF (30 mL) was added TEA (5.86 g, 57.95 mmol, 8.07 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 0.5 hr. To the reaction mixture was added ethyl (E)-4-bromopent-2-enoate (4 g, 19.32 mmol, 1 eq) at 25°C. The reaction mixture was heated to 30°C and was stirred at 30°C for 12 hrs. The reaction mixture was filtered to remove the insoluble.

The filter liquor was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 50mL/min) and concentrated under reduced pressure to remove solvent. Compound ethyl (E)-4-(dimethylamino)pent-2-enoate (1.69 g, 9.87 mmol, 51.09% yield) was obtained as yellow oil.

Step 1.3 Synthesis of (E)-4-(dimethylamino)pent-2-enoic acid.



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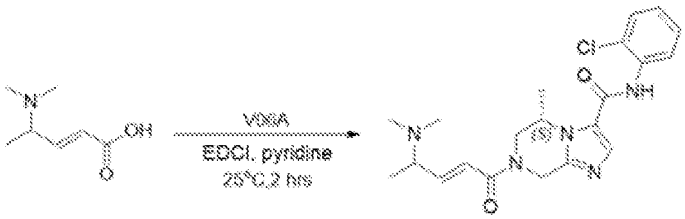
[01164] To a solution of ethyl (E)-4-(dimethylamino)pent-2-enoate (1.59 g, 9.29 mmol, 1 eq) in EtOH (11 mL) and H_2O (4 mL) was added $LiOH·H_2O$ (1.17 g, 27.86 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed ethyl (E)-4-(dimethylamino)pent-2-enoate was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was added HCl (3 M) to adjust pH = 3 at 0°C. Then the mixture was purified by prep-HPLC (column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1%- 5% B over 20.0 min. The residue was dried over lyophilization. Compound (E)-4-(dimethylamino)pent-2-enoic acid (2.29 g, crude) was obtained as white oil. LCMS: m/z 144.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.74 (dd, J = 16.0 Hz, 7.6 Hz, 1H), 5.93 (d, J = 15.6 Hz, 1H), 3.38 (t, J = 6.8 Hz, 1H), 2.28 (s, 6H), 1.17 (d, J = 6.8 Hz, 3H).

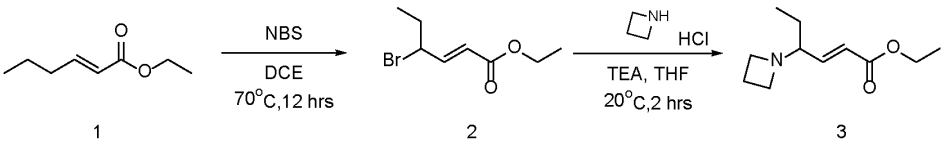
Step 1.4 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

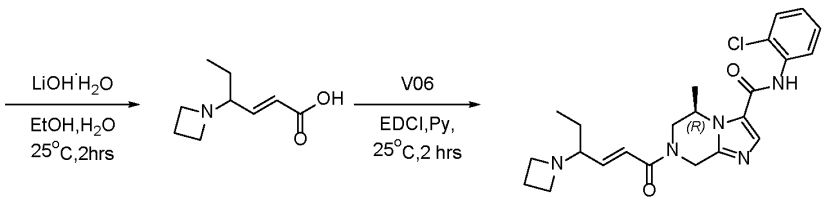


[01165] To a solution of (E)-4-(dimethylamino)pent-2-enoic acid (157.59 mg, 825.46 μmol, 1.2 eq) and (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (200 mg, 687.88 μmol, 1 eq) in Pyridine (3 mL) was added EDCI (263.74 mg, 1.38 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LC-MS showed (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide was consumed. One new peak with desired MS was detected. The reaction mixture was

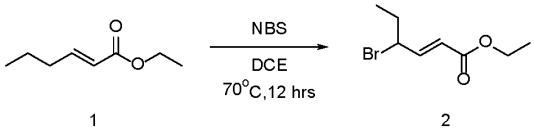
concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 15%- 50% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-3-carboxamide (74 mg, 174.81 μmol, 25.41% yield, 98.25% purity) was obtained as a white solid. LCMS: m/z 416.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.55-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.74-6.61 (m, 2H), 5.28-5.16 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.40-4.22 (m, 1H), 3.71 (d, J = 15.6 Hz, 0.5H), 3.20-3.22 (m, 0.5H), 3.17-3.10 (m, 1H), 2.14 (s, 6H), 1.30-1.22 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H).

Example 185: Synthesis of (5R)-7-((E)-4-(azetidin-1-yl)hex-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.





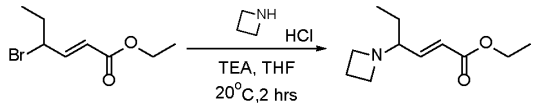
Step 1.1 Synthesis of ethyl (E)-4-bromohex-2-enoate



[01166] To a solution of ethyl (E)-hex-2-enoate (5 g, 35.16 mmol, 1 eq) in DCE (50 mL) was added NBS (9.39 g, 52.74 mmol, 1.5 eq) in portions at 0°C. The reaction mixture was warmed to 20°C and then heated to 70°C and stirred at 70°C for 12 hrs. The reaction mixture was cooled to 25°C and was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage ®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100mL/min), concentrated under reduced pressure to remove solvent. Compound ethyl (E)-4-bromohex-2-enoate (6.84 g, 30.94 mmol, 87.98% yield) was obtained as white oil. ^1H NMR (400 MHz, DMSO-d_6) δ 6.95-6.84

(m, 1H), 6.08 (d, *J* = 15.6 Hz, 1H), 4.91-4.80 (m, 1H), 4.18-4.11 (m, 2H), 1.96-1.88 (m, 2H), 1.25-1.19 (m, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).

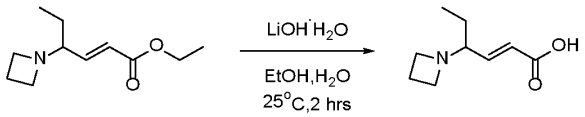
Step 1.2 Synthesis of ethyl (E)-4-(azetidin-1-yl)hex-2-enoate.



2 3

[01167] To a solution of azetidine (825.15 mg, 8.82 mmol, 975.35 µL, 1.5 eq, HCl) in THF (15 mL) was added TEA (1.78 g, 17.64 mmol, 2.46 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 0.5 hr and then ethyl (E)-4-bromohex-2-enoate (1.3 g, 5.88 mmol, 1 eq) was added at 25°C. The reaction mixture was stirred at 25°C for 12 hrs. The mixture reaction filtered to remove the insoluble. The filter liquor was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography **(**Biotage ®; 20 g SepaFlash® Silica Flash Column, Eluent of 10~30% Ethyl acetate/Petroleum ether gradient @ 50mL/min**)** and concentrated under reduced pressure to remove solvent. Compound ethyl (E)-4-(azetidin-1-yl)hex-2-enoate (1.6 g, 8.11 mmol, 26.22% yield) was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.52 (dd, *J* = 15.6 Hz, 7.6 Hz, 1H), 5.92 (d, *J* = 16.0 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 8.0 Hz, 4H), 2.75-2.68 (m, 1H), 1.96-1.86 (m, 2H), 1.47-1.44 (m, 1H), 1.32-1.08 (m, 4H), 0.73 (t, *J* = 7.2 Hz, 3H).

Step 1.3 Synthesis of (E)-4-(azetidin-1-yl)hex-2-enoic acid.

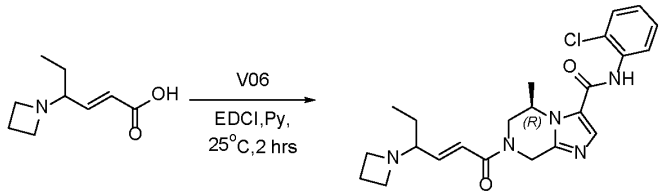


3 Acid 39

[01168] To a solution of ethyl (E)-4-(azetidin-1-yl)hex-2-enoate (1.5 g, 7.60 mmol, 1 eq) in EtOH (6 mL) and H_2O (3 mL) was added LiOH·H2O (638.10 mg, 15.21 mmol, 2 eq) at 20°C. The reaction mixture was stirred at 20°C for 2 hrs. LC-MS showed ethyl (E)-4-(azetidin-1-yl)hex-2-enoate was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was added HCl (3M) to adjust pH =3 at 0°C. The residue was purified by prep-HPLC column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 1%-10% B over 20.0 min. The residue was dried over lyophilization. Compound (E)-4-(azetidin-1-yl)hex-2-enoic acid (0.991 g, 5.86 mmol, 77.02% yield) was obtained as yellow oil. LCMS: m/z 170.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.587 (s, 1H), 6.52 (dd, *J* = 15.6 Hz, 8.8 Hz, 1H), 6.18 (d, *J* = 15.6 Hz,

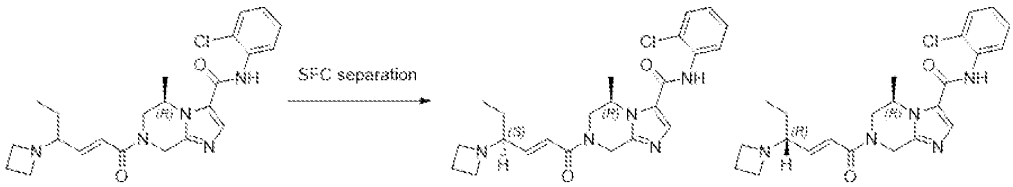
1H), 3.96 (d, *J* = 57.2 Hz, 5H), 2.43-2.28 (m, 1H), 2.18 (s, 1H), 1.79-1.67 (m, 1H), 1.57-1.45 (m, 1H), 0.80 (t, *J* = 7.6 Hz, 3H).

Step 1.4 Synthesis of (5R)-7-((E)-4-(azetidin-1-yl)hex-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



[01169] To a solution of (E)-4-(azetidin-1-yl)hex-2-enoic acid (64.02 mg, 378.34 μmol, 1.1 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (100 mg, 343.94 μmol, 1 eq) in Pyridine (2 mL) was added EDCI (131.87 mg, 687.88 μmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Phenomenex Genimi NX C_{18} 150 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:15%-40% B over 8.0 min). The residue was dried over lyophilization. Compound (5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (135 mg, 305.46 μmol, 88.81% yield) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$. HPLC: 93.45% purity. ^1H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.58-7.50 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz,1H), 7.29 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.74-6.63 (m, 1H), 6.48-6.36 (m, 1H), 5.29-5.17 (m, 1H), 5.05-5.00 (m, 1H), 4.73-4.51 (m, 1H), 4.40-4.18 (m, 1H), 3.76-3.67 (m, 0.5H), 3.27-3.23 (m, 0.5H), 3.13-2.99 (m, 4H), 2.78-2.73 (m, 1H), 1.95-1.85 (m, 2H), 1.50-1.42 (m, 1H), 1.32-1.15 (m, 4H), 0.75 (q, *J* = 7.2 Hz, 3H).

Example 186: Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-7-[(E,4R)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



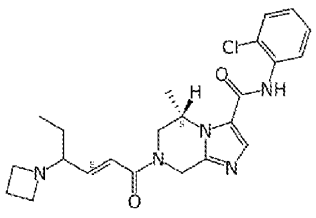
[01170] (5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.13 g, 294.15 μmol, 1 eq) was separated by SFC (column: ChiralPak IH, 250 * 30 mm, 10 um; mobile phase: [CO_2-EtOH(0.1% NH_3H_2O)]; B%:30%, isocratic elution mode) to give (5R)-7-[(E,4R)-4-(azetidin-1-yl)hex-2-enoyl] -N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (50 mg, 113.13 μmol, 38.46% yield) and (5R)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl] -N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (50 mg, 113.13 μmol, 38.46% yield) were obtained as a white solid.

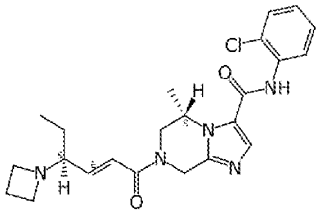
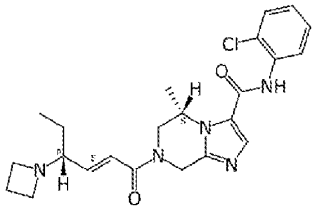
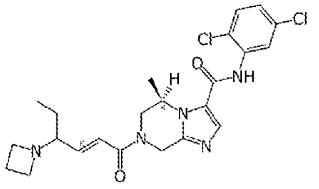
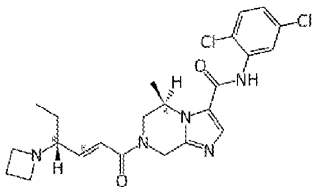
[01171] LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.58-7.50 (m, 2H), 7.42-7.34 (m, 1H), 7.33-7.27 (m, 1H), 6.76-6.62 (m, 1H), 6.49-6.34 (m, 1H), 5.32-5.15 (m, 1H), 5.05 (d, J = 1.2 Hz, 1H), 4.74-4.52 (m, 1H), 4.36-4.24 (m, 1H), 3.79-3.69 (m, 0.5H), 3.24 (d, J = 2.4 Hz, 0.5H), 3.19-2.98 (m, 4H), 2.90-2.73 (m, 1H), 2.06-1.87 (m, 2H), 1.56-1.43 (m, 1H), 1.33-1.21 (m, 4H), 0.76 (t, J = 7.2 Hz, 3H).

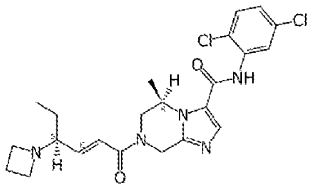
[01172] LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.58-7.50 (m, 2H), 7.40-7.35 (m, 1H), 7.32-7.26 (m, 1H), 6.73-6.58 (m, 1H), 6.52-6.31 (m, 1H), 5.30-5.16 (m, 1H), 5.05 (s, 1H), 4.73-4.52 (m, 1H), 4.40-4.20 (m, 1H), 3.78-3.65 (m, 0.5H), 3.23 (d, J = 2.4 Hz, 0.5H), 3.16-3.01 (m, 4H), 2.87-2.70 (m, 1H), 1.93 (s, 2H), 1.54-1.44 (m, 1H), 1.32-1.19 (m, 4H), 0.83-0.67 (m, 3H).

[01173] Compounds in Table S were synthesized following the procedure for (5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

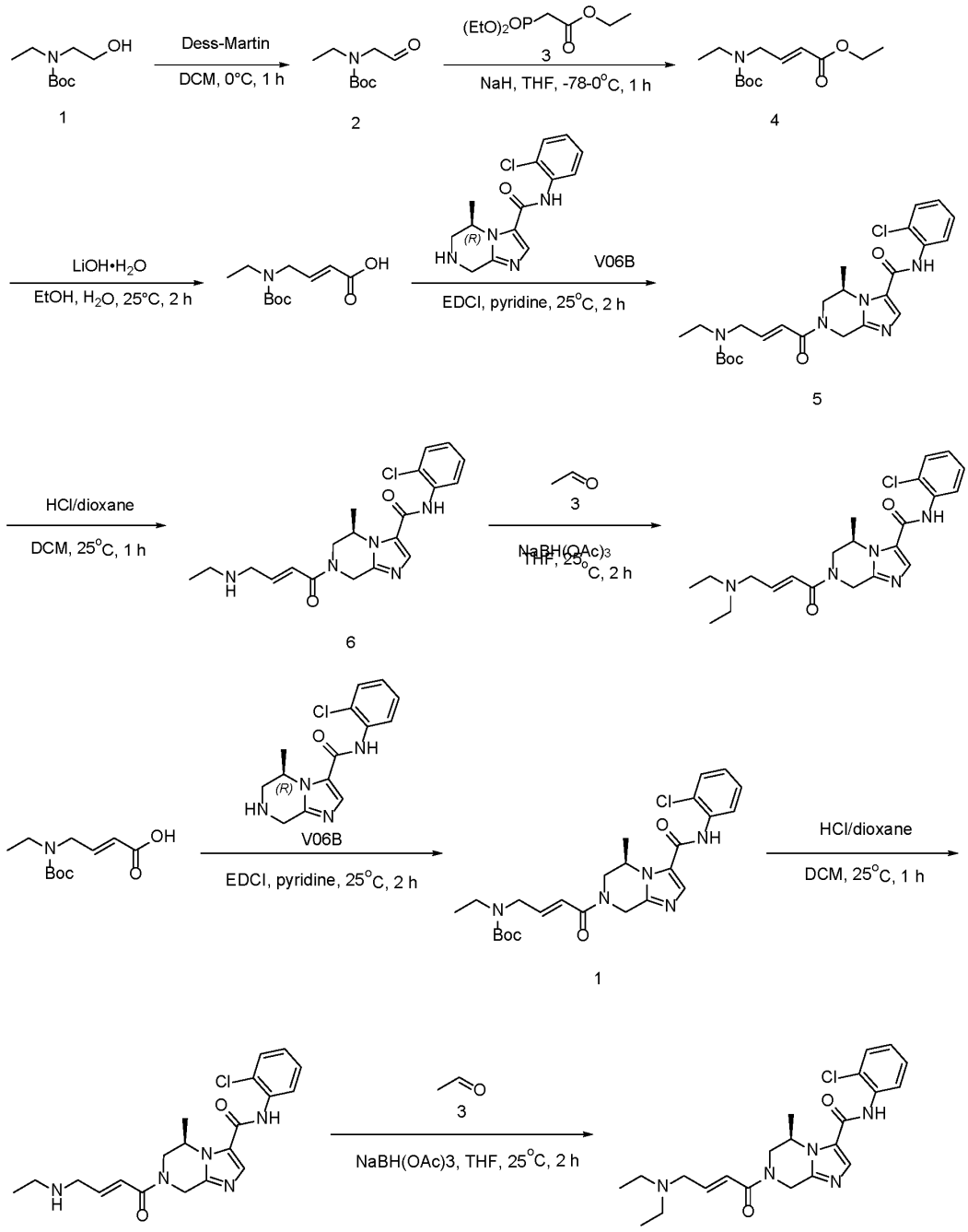
Table S

Name	Structure	NMR	LCMS	SFC conditions
(5S)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br.s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.67-6.63 (m, 1H), 6.50-6.36 (m, 1H), 5.28-5.16 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.29 (t, J = 17.6 Hz, 0.5H), 3.70 (d, J = 14.4 Hz, 0.5H), 3.08-3.02 (m, 4H), 2.76-2.73 (m, 1H), 1.93-1.89 (m, 2H), 1.50-1.43 (m, 1H), 1.29-1.24 (m, 4H), 0.77-0.72 (m, 3H).	LCMS: m/z 442.2 $[M+H]^+$	

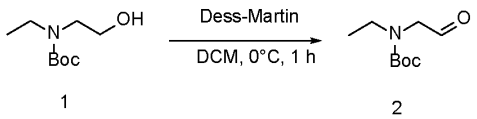
Name	Structure	NMR	LCMS	SFC conditions
(5S)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (br.s, 1H), 7.89 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 14.4 Hz, 1H), 6.48-6.37 (m, 1H), 5.28-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.30 (t, *J* = 17.2 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 0.5H), 3.20-3.15 (m, 0.5H), 3.10 (s, 4H), 2.79 (s, 1H), 1.94-1.91 (m, 2H), 1.48 (s, 1H), 1.29-1.24 (m, 4H), 0.74 (t, *J* = 6.8 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$	
(5S)-7-[(E,4R)-4- (azetidin-1-yl)hex-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (br.s, 1H), 7.88 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 14.4 Hz, 1H), 6.46-6.40 (m, 1H), 5.29-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.35-4.24 (m, 1H), 3.79-3.69 (m, 0.7H), 3.20-3.15 (m, 0.3H), 3.10 (s, 4H), 2.78 (s, 1H), 1.93-1.91 (m, 2H), 1.51-1.45 (m, 1H), 1.28-1.25 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$	
(5R)-7-[(E)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.91 (br s, 1H), 7.89 (s, 1H), 7.70 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.48-6.37 (m, 1H), 5.30-5.15 (m, 1H), 5.06 (s, 1H), 4.70-4.55 (m, 1H), 4.36-4.23 (m, 1H), 3.70 (d, *J* = 14.0 Hz, 0.6H), 3.15-3.10 (m, 0.4H), 3.08-3.02 (m, 4H), 2.77-2.73 (m, 1H), 1.94-1.89 (m, 2H), 1.52-1.44 (m, 1H), 1.29-1.24 (m, 4H), 0.77-0.72 (m, 3H)	LCMS: m/z 476.1 $[M+H]^+$	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.65 (d, *J* = 14.8 Hz, 1H), 6.48-6.37 (m, 1H), 5.29-5.17 (m, 1H), 5.04 (s, 1H), 4.71-4.55 (m,	LCMS: m/z 476.1 $[M+H]^+$	SFC (column: Chiral Pak IH, 250 × 30 mm, 10 um; mobile phase: [CO_2 - EtOH (0.1%

Name	Structure	NMR	LCMS	SFC conditions
a]pyrazine-3-carboxamide		1H), 4.34-4.25 (m, 1H), 3.70 (d, *J* = 13.4 Hz, 0.6H), 3.15-3.10 (m, 0.4H), 3.09-3.04 (m, 4H), 2.78-2.74 (m, 1H), 1.95-1.88 (m, 2H), 1.52-1.42 (m, 1H), 1.29-1.25 (m, 4H), 0.76-0.72 (m, 3H).		$NH_3 \cdot H_2O$)]; B%: 30%, isocratic elution mode).
(5R)-7-[(E,4S)-4-(azetidin-1-yl)hex-2-enoyl]-N-(2,5-dichlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.91 (s, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.67 (d, *J* = 14.8 Hz, 1H), 6.46-6.40 (m, 1H), 5.30-5.18 (m, 1H), 5.04 (s, 1H), 4.71-4.56 (m, 1H), 4.29 (t, *J* = 15.6 Hz, 1H), 3.72-3.68 (d, *J* = 14.4 Hz, 0.6H), 3.15-3.10 (m, 0.4H), 3.08 (s, 4H), 2.78 (s, 1H), 1.93-1.90 (m, 2H), 1.52-1.43 (m, 1H), 1.29-1.21 (m, 4H), 0.75 (t, *J* = 7.6 Hz, 3H).	LCMS: m/z 476.1 $[M+H]^+$	SFC (column: Chiral Pak IH, 250 × 30 mm, 10 um; mobile phase: [CO_2 - EtOH (0.1% $NH_3 \cdot H_2O$)]; B%: 30%, isocratic elution mode).

Example 187: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-N-(2-chlorophenyl)-7-[(E)-4-(diethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



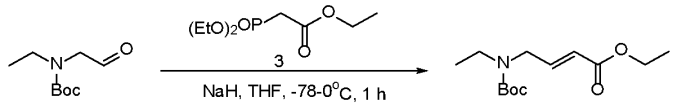
Step 1.1 Synthesis of tert-butyl N-ethyl-N-(2-oxoethyl)carbamate



[01174] To a solution of tert-butyl N-ethyl-N-(2-hydroxyethyl)carbamate (15 g, 79.26 mmol, 1 *eq*) in DCM (300 mL) was added Dess-Martin (34.29 g, 80.84 mmol, 1.02 *eq*) at 0°C. The

mixture was stirred at 0°C for 1 h. The reaction mixture was quenched by addition of aq. $NaHCO_3$ (100 mL) and filtered. Then the filtrate was extracted with DCM (150 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage ®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100mL/min). Compound tert-butyl N-ethyl-N-(2-oxoethyl)carbamate (14 g, 74.77 mmol, 94.34% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.46 (d J = 10.8 Hz, 1H), 3.97 (s, 2H), 3.23-3.22 (m, 2H), 1.45-1.33 (m, 9H), 1.05-0.98 (m, 3H).

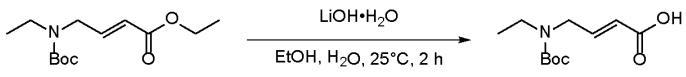
Step 1.2 Synthesis of ethyl (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoate



2 4

[01175] To a solution of NaH (3.59 g, 89.73 mmol, 60% purity, 1.2 *eq*) in THF (200 mL) was added ethyl 2-diethoxyphosphorylacetate (20.12 g, 89.73 mmol, 17.80 mL, 1.2 *eq*) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl N-ethyl-N-(2-oxoethyl)carbamate (14 g, 74.77 mmol, 1 *eq*) in THF (50 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (100 mL) at 0°C, and then diluted with EtOAc (80 mL x 2). The combined organic phase was washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (**B**iotage ®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound ethyl (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoate (10.4 g, 40.42 mmol, 54.05% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.79-6.74 (m, 1H), 5.81 (d, J = 15.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.93 (d, J = 4.4 Hz, 2H), 3.16 (d, J = 5.6 Hz, 2H), 1.39 (s, 9H), 1.24-1.19 (m, 3H), 1.03-1.00 (m, 3H).

1.3 Synthesis of (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoic acid

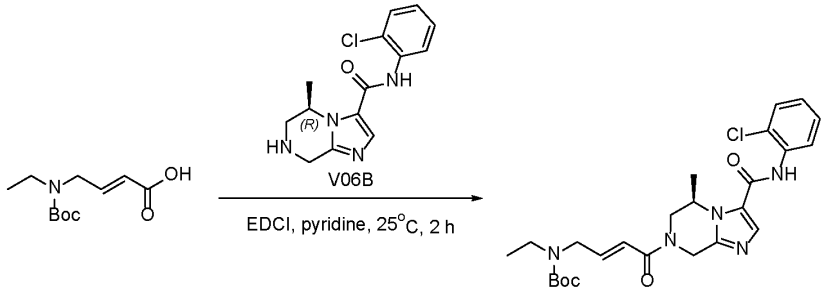


4

[01176] To a solution of ethyl (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoate (10.4 g, 40.42 mmol, 1 *eq*) in EtOH (100 mL) and H_2O (20 mL) was added LiOH•H_2O (3.39 g, 80.83

mmol, 2 *eq*) at 25°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated to remove EtOH, the residue was quenched with water (20 mL), the residue was adjusted pH = 5 with 4N HCl, and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoic acid (9.2 g, 40.13 mmol, 99.29% yield) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.32 (br.s, 1H), 6.73-6.66 (m, 1H), 5.76-5.72 (m, 1H), 3.90 (d, J = 4.4 Hz, 2H), 3.17-3.15 (m, 2H), 1.43-1.39 (m, 9H), 1.06-1.00 (m, 3H).

Step 1.3.1 Synthesis of tert-butyl N-[(E)-4-[(5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-N-ethyl-carbamate



1

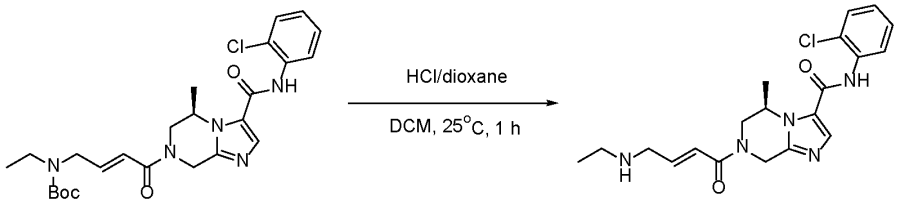
[01177] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (800 mg, 2.44 mmol, 1 eq, HCl) in DCM (8 mL) were added (E)-4-[tert-butoxycarbonyl(ethyl)amino]but-2-enoic acid (672.66 mg, 2.93 mmol, 1.2 eq), DIEA (1.26 g, 9.78 mmol, 1.70 mL, 4 eq) and T_4P (1.76 g, 4.89 mmol, 2 eq) in one portion at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 h. The reaction mixture was quenched with water (10 mL) and stirred for 2 min at 25°C. The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 75 mL/min) to give tert-butyl N-[(E)-4-[(5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-N-ethyl-carbamate (900 mg, 1.79 mmol, 73.33% yield) as yellow oil.

[01178] LCMS: m/z 502.0 $[M+H]^+$.

[01179] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.69-6.59 (m, 2H),

5.29-5.06 (m, 2H), 4.70-4.57 (m, 1H), 4.31-4.22 (m, 1H), 3.95-3.94 (m, 2H), 3.72 (d, *J* = 12.0 Hz, 0.5H), 3.29-3.25 (m, 0.5H), 3.20-3.16 (m, 2H), 1.40 (s, 9H), 1.29-1.25 (m, 3H), 1.04 (t, *J* = 6.8 Hz, 3H).

1.3.2 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



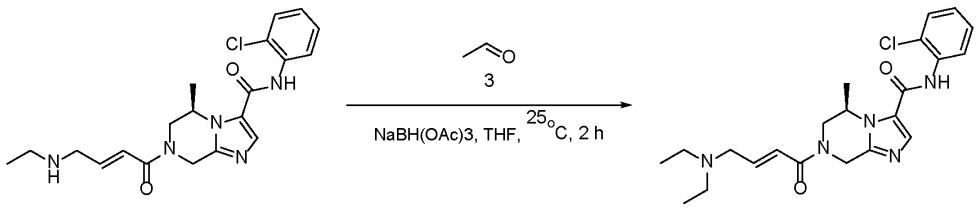
1

[01180] To a solution of tert-butyl N-[(E)-4-[(5R)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-N-ethyl-carbamate (900 mg, 1.79 mmol, 1 eq) in DCM (10 mL) was added HCl/dioxane (4 M, 4.74 mL, 10.57 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 250 * 50 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-40% B over 10.0 min) to give (5R)-N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (550.1 mg, 11.66 μmol, 57.41% yield, 91.90% purity) as a yellow solid, 5.1 mg was for delivery, the rest was used to prepare the title compound.

[01181] LCMS: m/z 402.1 $[M+H]^+$.

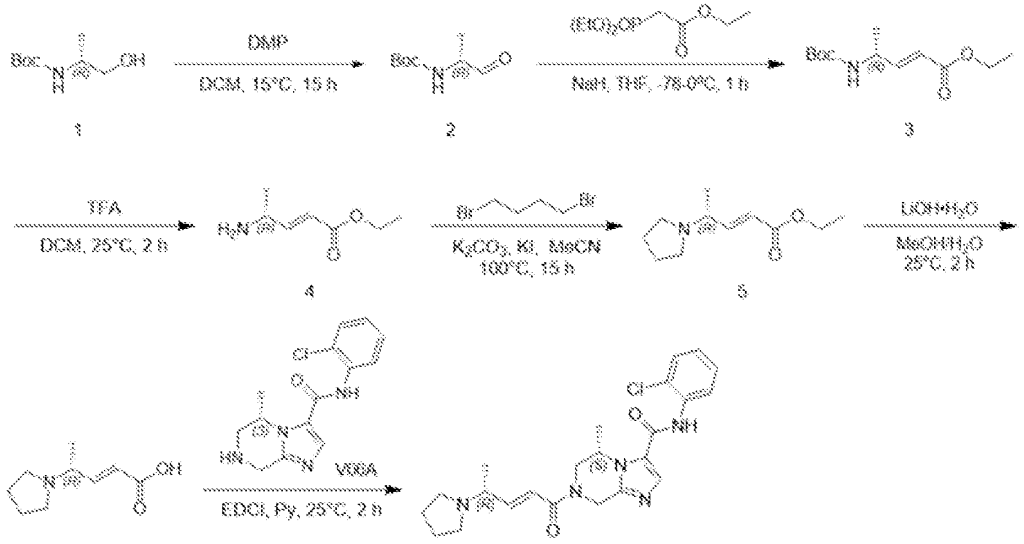
[01182] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.82-6.64 (m, 2H), 5.28-5.20 (m, 1H), 5.05 (s, 1H), 4.69-4.54 (m, 1H), 4.32-4.25 (m, 1H), 3.71-3.65 (m, 1H), 3.25-3.22 (m, 2H), 2.54-2.52 (m, 2H), 1.30-1.25 (m, 3H), 1.02 (t, *J* = 7.2 Hz, 3H).

Step 1.3.3 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(diethylamino)but-2-enoyl]-5-methyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

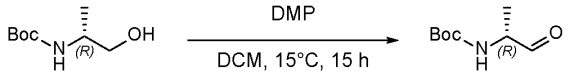


[01183] To a solution of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(ethylamino)but-2-enoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (200 mg, 497.65 μmol, 1 eq) in THF (2 mL) were added ACETALDEHYDE (5 M, 149.29 μL, 1.5 eq) and $NaBH(OAc)_3$ (210.94 mg, 995.30 μmol, 2 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was poured into water (1 mL) at 25°C and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 * 40 * 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-60% B over 8.0 min) to give (5R)-N-(2-chlorophenyl)-7-[(E)-4- (diethylamino)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (230.4 mg, 528.65 μmol, 53.11% yield, 98.65% purity) as a white solid. LCMS: m/z 430.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.80-6.71 (m, 2H), 5.29-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.30-4.25 (m, 1H), 3.70 (d, J = 13.6 Hz, 0.6H), 3.28-3.27 (m, 0.4H), 3.22 (d, J = 4.0 Hz, 2H), 2.47-2.43 (m, 4H), 1.29-1.28 (m, 3H), 0.97 (t, J = 7.2 Hz, 6H).

Example 188: Synthesis of (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



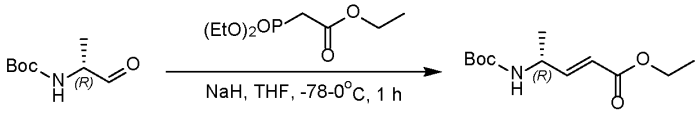
Step 1.1 Synthesis of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl] carbamate -



1 2

[01184] To a solution of tert-butyl N-[(1R)-2-hydroxy-1-methyl-ethyl] carbamate (40 g, 228.28 mmol, 1 *eq*) in DCM (800 mL) was added Dess-Martin (116.19 g, 273.93 mmol, 84.87 mL, 1.2 *eq*) at 15°C. The reaction mixture was stirred at 15°C for 15 h. The reaction mixture was quenched by sat. aq. $NaHCO_3$ (200 mL) at 0°C, and then the mixture was filtered over a celite pad, the filtrate was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl] carbamate (35 g, 202.07 mmol, 88.52% yield) was obtained as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.56 (s, 1H), 5.13 (s, 1H), 4.23 (t, J = 6.0 Hz, 1H), 1.45 (s, 9H), 1.33 (d, J = 7.6 Hz, 3H).

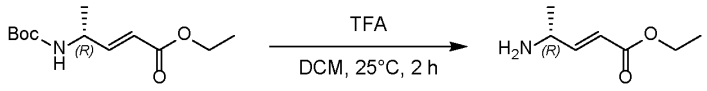
1.2 Synthesis of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate



2 3

[01185] To a solution of NaH (5.54 g, 138.56 mmol, 60% purity, 1.2 *eq*) in THF (150 mL) was added ethyl 2-diethoxyphosphorylacetate (31.06 g, 138.56 mmol, 27.49 mL, 1.2 *eq*) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl] carbamate (20 g, 115.47 mmol, 1 *eq*) in THF (150 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (200 mL) at 0°C, and then diluted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (200 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 120 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (22 g, 90.42 mmol, 78.31% yield) was obtained as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.91-6.86 (m, 1H), 5.93-5.89 (m, 1H), 4.51-4.37 (m, 1H), 4.23-4.12 (m, 2H), 1.45 (s, 9H), 1.31-1.25 (m, 6H).

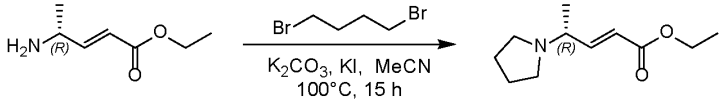
Step 1.3 Synthesis of ethyl (E,4R)-4-aminopent-2-enoate



3 4

[01186] To a solution of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (16 g, 65.76 mmol, 1 *eq*) in DCM (200 mL) was added TFA (30.70 g, 269.24 mmol, 20 mL, 4.09 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The mixture was concentrated under reduced pressure. Compound ethyl (E,4R)-4-aminopent-2-enoate (20 g, crude, TFA) was obtained as brown oil. LCMS: m/z 144.3 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.95-6.89 (m, 1H), 6.12 (d, J = 16.0 Hz, 1H), 4.26-4.16 (m, 3H), 1.53 (d, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H).

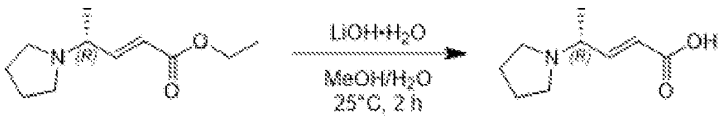
Step 1.4 Synthesis of ethyl (E,4R)-4-pyrrolidin-1-ylpent-2-enoate



4 5

[01187] A mixture of ethyl (E,4R)-4-aminopent-2-enoate (5 g, 19.44 mmol, 1 *eq*, TFA), 1,4-dibromobutane (6.30 g, 29.16 mmol, 3.52 mL, 1.5 *eq*), K_2CO_3 (13.43 g, 97.20 mmol, 5 *eq*) and KI (322.70 mg, 1.94 mmol, 0.1 *eq*) in MeCN (100 mL) was degassed and purged with N_2 for 3 times at 25°C, and then the mixture was stirred at 100°C for 15 h under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated. Compound ethyl (E,4R)-4-pyrrolidin-1-ylpent-2-enoate (4 g, crude) was obtained as brown oil. LCMS: m/z 198.2 $[M+H]^+$.

Step 1.5 Synthesis of (E,4R)-4-pyrrolidin-1-ylpent-2-enoic acid

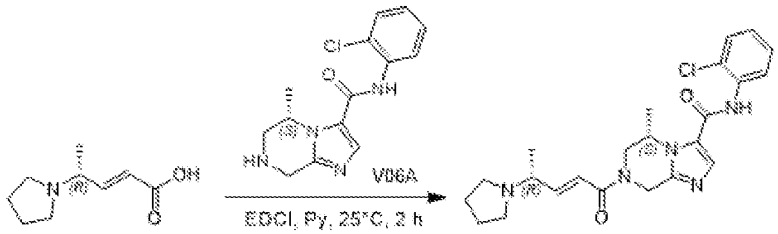


5

[01188] To a solution of ethyl (E,4R)-4-pyrrolidin-1-ylpent-2-enoate (4 g, 20.28 mmol, 1 *eq*) in MeOH (30 mL) and H_2O (10 mL) was added LiOH•H_2O (2.13 g, 50.69 mmol, 2.5 *eq*) at 25°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated, the residue was adjusted pH = 4 with 4 N HCl. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 0%-30% B over 18.0 min). Compound (E,4R)-4-pyrrolidin-1-ylpent-2-enoic acid (1.8 g, 10.64 mmol, 52.46% yield) was obtained as a white solid. LCMS: m/z 170.2 $[M+H]^+$.

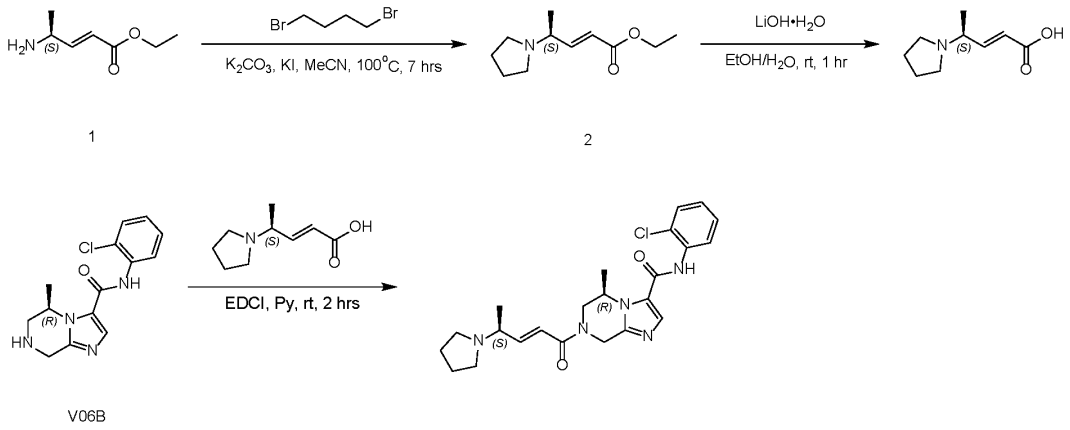
^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.86-12.63 (m, 1H), 11.65-11.56 (m, 1H), 6.87-6.81 (m, 1H), 6.15 (d, J = 15.6 Hz, 1H), 4.08-4.05 (m, 1H), 3.47-3.34 (m, 2H), 2.98 (s, 2H), 2.12-1.76 (m, 4H), 1.43 (d, J = 6.8 Hz, 3H).

Step 1.6 Synthesis of (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



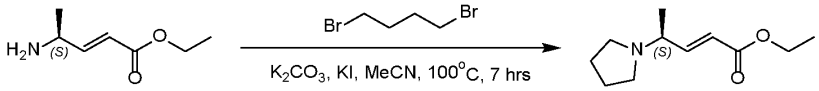
[01189] To a solution of (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.07 g, 240.76 µmol, 1 *eq*) and (E,4R)-4-pyrrolidin-1-ylpent-2-enoic acid (48.89 mg, 288.91 µmol, 1.2 *eq*) in pyridine (2 mL) was added EDCI (92.31 mg, 481.52 µmol, 2 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-55% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.0365 g, 81.07 µmol, 33.67% yield, 98.158% purity) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.4 Hz, 1.6 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.69-6.68 (m, 2H), 5.27-5.18 (m, 1H), 5.04 (s, 1H), 4.70-4.56 (m, 1H), 4.32-4.26 (m, 1H), 3.69 (d, J = 13.6 Hz, 1H), 3.34 (s, 1H), 3.29-3.23 (m, 1H), 3.04-3.03 (m, 1H), 2.44-2.41 (m, 2H), 1.66 (s, 4H), 1.30-1.24 (m, 3H), 1.16 (d, J = 5.6 Hz, 3H).

Example 189: Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



1 2 V06B

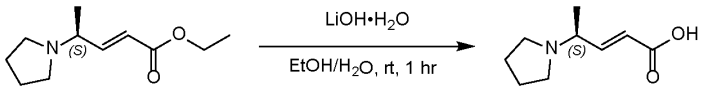
Step 3.3.1 Synthesis of ethyl (E,4S)-4-pyrrolidin-1-ylpent-2-enoate



1 2

[01190] A mixture of ethyl (E,4S)-4-aminopent-2-enoate (5.00 g, 27.83 mmol, 1 *eq*, HCl), 1,4-dibromobutane (7.21 g, 33.40 mmol, 4.03 mL, 1.2 *eq*), K_2CO_3 (19.23 g, 139.16 mmol, 5 *eq*) and KI (462.02 mg, 2.78 mmol, 0.1 *eq*) in MeCN (100 mL) were stirred at 100°C for 7 hrs. The reaction mixture was filtered, and the filtrate was concentrated. Compound ethyl (E,4S)-4-pyrrolidin-1-ylpent-2-enoate (5.5 g, crude) was obtained as brown oil. LCMS: m/z 198.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.76 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 5.94 (d, J=15.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.01-2.97 (m, 1H), 2.47-2.40 (m, 4H), 1.69-1.62 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H).

Step 3.3.2 Synthesis of (E,4S)-4-pyrrolidin-1-ylpent-2-enoic acid

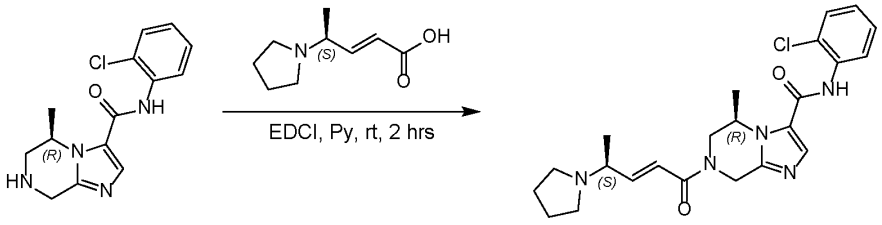


2

[01191] To a solution of ethyl (E,4S)-4-pyrrolidin-1-ylpent-2-enoate (5.5 g, 27.88 mmol, 1 *eq*) in EtOH (80 mL) and H_2O (16 mL) was added LiOH•H_2O (2.92 g, 69.70 mmol, 2.5 *eq*) at 25°C. The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated to remove EtOH, the residue was adjusted pH=5 with 4N HCl. The residue was purified by prep-HPLC (column: Phenomenex Titank C_{18} Bulk 250 * 70 mm 10 u; mobile phase: [H_2O (0.04%HCl)-ACN]; gradient:0%-10% B over 13.0 min). Compound (E,4S)-4-pyrrolidin-1-ylpent-2-enoic acid (1.7 g, 10.05 mmol, 36.03% yield) was obtained as a white solid.

[01192] LCMS: m/z 170.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.74 (dd, J = 15.6 Hz, 8.4 Hz, 1H), 5.98 (d, J =15.6 Hz, 1H), 3.49-3.46 (m, 1H), 2.82-2.78 (m, 4H), 1.81-1.77 (m, 4H), 1.6 (d, J = 6.4 Hz, 3H).

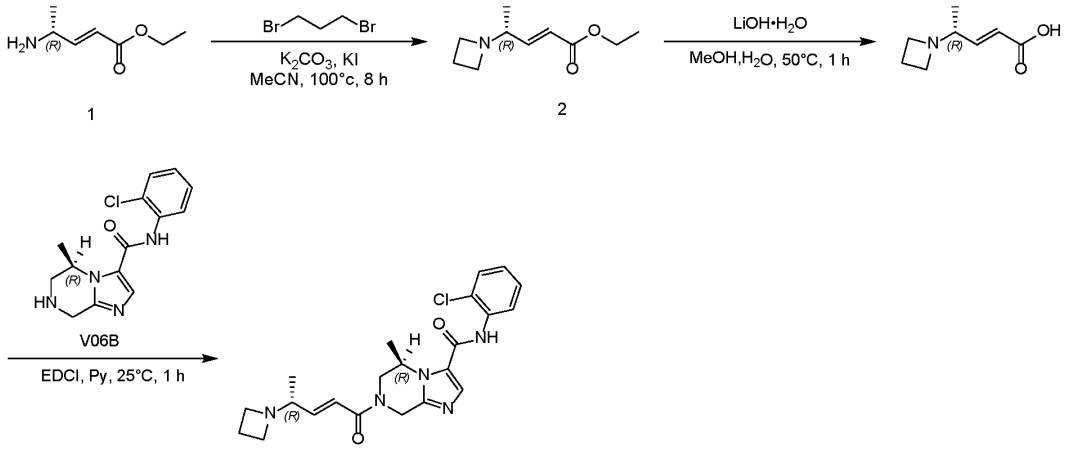
Step 3.3.3 Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



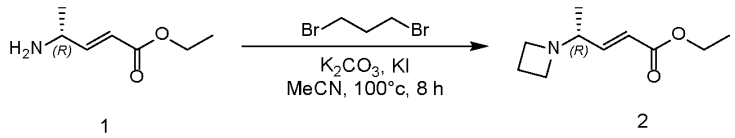
V06B

[01193] To a solution of (E,4S)-4-pyrrolidin-1-ylpent-2-enoic acid (698.42 mg, 4.13 mmol, 1.2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1 g, 3.44 mmol, 1 eq) in pyridine (15 mL) was added EDCI (1.32 g, 6.88 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C_{18} 250 * 50 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 10.0 min). Compound (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (1.0 g, 2.24 mmol, 65.14% yield, 99.021% purity) was obtained as a yellow solid. LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 2.0 Hz, 2H), 7.38 (td, J = 7.6 Hz, 2.0 Hz, 1H), 7.29 (td, J = 7.6 Hz, 2.0 Hz, 1H), 6.70-6.67 (m, 2H), 5.27-5.19 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.32-4.25 (m, 1H), 3.71-3.68 (m, 0.5H), 3.29-3.23 (m, 0.5H), 3.04-3.01 (m, 1H), 2.48-2.42 (m, 4H), 1.70-1.67 (m, 4H), 1.30-1.26 (m, 3H), 1.16-1.15 (m, 3H).

Example 190: Synthesis of (5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

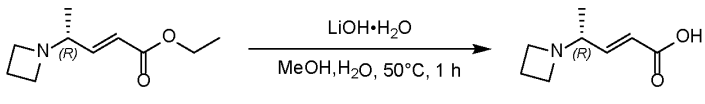


Step 1.1 Synthesis of ethyl (E,4R)-4-(azetidin-1-yl)pent-2-enoate -



[01194] A mixture of ethyl (E,4R)-4-aminopent-2-enoate (1.4 g, 7.79 mmol, 1 *eq*, HCl), 1,3-dibromopropane (1.57 g, 7.79 mmol, 794.62 µL, 1 *eq*), K_2CO_3 (3.23 g, 23.38 mmol, 3 *eq*) and KI (129.37 mg, 779.32 µmol, 0.1 *eq*) in MeCN (20 mL) was degassed and purged with N_2 for 3 times at 25°C, and then the mixture was heated to 100°C and stirred at 100°C for 8 hr under N_2 atmosphere. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (Biotage ®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound ethyl (E,4R)-4-(azetidin-1-yl)pent-2-enoate (0.5 g, crude) was obtained as brown oil. LCMS: m/z 184.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.74 (dd, J = 16.0 Hz, 7.2 Hz, 1H), 5.92 (dd, J = 16.0 Hz, 0.8 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.18 (t, J = 6.8 Hz, 4H), 2.90-2.87 (m, 1H), 2.08-2.01 (m, 2H), 1.32- 1.28 (m, 4H), 1.06 (d, J = 6.4 Hz, 3H).

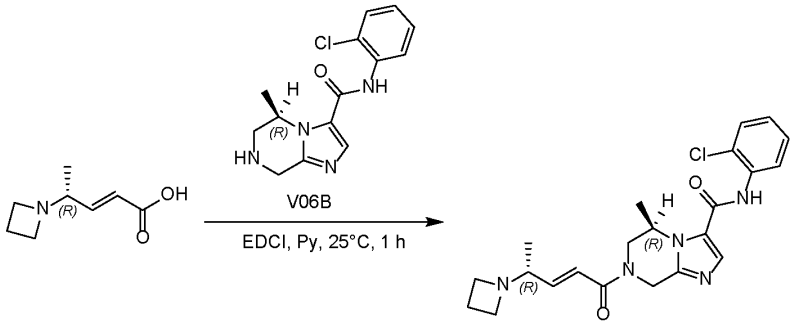
Step 1.2 Synthesis of (E,4R)-4-(azetidin-1-yl)pent-2-enoic acid



[01195] To a solution of ethyl (E,4R)-4-(azetidin-1-yl)pent-2-enoate (0.45 g, 2.46 mmol, 1 *eq*) in MeOH (6 mL) and H_2O (2 mL) was added LiOH•H_2O (257.63 mg, 6.14 mmol, 2.5 *eq*) at 25°C. The mixture was heated to 50°C and stirred at 50°C for 1 hr. The mixture was concentrated to remove MeOH, the residue was adjusted pH=4 with 4 N HCl, and then the mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna

C_{18} 250 * 50 mm * 15 um; mobile phase: [H_2O (0.04%HCl)-ACN]; gradient:1%-5% B over 10.0 min). Compound (E,4R)-4-(azetidin-1-yl)pent-2-enoic acid (0.4 g, crude) was obtained as a white solid. LCMS: m/z 156.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.60 (dd, J = 15.6 Hz, 3.6Hz, 1H), 6.01 (d, J = 15.6 Hz, 1H), 3.58 (br.s, 5H), 2.10 (q, J = 7.6 Hz, 2H), 1.11 (d, J = 6.4 Hz, 3H).

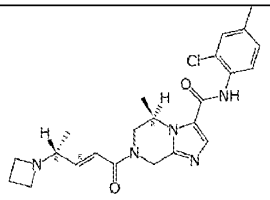
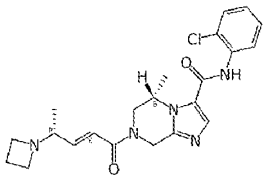
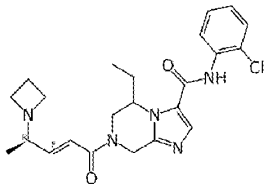
Step 1.3 Synthesis of (5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

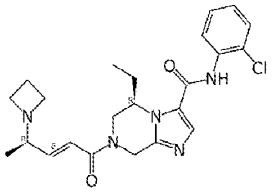
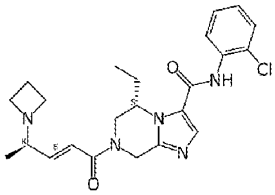
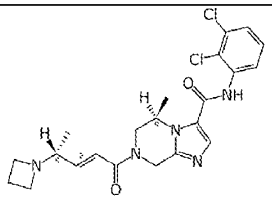


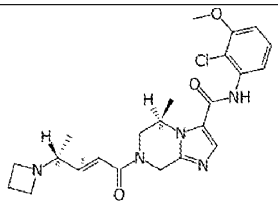
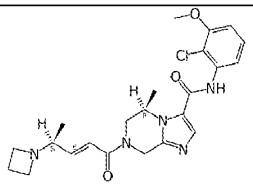
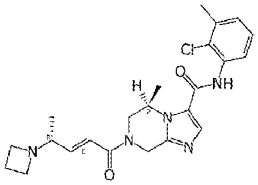
[01196] A mixture of (E,4R)-4-(azetidin-1-yl)pent-2-enoic acid (29.36 mg, 189.17 µmol, 1.1 *eq*), (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (50 mg, 171.97 µmol, 1 *eq*) and EDCI (65.93 mg, 343.94 µmol, 2 *eq*) in Py (2 mL) was stirred at 25°C for 1 hr under N_2 atmosphere. The reaction mixture was concentrated to remove Py. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 25 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 1%- 35% B over 8.0 min). Compound (5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (29 mg, 66.83 µmol, 38.86% yield, 98.61% purity) was obtained as a white solid. LCMS: m/z 428.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.87 (br.s, 1H), 7.89 (s, 1H), 7.59-7.51 (m, 2H), 7.38-7.36 (m, 1H), 7.31-7.29 (m, 1H), 6.66-6.62 (m, 1H), 6.56-6.49 (m, 1H), 5.28-5.15 (m, 1H), 5.11-4.99 (m, 1H), 4.73-4.52 (m, 1H), 4.35-4.21 (m, 1H), 3.70 (d, J = 12.8 Hz, 0.5H), 3.28-3.17 (m, 0.5H), 3.13-2.99 (m, 4H), 2.97-2.90 (m, 1H), 1.91-1.88 (m, 2H), 1.29-1.23 (m, 3H), 0.95 (d, J = 6.4 Hz, 3H).

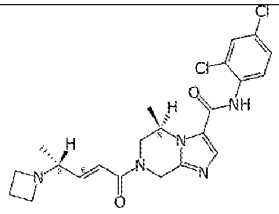
[01197] Compounds in Table T were synthesized following the procedure for (5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table T

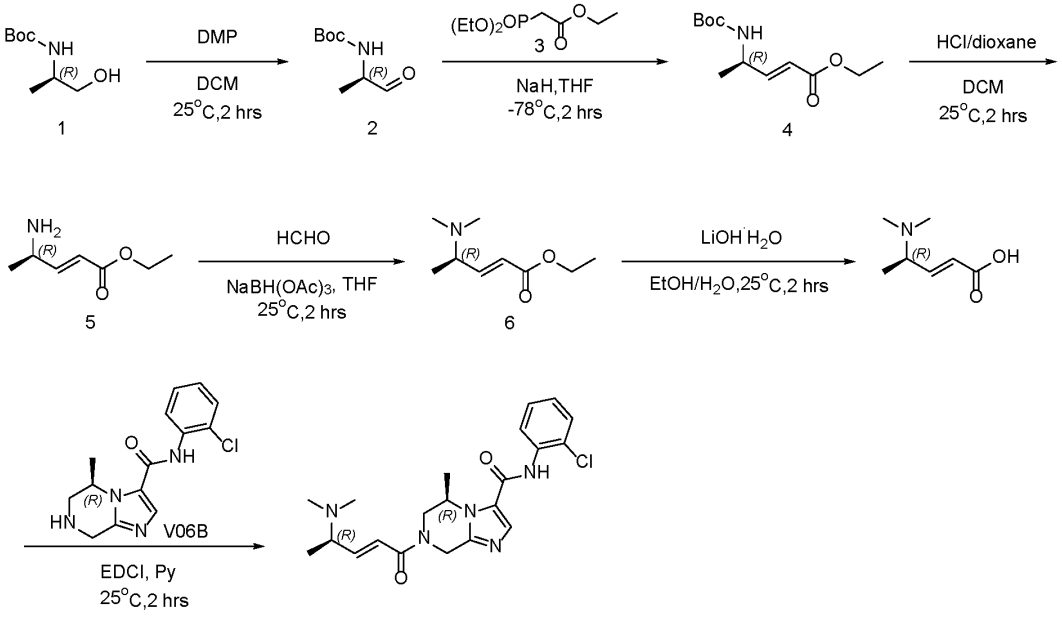
Name	Structure	NMR	LCMS	SFC conditions
(R)-7-((R,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chloro-4-methylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.79 (s, 1H), 7.86 (s, 1H), 7.38-7.36 (m, 2H), 7.19-7.17 (m, 1H), 6.68-6.62 (m, 1H), 6.52-6.45 (m, 1H), 5.27-5.16 (m, 1H), 5.04 (br.s, 1H), 4.69-4.55 (m, 1H), 4.31-4.23 (m, 1H), 3.69 (d, *J* = 12.4 Hz, 0.5H), 3.24-3.21 (m, 0.5H), 3.08-3.05 (m, 4H), 2.92 (q, *J* = 5.6 Hz, 1H), 2.32 (s, 3H), 1.92-1.88 (m, 2H), 1.28-1.22 (m, 3H), 0.96 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$	
(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)- 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.87 (s, 1H), 7.88 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.37 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.67-6.61 (m, 1H), 6.55-6.46 (m, 1H), 5.26-5.17 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.28 (t, *J* = 14.4 Hz, 1H), 3.69 (d, *J* = 11.6 Hz, 0.5H), 3.25-3.21 (m, 0.5H), 3.08 (t, *J* = 6.8 Hz, 4H), 2.96-2.89 (m, 1H), 1.94-1.87 (m, 2H), 1.29-1.23 (m, 3H), 0.95 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 428.2 $[M+H]^+$	
7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.38 (td, *J* = 6.4 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 6.66-6.51 (m, 2H), 5.21-5.19 (m, 1H), 4.84-4.66 (m, 2H), 4.30-4.26 (m, 1H), 3.66-3.63 (m, 0.5H), 3.17-3.14 (m, 0.5H), 3.10-3.06 (m, 4H), 2.95-2.90 (m, 1H), 1.93-1.89 (m, 2H), 1.70-1.68 (m, 1H), 1.47-1.42 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 442.1 $[M+H]^+$	

Name	Structure	NMR	LCMS	SFC conditions
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.88-9.87 (m, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.31 (td, *J* = 7.6 Hz, 0.8 Hz, 1H), 6.66-6.62 (m, 1H), 6.51-6.49 (m, 1H), 5.22 (t, *J* = 18.8 Hz, 1H), 4.83-4.70 (m, 2H), 4.38-4.25 (m, 1H), 3.66-3.62 (m, 0.5H), 3.17-3.13 (m, 0.5H), 3.15-3.05 (m, 4H), 2.94-2.91 (m, 1H), 1.91-1.90 (m, 2H), 1.70-1.68 (m, 1H), 1.46-1.36 (m, 1H), 0.96 (t, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 442.1 $[M+H]^+$	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.88 (m, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.36 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.60-6.51 (m, 2H), 5.21 (t, *J* = 18.0 Hz, 1H), 4.83-4.66 (m, 2H), 4.41-4.30 (m, 1H), 3.66-3.62 (m, 0.5H), 3.17-3.13 (m, 0.5H), 3.15-3.08 (m, 4H), 2.95-2.92 (m, 1H), 1.92-1.89 (m, 2H), 1.71-1.70 (m, 1H), 1.46-1.45 (m, 1H), 0.96 (d, *J* = 5.2 Hz, 3H), 0.90 (t, *J* = 6.8 Hz, 3H).	LCMS: m/z 442.1 $[M+H]^+$	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,3-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.02 (s, 1H), 7.89 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 6.65-6.47 (m, 2H), 5.28-5.18 (m, 1H), 5.05 (s, 1H), 4.70-4.56 (m, 1H), 4.32-4.24 (m, 1H), 3.69 (d, *J* = 12.8 Hz, 0.6H), 3.25-3.21 (m, 0.4H), 3.08-3.04 (m, 4H), 2.95-2.89 (m, 1H), 1.92-1.89 (m, 2H), 1.29-1.25 (m, 3H), 0.96 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 462.1/464.1 $[M+H]^+$	

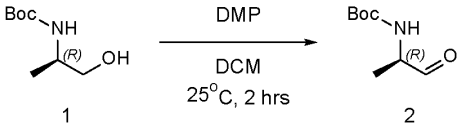
Name	Structure	NMR	LCMS	SFC conditions
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chloro-3-methoxy-phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.78 (s, 1H), 7.91 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.66-6.61 (m, 1H), 6.52-6.46 (m, 1H), 5.29-5.16 (m, 1H), 5.04 (s, 1H), 4.69-4.53 (m, 1H), 4.31-4.23 (m, 1H), 3.87 (s, 3H), 3.71-3.64 (m, 1H), 3.07 (d, *J* = 5.2 Hz, 4H), 2.95-2.88 (m, 1H), 1.91-1.88 (m, 2H), 1.28-1.24 (m, 3H), 0.96 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 458.2 $[M+H]^+$	
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chloro-3-methoxy-phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.78 (s, 1H), 7.88 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.66-6.60 (m, 1H), 6.54-6.49 (m, 1H), 5.28-5.15 (m, 1H), 5.04 (s, 1H), 4.71-4.52 (m, 1H), 4.31-4.24 (m, 1H), 3.87 (s, 3H), 3.70-3.67 (m, 1H), 3.08 (t, *J* = 7.2 Hz, 4H), 2.95-2.90 (m, 1H), 1.91 (q, *J* = 6.8Hz, 2H), 1.28-1.24 (m, 3H), 0.95 (d, *J* = 5.6 Hz, 3H).	LCMS: m/z 458.1 $[M+H]^+$	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.81 (s, 1H), 7.88 (s, 1H), 7.37-7.35 (m, 1H), 7.27-7.26 (m, 2H), 6.66-6.62 (m, 1H), 6.52-6.47 (m, 1H), 5.28-5.17 (m, 1H), 5.04 (br.s, 1H), 4.69-4.56 (m, 1H), 4.31-4.24 (m, 1H), 3.70 (d, J = 13.2 Hz, 0.5H), 3.27-3.22 (m, 0.5H), 3.08-3.07 (m, 4H), 2.92 (q, J = 5.6 Hz, 1H), 2.38 (s, 3H), 1.92-1.89 (m, 2H), 1.28-1.24 (m, 3H), 0.96 (d, J = 6.4 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$	

Name	Structure	NMR	LCMS	SFC conditions
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,4-dichlorophenyl) -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.92 (s, 1H), 7.89 (s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.65-6.62 (m, 1H), 6.52-6.47 (m, 1H), 5.28-5.23 (m, 1H), 5.03 (s, 1H), 4.69-4.57 (m, 1H), 4.32-4.24 (m, 1H), 3.71-3.67 (m, 0.5H), 3.24-3.22 (m, 0.5H), 3.08-3.03 (m, 4H), 2.93-2.90 (m, 1H), 1.92-1.88 (m, 2H), 1.28-1.23 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 462.1/464.1 $[M+H]^+$	

Example 191: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



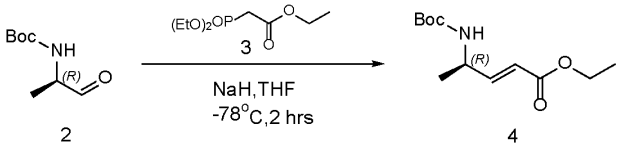
Step 1.1 Synthesis of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate



[01198] To a solution of tert-butyl N-[(1R)-2-hydroxy-1-methyl-ethyl]carbamate (10.00 g, 57.07 mmol, 1 eq) in DCM (100 mL) was added DMP (33.89 g, 79.90 mmol, 24.76 mL, 1.4

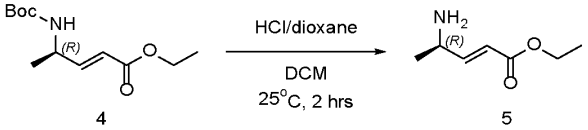
eq) in portions at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hrs. The reaction mixture was added aq. $NaHCO_3$ to adjust pH = 7 at 0°C. The reaction mixture was extracted with DCM (40 mL x 3), the combined organic phase was washed with brine (40 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 120 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 120 mL/min). Compound tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate (6.7 g, 38.68 mmol, 67.78% yield) was obtained as white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.33 (d, J = 6.4 Hz, 1H), 3.89-3.81 (m, 1H), 1.39 (s, 9H), 1.12 (d, J = 7.2 Hz, 3H).

Step 1.2 Synthesis of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate



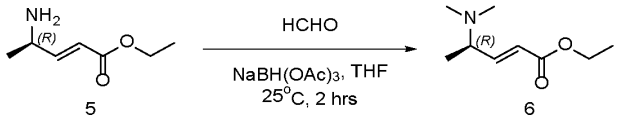
[01199] To a solution of NaH (1.86 g, 46.42 mmol, 60% purity, 1.2 eq) in THF (60 mL) was added dropwise ethyl 2-diethoxyphosphorylacetate (10.41 g, 46.42 mmol, 9.21 mL, 1.2 eq) at -78°C under N_2 atmosphere. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate (6.7 g, 38.68 mmol, 1 eq) in THF (60 mL) was added dropwise into the reaction mixture at -78°C, then the reaction mixture was stirred at -78°C for 2 hrs. The reaction mixture was quenched by addition of H_2O (200 mL) at 0°C. Then the reaction mixture was warmed to 25°C and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotag®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (5 g, 19.84 mmol, 51.30% yield) was obtained as white oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 7.6 Hz, 1H), 6.80 (dd, J = 16.0 Hz, 5.6 Hz, 1H), 5.80 (dd, J = 16.0 Hz, 1.6 Hz, 1H), 4.20-4.19 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 1.38 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 7.2 Hz, 3H).

Step 1.3 Synthesis of ethyl (E,4R)-4-aminopent-2-enoate.



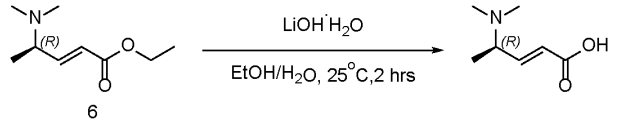
[01200] To a solution of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (5 g, 20.55 mmol, 1 eq) in DCM (50 mL) was added HCl/dioxane (4 M, 50 mL, 9.73 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound ethyl (E,4R)-4-aminopent-2-enoate (5.2 g, crude) was obtained as yellow oil. LCMS: m/z 144.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 2H), 6.87 (dd, J =16.0 Hz, 6.0 Hz, 1H), 6.11 (dd, J = 16.0 Hz, 1.6 Hz, 1H), 4.16 (q, J = 6.8 Hz, 2H), 4.02 (s, 1H), 1.33 (d, J = 6.4 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H).

Step 1.4 Synthesis of ethyl (E,4R)-4-(dimethylamino)pent-2-enoate.



[01201] To a solution of ethyl (E,4R)-4-aminopent-2-enoate (2 g, 13.97 mmol, 1 eq) in THF (20 mL) was added HCHO (3.40 g, 41.90 mmol, 3.12 mL, 37% purity, 3 eq), and then $NaBH(OAc)_3$ (8.88 g, 41.90 mmol, 3 *eq*) was added at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was added water (60 ml). The reaction mixture was added Na_2CO_3 to adjust pH = 10 at 0°C. The reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL x 1). The reaction mixture was concentrated under reduced pressure to remove solvent. Compound ethyl (E,4R)-4-(dimethylamino)pent-2-enoate (1.8 g, 10.51 mmol, 75.26% yield) was obtained as white oil. LCMS: m/z 172.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 6.80 (dd, J = 16.0 Hz, 7.6 Hz, 1H), 5.95 (d, J = 15.6 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.24-3.19 (m, 1H), 2.18 (s, 6H), 1.21 (t, J = 6.8 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H).

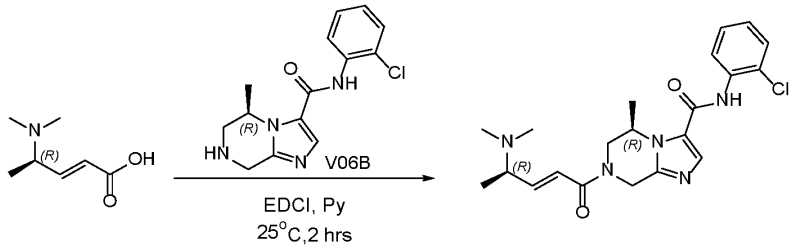
1.5 Synthesis of (E,4R)-4-(dimethylamino)pent-2-enoic acid.



[01202] To a solution of ethyl (E,4R)-4-(dimethylamino)pent-2-enoate (1.8 g, 10.51 mmol, 1 eq) in EtOH (15 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (1.32 g, 31.54 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was added HCl (3 M) to adjust pH = 4 at 0°C. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1%- 5% B over 20.0 min). The residue was dried over lyophilization. Compound (E,4R)-4-(dimethylamino)pent-2-enoic acid (0.6 g, 4.19 mmol, 39.86% yield) was obtained as a white solid. LCMS: m/z 144.2

[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 11.77 (s, 1H), 6.86 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 6.17 (d, J = 15.6 Hz, 1H), 4.13-4.08 (m, 1H), 2.62 (s, 6H), 1.40 (d, J = 6.8 Hz, 3H).

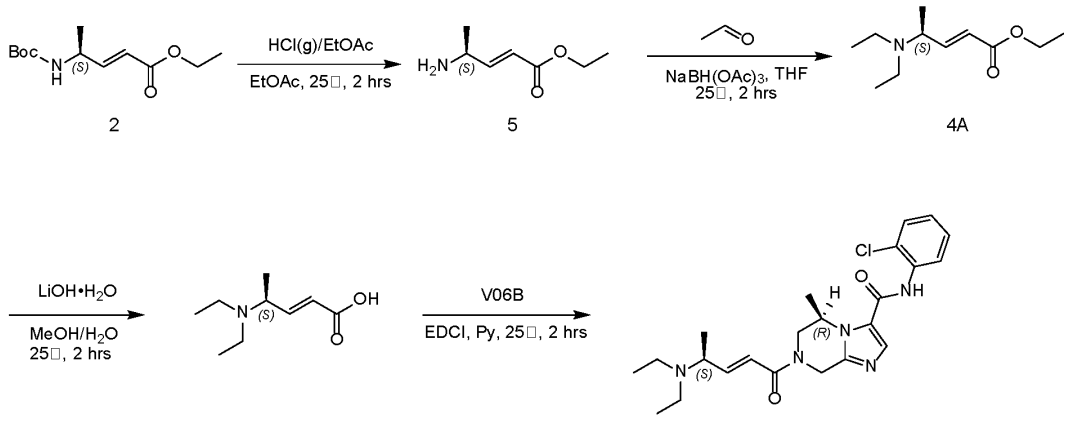
Step 1.6 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



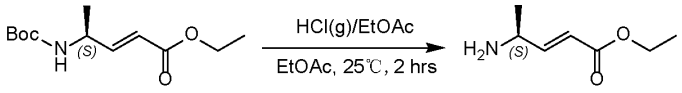
[01203] To a solution of (E,4R)-4-(dimethylamino)pent-2-enoic acid (52.51 mg, 366.74 µmol, 1.2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (100 mg, 305.62 µmol, 1 eq, HCl) in Pyridine (1 mL) was added EDCI (117.17 mg, 611.23 µmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 8.0 min). The residue was dried over lyophilization. Compound (5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (20 mg, 47.96 µmol, 15.69% yield, 99.73% purity) was obtained as a white solid.

[01204] LCMS: m/z 416.1 [M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 9.85 (s, 1H), 7.89 (s, 1H), 7.55-7.52 (m, 2H), 7.40-7.35 (m, 1H), 7.29 (t, J = 8.0 Hz, 1H), 6.74-6.60 (m, 2H), 5.28-5.19 (m, 1H), 5.05 (s, 1H), 4.70-4.56 (m, 1H), 4.34-4.25 (m, 1H), 3.71-3.67 (m, 0.5H), 3.26-3.25 (m, 0.5H), 3.12(t, J = 6.0 Hz, 1H), 2.14 (s, 6H), 1.29-1.24 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H).

Example 192: (5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

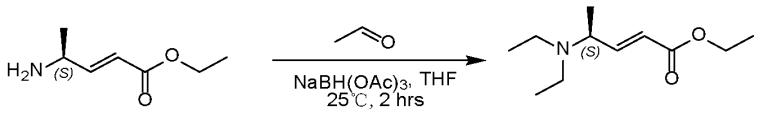


Step 1.1 Synthesis of ethyl (E,4S)-4-aminopent-2-enoate



[01205] To a solution of ethyl (E,4S)-4-(tert-butoxycarbonylamino)pent-2-enoate (1.8 g, 7.40 mmol, 1 eq) in EtOAc (18 mL) was added HCl/EtOAc (4 M, 18.50 mL, 10 eq) at 25°C, and the mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was used directly to next step. Compound ethyl (E,4S)-4-aminopent-2-enoate (1.8 g, 7.01 mmol, 94.80% yield) was obtained as a yellow oil. LCMS: m/z 144.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.56 (s, 2H), 7.02-6.96 (m, 1H), 6.20-6.15 (m, 1H), 4.20-4.15 (m, 3H), 2.11 (s, 3H), 1.27-1.24 (m, 3H).

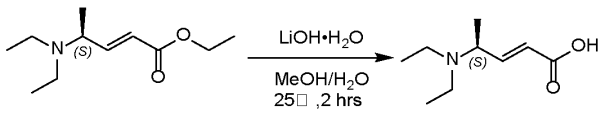
Step 1.2 Synthesis of ethyl (E,4S)-4-(diethylamino)pent-2-enoate



[01206] To a solution of ethyl (E,4S)-4-aminopent-2-enoate (1.8 g, 7.01 mmol, 1 *eq*) in tetrahydrofuran (18 mL) was added CH_3CHO (5 M, 3.51 mL, 2.5 *eq*) at 25°C, and the mixture was stirred at 25°C for 20 mins, then $NaBH(OAc)_3$ (4.46 g, 21.04 mmol, 3 *eq*) was added to the mixture. The mixture was stirred at 25°C for 2 hrs. Saturated sodium carbonate solution was added to the mixture solution to adjust pH = 9 at 25°C, and extracted with ethyl acetate 150 mL (50 mL × 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue, which was used directly to next step. Compound ethyl (E,4S)-4-(diethylamino)pent-2-enoate (0.8 g, 4.01 mmol, 57.23% yield) was obtained as a yellow oil. LCMS: m/z 200.0 $[M+H]^+$. ^1H

NMR (DMSO-d_6, 400 MHz) δ 7.00-6.92 (m, 1H), 5.86 (d, J = 15.6 Hz,1H), 4.19 (q, J = 7.2 Hz, 2H), 3.52-3.45 (m, 1H), 2.60-2.44 (m, 4H), 1.29 (t, J = 7.2 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 7.2 Hz, 6H).

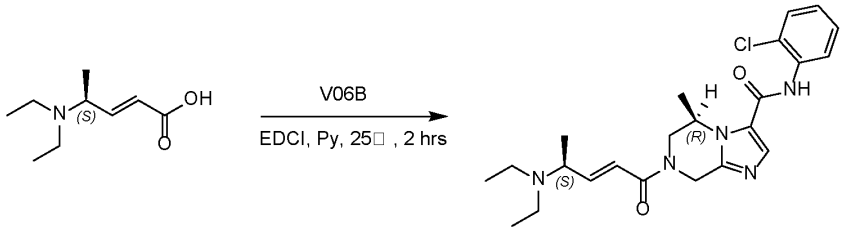
Step 1.3 Synthesis of (E,4S)-4-(diethylamino)pent-2-enoic acid



4A

[01207] To a solution of ethyl (E,4S)-4-(diethylamino)pent-2-enoate (0.8 g, 4.01 mmol, 1 *eq*) in methanol (5 mL) and H_2O (2.5 mL) was added LiOH•H_2O (505.36 mg, 12.04 mmol, 3 *eq*) at 25°C, and the mixture was stirred at 25°C for 2 hrs. The mixture was concentrated under reduced pressure to remove methanol, then aqueous phase was extracted with methyl tert-butyl ether 10 mL (5 mL × 2). Then aqueous phase was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 × 40 × 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 1% - 10% B over 8.0 min). Compound (E,4S)-4-(diethylamino)pent-2-enoic acid (300 mg, 1.75 mmol, 43.64% yield) was obtained as a white solid. LCMS: m/z 172.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.61 (br.s, 1H) 6.83 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 6.06 (d, J = 15.6 Hz, 1H), 3.84-3.77 (m, 1H), 3.01 (q, J = 6.8 Hz, 4H), 1.41 (d, J = 6.8 Hz, 3H), 1.24 (t, J = 7.2 Hz, 6H).

Step 1.4 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

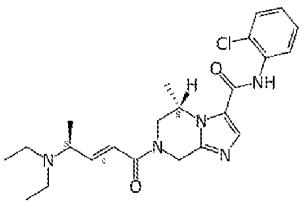
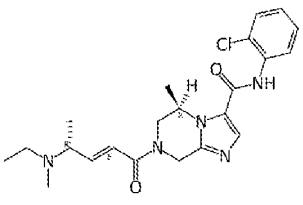
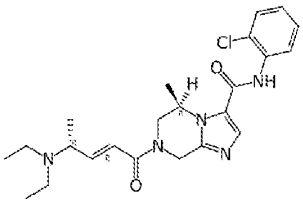


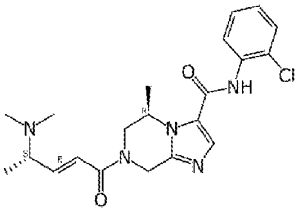
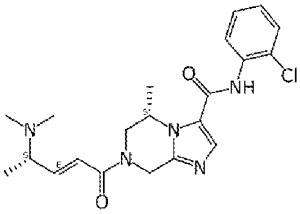
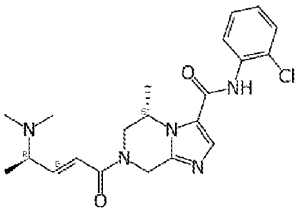
[01208] A mixture of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine- 3-carboxamide (70 mg, 240.76 μmol, 1 *eq*), (E,4S)-4-(diethylamino)pent-2-enoic acid (49.47 mg, 288.91 μmol, 1.2 *eq*) and EDCI (92.31 mg, 481.52 μmol, 2 *eq*) in pyridine (2 mL) was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 × 40 × 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15% - 65% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-

carboxamide (35.5 mg, 79.49 μmol, 33.02% yield) was obtained as a pale yellow solid. LCMS: m/z 444.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br.s, 1H), 7.89 (s, 1H), 7.55-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.77-6.71 (m, 1H), 6.61-6.58 (m, 1H), 5.28-5.20 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.33-4.25 (m, 1H), 3.72-3.68 (m, 1H), 3.50-3.47 (m, 1H), 3.27-3.22 (m, 1H), 2.45-2.36 (m, 3H), 1.29-1.27 (m, 3H), 1.12 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 6.8 Hz, 6H).

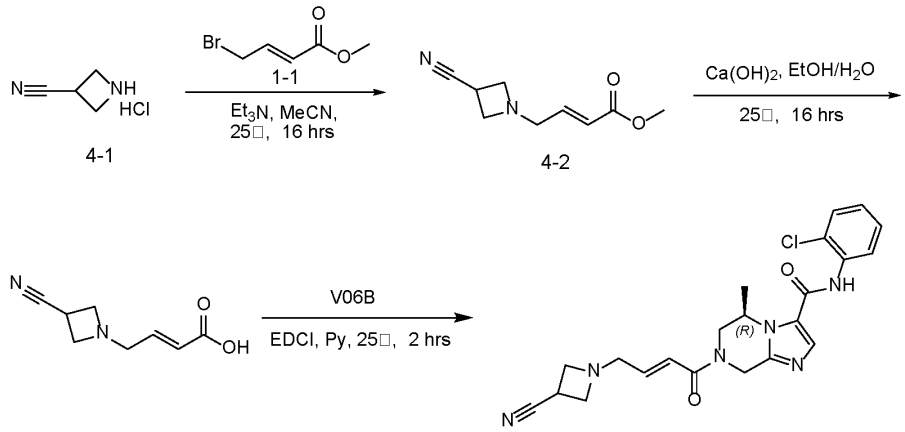
Compounds in Table U were synthesized following the procedure for synthesis of (5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table U

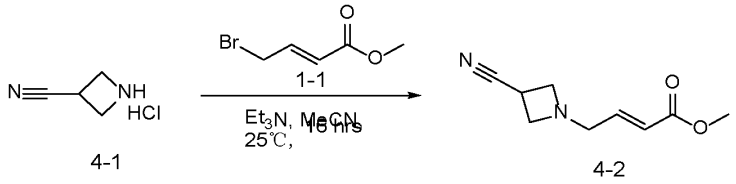
Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-(diethylamino)pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.77-6.69 (m, 1H), 6.64-6.60 (m, 1H), 5.29-5.21 (m, 1H), 5.05 (s, 1H), 4.70-4.56 (m, 1H), 4.29 (t, J = 17.6 Hz, 1H), 3.70 (d, J = 12.0 Hz, 0.5H), 3.53-3.46 (m, 1H), 3.28-3.23 (m, 1.5H), 2.42-2.37 (m, 3H), 1.29-1.25 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 6.4 Hz, 6H).	LCMS: m/z 444.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-$d6$, 400 MHz) δ 9.85 (br.s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.76-6.60 (m, 2H), 5.29-5.21 (m, 1H), 5.05-5.04 (m, 1H), 4.69-4.57 (m, 1H), 4.34-4.25 (m, 1H), 3.70 (d, J = 12.8 Hz, 0.6H), 3.26-3.22 (m, 1.4H), 2.44-2.32 (m, 2H), 2.13 (s, 3H), 1.29-1.25 (m, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 6.0 Hz, 3H)	LCMS: m/z 430.4 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E,4R)-4-(diethylamino)pent-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (400 MHz, DMSO-$d6$) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.60-7.49 (m, 2H), 7.42-7.34 (m, 1H), 7.33-7.26 (m, 1H), 6.79-6.68 (m, 1H), 6.67-6.57 (m, 1H), 5.31-5.19 (m, 1H), 5.05 (s, 1H), 4.73-4.54 (m, 1H), 4.37-4.23 (m, 1H), 3.76-3.62 (m, 0.5H), 3.55-3.45 (m, 1H), 3.31-3.30 (m, 0.5H),	LCMS: m/z 444.2 $[M+H]^+$

Name	Structure	NMR	LCMS
		3.30-3.15 (m, 2H), 2.46-2.35 (m, 2H), 1.33-1.20 (m, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 6.0 Hz, 6H).	
(5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-(dimethylamino)pent-2-enoyl]-5 -methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.27 (m, 1H), 6.71-6.65 (m, 2H), 5.27-5.21 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.34-4.26 (m, 1H), 3.72-3.68 (m, 0.5H), 3.28-3.21 (m, 0.5H), 3.17-3.08 (m, 1H), 2.15 (s, 6H), 1.30-1.26 (m, 3H), 1.12 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 416.0 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-7-[(E,4S)-4-(dimethylamino)pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.74-6.61 (m, 2H), 5.28-5.21 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.34-4.25 (m, 1H), 3.71-3.68 (m, 0.5H), 3.24-3.22 (m, 0.5H), 3.15-3.08 (m, 1H), 2.14 (s, 6H), 1.29-1.25 (m, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).	LCMS: m/z 416.2 [M+H]+
(5S)-N-(2-chlorophenyl)-7-[(E,4R)-4-(dimethylamino)pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.73-6.61 (m, 2H), 5.27-5.21 (m, 1H), 5.06 (br.s, 1H), 4.70-4.57 (m, 1H), 4.34-4.26 (m, 1H), 3.70 (d, *J* = 13.2 Hz, 0.5H), 3.29-3.28 (m, 0.5H), 3.16-3.10 (m, 1H), 2.15 (s, 6H), 1.30-1.26 (m, 3H), 1.11 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 416.1 $[M+H]^+$

Example 193: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



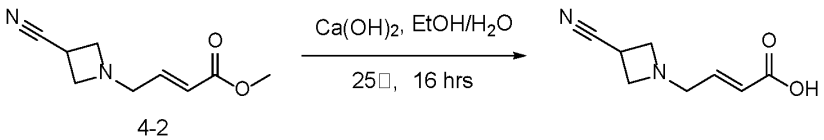
Step 1.1 Synthesis of methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate



[01209] To a solution of azetidine-3-carbonitrile (7.95 g, 67.03 mmol, 1.2 eq, HCl) in acetonitrile (100 mL) was added Et_3N (16.96 g, 167.59 mmol, 23.33 mL, 3 eq) in one portion and stirred at 25°C for 10 mins, then the mixture was added dropwise methyl (E)-4-bromobut-2-enoate (10 g, 55.86 mmol, 6.57 mL, 1 eq) at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 16 hrs. The reaction mixture was quenched by addition of ice-water (300 mL) at 0°C, and then extracted with ethyl acetate (150 mL × 3). The combined organic layers were washed with brine (150 mL×1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 160 g Sepa Flash® Silica Flash Column, Eluent of 0~43% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate (6 g, 29.97 mmol, 53.64% yield) was obtained as a yellow oil.

[01210] LCMS: m/z 180.9 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.84-6.78 (m, 1H), 6.00-5.96 (m, 1H), 3.76 (s, 3H), 3.68-3.62 (m, 2H), 3.38-3.32 (m, 3H), 3.27-3.23 (m, 2H).

1.2 Synthesis of (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid

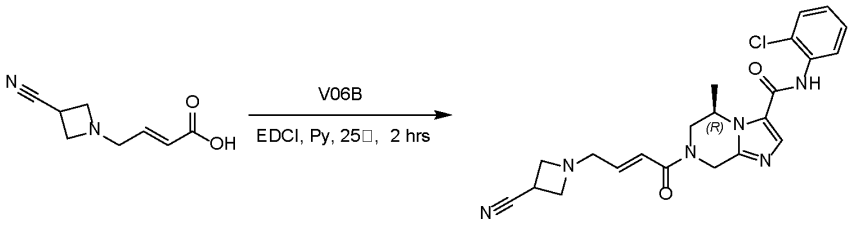


[01211] To a solution of methyl (E)-4-(3-cyanoazetidin-1-yl)but-2-enoate (6 g, 33.30 mmol, 1 eq) in ethanol (30 mL) and H_2O (60 mL) was added $Ca(OH)_2$ (12.33 g, 166.48 mmol, 5.51 mL,

5 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. The mixture was filtered and the filter cake was washed with ethanol, then the filtrate was concentrated under reduced pressure to remove ethanol. The reaction mixture was cooled to 0°C and adjusted to pH = 3 with HCl (2 M) at 0°C, then the crude product was purified by prep-HPLC (column: Welch Xtimate C_{18} 180 × 70 mm × 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; B%: 0%, isocratic elution mode). Compound (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid (1.5 g, 9.03 mmol, 27.11% yield) was obtained as a white solid.

[01212] LCMS: m/z 167.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.47-6.40 (m, 1H), 5.81 (d, J = 15.6 Hz, 1H), 3.50-3.39 (m, 3H), 3.31-3.20 (m, 2H), 3.17-3.08 (m, 2H).

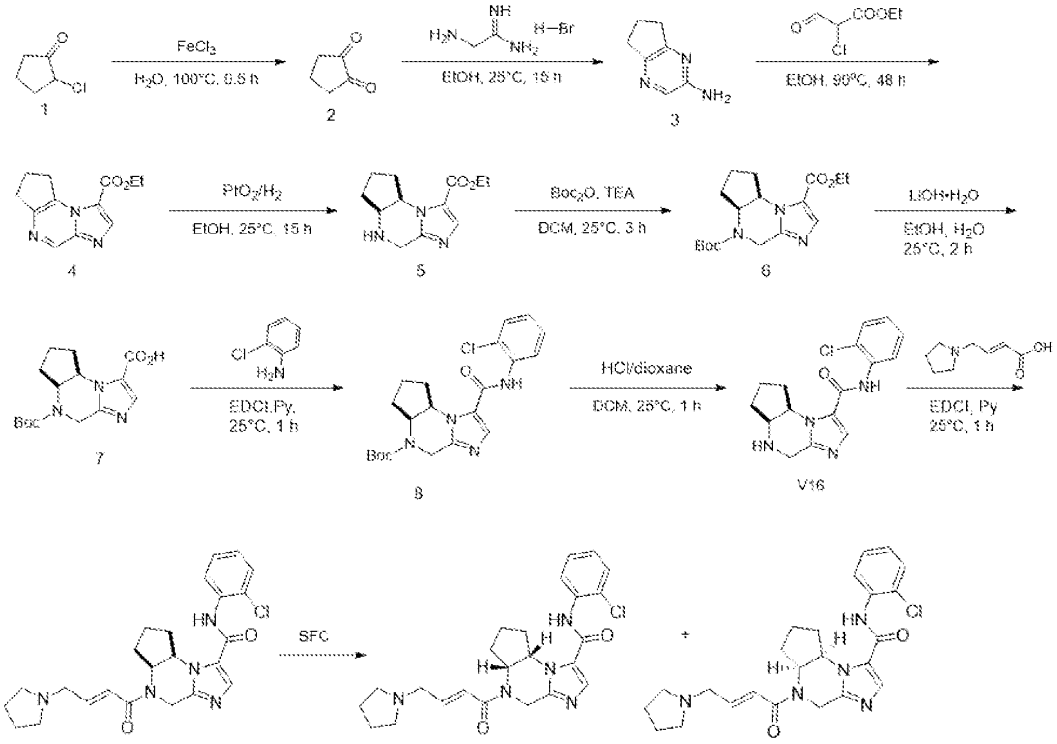
1.3 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



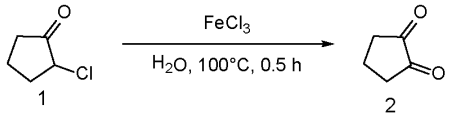
[01213] A mixture of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine- 3-carboxamide (100 mg, 343.94 μmol, 1 eq), (E)-4-(3-cyanoazetidin-1-yl)but-2-enoic acid (68.59 mg, 412.73 μmol, 1.2 eq) and EDCI (131.87 mg, 687.88 μmol, 2 eq) in pyridine (2 mL) was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove pyridine. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 × 40 × 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15% - 55% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-cyanoazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (70.8 mg, 159.76 μmol, 46.45% yield) was obtained as a yellow solid. LCMS: m/z 439.1 $[M+H]^+$. HPLC: 99.04% purity. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.53 (td, J = 8.4 Hz, 1.6 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.69-6.57 (m, 2H), 5.27-5.17 (m, 1H), 5.06-5.05 (m, 1H), 4.70-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.49 (s, 3H), 3.30 (s, 2H), 3.22 (d, J = 4.0 Hz, 2H), 1.29-1.25 (m, 3H).

Example 194: Synthesis of *cis*-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10- triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide; Synthesis of (2S,6R)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]- 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide and (2R,6S)-N-(2 -

chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide.

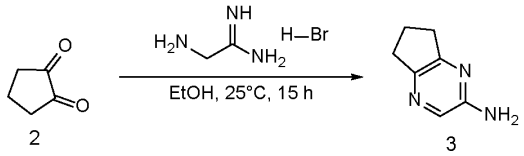


Step 1.1 Synthesis of cyclopentane-1,2-dione



[01214] 2-chlorocyclopentanone (5 g, 42.17 mmol, 4.22 mL, 1*eq*) in H_2O (100 mL) was heated to 100°C, to which a preheated solution of $FeCl_3$ (13.68 g, 84.34 mmol, 2 *eq*) was added. Reaction mixture was stirred at 100°C for 0.5 h. The reaction mixture was cooled to 25°C, and then extracted with DCM (30 mL x 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound cyclopentane-1,2-dione (3.5 g, crude) was obtained as a brown oil. LCMS: m/z 99.1 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.57 (t, *J* = 3.2 Hz, 1H), 5.61 (s, 1H), 2.54-2.52 (m, 2H), 2.47-2.45 (m, 2H).

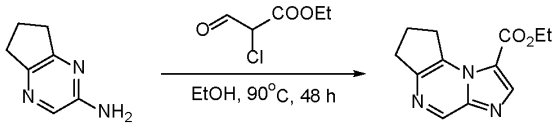
Step 1.2 Synthesis of 6,7-dihydro-5H-cyclopenta[b]pyrazin-3-amine -



2 3

[01215] To a solution ocyclopentane-1,2-dione (3.5 g, 35.68 mmol, 1 *eq*) in EtOH (30 mL) at 0°C, 2-aminoacetamidine;dihydrobromide (8.38 g, 35.68 mmol, 1 *eq*) was added. Reaction mixture was stirred for 10 min. Then pH of the reaction mixture was adjusted to 8-9 by using ammonium hydroxide solution. Then the reaction mixture was stirred at 25°C for 15 h. The reaction mixture was quenched by addition water (50 mL) at 25°C, and then the mixture was adjusted pH=7 with 4N HCl and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60mL/min). Compound 6,7-dihydro-5H-cyclopenta[b]pyrazin-3-amine (0.95 g, 7.03 mmol, 19.70% yield) was obtained as a white solid. LCMS: m/z 136.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (s, 1H), 6.03 (s, 2H), 2.74-2.69 (m, 4H), 2.05-1.97 (m, 2H).

1.3 Synthesis of ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-2(6),7,9,11-tetraene-12-carboxylate

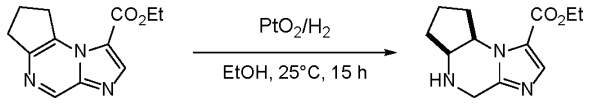


3 4

[01216] A mixture of 6,7-dihydro-5H-cyclopenta[b]pyrazin-3-amine (0.95 g, 7.03 mmol, 1 *eq*) and ethyl 2-chloro-3-oxo-propanoate (2.12 g, 14.06 mmol, 2 *eq*) in EtOH (20 mL) was heated to 90°C and then the mixture was stirred at 90°C for 48 h under N_2 atmosphere. The reaction mixture was quenched by addition water (20 mL) at 25°C, and then adjusted pH=7 with sat.aq $NaHCO_3$ and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 45 mL/min). Compound ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-2(6),7,9,11-tetraene-12-carboxylate (1 g, 4.32 mmol, 61.53% yield) was obtained as a brown solid. LCMS: m/z 232.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.02 (s, 1H), 8.36 (s, 1H), 4.33 (q, J = 7.2

Hz, 2H), 3.55 (t, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.22-2.14 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

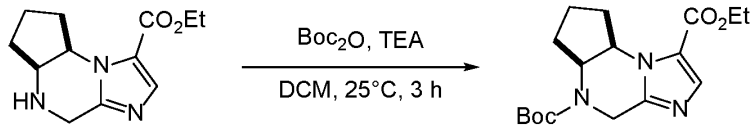
Step 1.4 Synthesis of ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxylate



4 5

[01217] To a solution of PtO2 (98.20 mg, 432.43 μmol, 0.1 *eq*) in EtOH (20 mL) was added ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-2(6),7,9,11-tetraene-12-carboxylate (1 g, 4.32 mmol, 1 *eq*) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 15 h under H_2 (15 Psi). The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. Compound ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxylate (1 g, crude) was obtained as brown oil. LCMS: m/z 236.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.57 (s, 1H), 4.53-4.51 (m, 1H), 4.26-4.21 (m, 2H), 3.94-3.77 (m, 2H), 3.78 (t, *J* = 5.2 Hz, 1H), 2.81-2.62 (m, 1H), 2.31-2.28 (m, 1H), 1.98-1.77 (m, 2H), 1.63-1.58 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H).

Step 1.5 Synthesis of O7-tert-butyl O12-ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-7,12-dicarboxylate

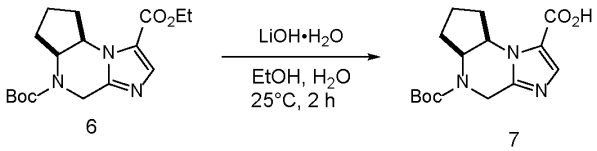


5 6

[01218] To a solution of ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxylate (1.1 g, 4.68 mmol, 1 *eq*) in DCM (20 mL) was added TEA (567.70 mg, 5.61 mmol, 780.88 μL, 1.2 *eq*) and Boc_2O (1.02 g, 4.68 mmol, 1.07 mL, 1 *eq*) at 25°C. The mixture was stirred at 25°C for 3 h. The reaction mixture was cooled to 0°C and adjusted pH=6 with sat.aq. citric acid at 0°C. The reaction mixture was warmed up to 25°C and to the reaction mixture was added water (20 mL), extracted with DCM (20 mL x 3), the combined organic phase was washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound O7-tert-butyl O12-ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-7,12-dicarboxylate (1.6 g, crude) was obtained as a brown gum. LCMS: m/z 336.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.64 (s, 1H), 5.00-4.95 (m, 1H), 4.91- 4.81 (m,

2H), 4.28-4.22 (m, 3H), 2.35-2.30 (m, 1H), 1.99-1.89 (m, 1H), 1.82-1.70 (m, 1H), 1.61-1.48 (m, 3H), 1.48-1.38 (m, 9H), 1.28 (t, *J* = 7.2 Hz, 3H).

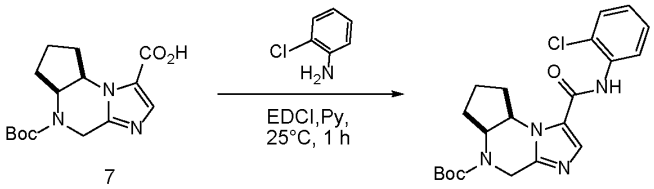
1.6 Synthesis of 7-tert-butoxycarbonyl-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene- 12-carboxylic acid



6 7

[01219] To a solution of O7-tert-butyl O12-ethyl 1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-7,12-dicarboxylate (1.6 g, 4.77 mmol, 1 *eq*) in EtOH (20 mL) and H_2O (5 mL) was added LiOH•H_2O (500.46 mg, 11.93 mmol, 2.5 *eq*) at 25°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure and then cooled to 0°C, adjusted pH=4 with 4 M HCl at 0°C. The reaction mixture was warmed up to 25°C and the reaction mixture was extracted with DCM (20 mL x 5), the combined organic phase was washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound7-tert-butoxycarbonyl-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxylic acid (1.4 g, crude) was obtained as brown gum. LCMS: m/z 308.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.53 (br.s, 1H), 7.71 (s, 1H), 5.05-5.01 (m, 1H), 4.92 (d, *J* = 17.6 Hz, 1H), 4.81 (q, *J* = 8.4 Hz, 1H), 4.27 (d, *J* = 17.2 Hz, 1H), 2.38-2.32 (m, 1H), 1.98-1.91 (m, 1H), 1.80-1.71 (m, 1H), 1.65-1.42 (m, 3H),1.41 (s, 9H).

Step 1.7 Synthesis of tert-butyl 12-[(2-chlorophenyl)carbamoyl]-1,7,10-triazatricyclo [7.3.0.0^{2,6}]dodeca-9,11-diene-7-carboxylate

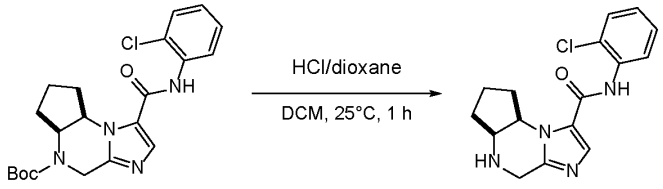


7 8

[01220] A mixture of 7-tert-butoxycarbonyl-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12- carboxylic acid (1.3 g, 4.23 mmol, 1 *eq*), 2-chloroaniline (593.56 mg, 4.65 mmol, 490.54 µL, 1.1 *eq*) and EDCI (1.62 g, 8.46 mmol, 2 *eq*) in Py (15 mL) was stirred at 25°C for 1 h under N_2 atmosphere. The reaction mixture was concentrated to remove Py, then the mixture was adjusted pH = 5 with 4 N HCl, and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica

gel chromatography (Biotage ®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50 % Ethyl acetate/Petroleum ether gradient @ 45 mL/min). Compound tert-butyl 12-[(2-chlorophenyl)carbamoyl]-1,7,10-triazatricyclo[7.3.0.$0^{2,6}$]dodeca- 9,11-diene-7-carboxylate (0.75 g, 1.80 mmol, 42.53% yield) was obtained as brown gum. LCMS: m/z 417.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.81 (s, 1H), 7.55-7.52 (m, 2H), 7.41-7.34 (m, 1H), 7.32-7.25 (m, 1H), 5.11-5.02 (m, 1H), 4.90 (d, J = 17.6 Hz, 1H), 4.83-4.79 (m, 1H), 4.25 (d, J = 17.2 Hz, 1H), 2.32-2.25 (m, 1H), 1.98-1.88 (m, 1H), 1.80-1.69 (m, 1H), 1.63-1.45 (m, 3H), 1.42 (s, 9H).

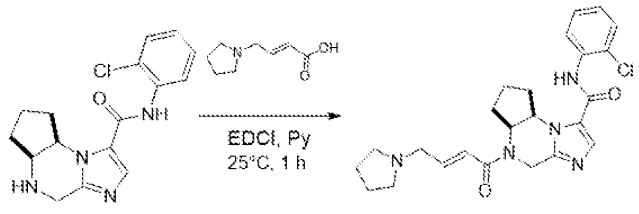
Step 1.8 Synthesis of N-(2-chlorophenyl)-1,7,10-triazatricyclo[7.3.0.$0^{2,6}$]dodeca-9,11-diene-12- carboxamide (V16)



8 V16

[01221] To a solution of tert-butyl 12-[(2-chlorophenyl)carbamoyl]-1,7,10-triazatricyclo[7.3.0.$0^{2,6}$] dodeca-9,11-diene-7-carboxylate (0.75 g, 1.80 mmol, 1 *eq*) in DCM (5 mL) was added HCl/dioxane (4 M, 4 mL) at 25°C. The mixture was stirred at 25°C for 1 hr. The mixture was concentrated under reduced pressure. Compound N-(2-chlorophenyl)-1,7,10-triazatricyclo[7.3.0.$0^{2,6}$]dodeca-9,11-diene-12- carboxamide (V16) (0.7 g, crude, HCl) was obtained as a brown solid. LCMS: m/z 317.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.28 (s, 1H), 8.13 (s, 1H), 7.60-7.55 (m, 1H), 7.52-7.47 (m, 1H), 7.44-7.36 (m, 1H), 7.36-7.29 (m, 1H), 5.18-5.09 (m, 2H), 4.48 (s, 2H), 4.09 (t, J = 5.6 Hz, 1H), 2.47-2.36 (m, 1H), 2.27-2.14 (m, 1H), 2.05-1.88 (m, 3H), 1.74-1.61 (m, 1H).

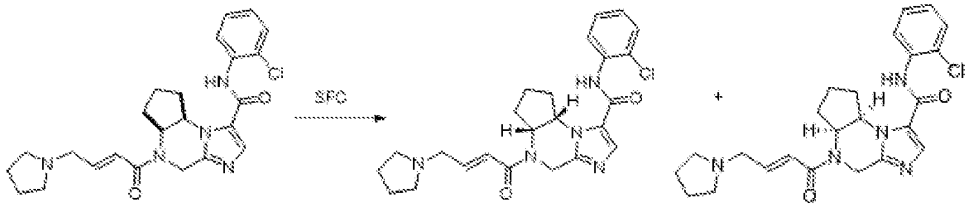
Step 1.9 Synthesis of N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.$0^{2,6}$]dodeca-9,11-diene-12-carboxamide



V16

[01222] A mixture of N-(2-chlorophenyl)-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide (100 mg, 283.09 μmol, 1 *eq*, HCl), (E)-4-pyrrolidin-1-ylbut-2-enoic acid (48.33 mg, 311.40 μmol, 1.1 *eq*) and EDCI (108.54 mg, 566.18 μmol, 2 *eq*) in Py (3 mL) was stirred at 25°C for 1 h. The mixture was concentrated to remove pyridine. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient:20%-60% B over 8.0 min). Compound N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide (55.7 mg, 118.77 μmol, 41.96% yield, 96.80% purity) was obtained as an off-white solid. LCMS: m/z 454.2 $[M+H]^+$. HPLC: 96.80% purity. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.89 (s, 1H), 7.82 (s, 1H), 7.59-7.49 (m, 2H), 7.42-7.34 (m, 1H), 7.33-7.24 (m, 1H), 6.72 (s, 2H), 5.46-4.82 (m, 3H), 4.25-4.03 (m, 1H), 3.25-3.16 (m, 2H), 2.48-2.41 (m, 4H), 2.36-2.26 (m, 1H), 2.04-1.91 (m, 1H), 1.89-1.75 (m, 1H), 1.74-1.43 (m, 7H).

Step 1.10 Synthesis of (2S,6R)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide and (2R,6S)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide



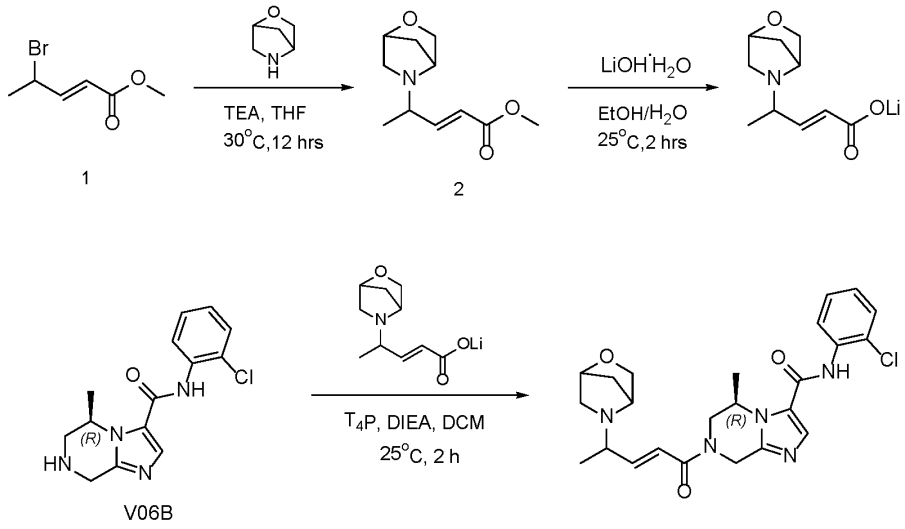
[01223] N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide (50.00 mg, 110.14 μmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-MeOH(0.1%NH_3H_2O)]; B%:50%, isocratic elution mode). Compound (2S,6R)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide (20.3 mg, 42.10 μmol, 38.22% yield, 94.15% purity) was obtained as a white solid. Compound(2R,6S)-N-(2-chlorophenyl)-7-[(E)-4-pyrrolidin-1-ylbut-2-enoyl]-1,7,10-triazatricyclo[7.3.0.0^{2,6}]dodeca-9,11-diene-12-carboxamide (17.7 mg, 38.83 μmol, 35.25% yield, 99.59% purity) was obtained as a white solid.

[01224] LCMS: m/z 454.2 [M+H].^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.82 (s, 1H), 7.57-7.50 (m, 2H), 7.41-7.34 (m, 1H), 7.32-7.26 (m, 1H), 6.72 (s, 2H), 5.55-4.73 (m, 3H), 4.68-

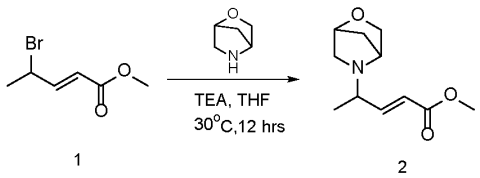
3.98 (m, 1H), 3.25-3.18 (m, 2H), 2.46-2.44 (m, 4H), 2.34-2.25 (m, 1H), 2.05-1.90 (m, 1H), 1.88-1.75 (m, 1H), 1.74-1.51 (m, 7H).

[01225] LCMS: m/z 454.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.82 (s, 1H), 7.57-7.49 (m, 2H), 7.41-7.34 (m, 1H), 7.32-7.25 (m, 1H), 6.72 (s, 2H), 5.48-4.87 (m, 3H), 4.70-3.94 (m, 1H), 3.24-3.17 (m, 2H), 2.46-2.40 (m, 4H), 2.34-2.26 (m, 1H), 2.03-1.91 (m, 1H), 1.89-1.75 (m, 1H), 1.72-1.51 (m, 7H).

Example 195: Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo [2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.1 Synthesis of methyl (E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoate



[01226] To a solution of 2-oxa-5-azabicyclo[2.2.1]heptane (1.03 g, 7.57 mmol, 7.31e-1 eq, HCl) and methyl (E)-4-bromopent-2-enoate (2 g, 10.36 mmol, 1 eq) in THF (20 mL) was added TEA (3.15 g, 31.08 mmol, 4.33 mL, 3 eq) at 20°C. The mixture was heated to 30°C and stirred at 30°C for 12 hrs. The reaction mixture was filtered to remove the insoluble. The filter liquor was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 20 g Sepa Flash® Silica Flash Column, Eluent of 50~100% Ethyl acetate/Petroleum ether gradient @ 50mL/min) and concentrated under reduced pressure to remove solvent. Compound methyl (E)-4-(2-oxa-5-

azabicyclo[2.2.1]heptan-5-yl) pent-2-enoate (1.1 g, 5.21 mmol, 50.26% yield) was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77-6.60 (m, 1H), 6.05 (dd, J = 17.6 Hz, 16.0 Hz, 1H), 4.31-4.30 (m, 1H), 3.82 (dd, J = 16.0 Hz, 7.6 Hz, 1H), 3.65 (s, 3H), 3.50 (dd, J = 7.6 Hz, 1.6 Hz, 0.5H), 3.47-3.42 (m, 1H), 3.37-3.29 (m, 1H), 3.28-3.21 (m, 0.5H), 2.84-2.78 (m, 1H), 2.38 (d, J = 9.6 Hz, 0.5H), 2.28 (d, J = 9.6 Hz, 0.5H), 1.71-1.64 (m, 1H), 1.57 (t, J = 9.2 Hz, 1H), 1.11-1.07 (m, 3H).

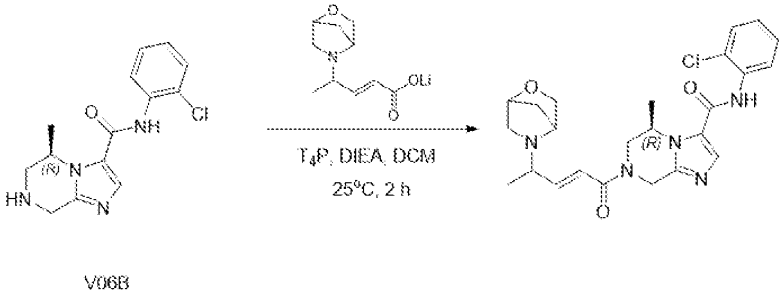
Step 1.2 Synthesis of [(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]oxylithium



3

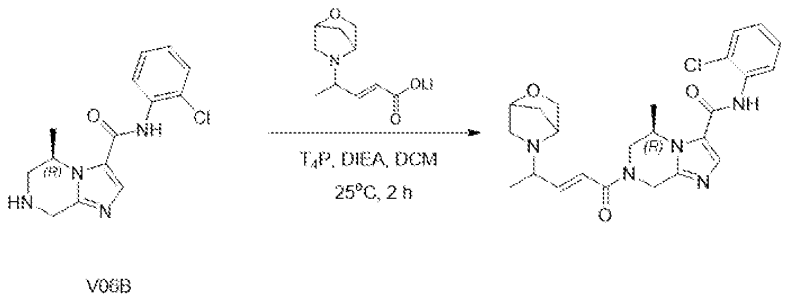
[01227] To a solution of methyl (E)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoate (1 g, 4.73 mmol, 1 eq) in EtOH (6 mL) and H_2O (3 mL) was added LiOH·H_2O (595.86 mg, 14.20 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. TLC (Petroleum ether: Ethyl acetate = 0:1, R_f = 0.03) indicated methyl(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl) pent-2-enoate was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound [(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]oxylithium (1.59 g, crude) was obtained as a yellow solid. LCMS: m/z 198.0 $[M+H]^+$.

Step 1.3 Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



V06B

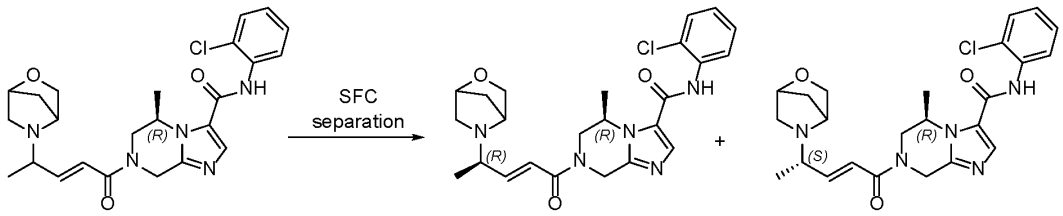
Step 1.3.1 Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo [2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



V08B

[01228] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine- 3-carboxamide (150 mg, 515.91 μmol, 1 eq) in DCM (2 mL) was added [(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]oxylithium (230.59 mg, 1.14 mmol, 2.2 eq) at 25°C. Then T_4P (483.24 mg, 670.69 μmol, 50% purity, 1.3 eq), DIEA (80.01 mg, 619.09 μmol, 107.83 μL, 1.2 eq) were added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was quenched with water (0.2 mL) at 25°C. The crude product was purified by prep-HPLC (column: Phenomenex Genimi NX C_{18} 150* 40 mm* 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 10%- 40% B over 8.0 min). The residue was dried over lyophilization to give compound (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (45.6 mg, 95.44 μmol, 18.50% yield, 98.36% purity) as a white solid. 5.6 mg for delivery, 40 mg for SFC separation. LCMS: m/z 470.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 6.77-6.70 (m, 1H), 6.61-6.56 (m, 1H), 5.27-5.19 (m, 1H), 5.04 (s, 1H), 4.70-4.56 (m, 1H), 4.32-4.25 (m, 2H), 3.93-3.82 (m, 1H), 3.71-3.60 (m, 1H), 3.52-3.50 (m, 0.5H), 3.48-3.45 (m, 1H), 3.39-3.37 (m, 0.5H), 3.28-3.22 (m, 1H), 2.88-2.77 (m, 1H), 2.39-2.36 (m, 1H), 1.70-1.68 (m, 1H), 1.57 (t, J = 10.0 Hz, 1H), 1.28-1.25 (m, 3H), 1.11-1.09 (m, 3H).

Example 196: Synthesis of (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



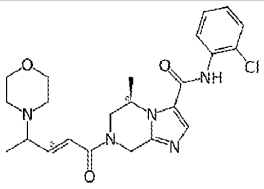
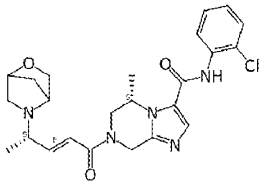
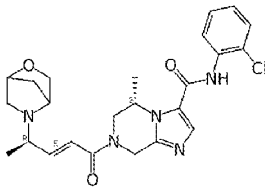
[01229] (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (40 mg, 85.11 μmol, 1 eq) was separated by SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2- MeOH(0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode) to give (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (13.4 mg, 28.66 μmol, 33.67% yield, 100% purity) and (5R)-N-(2-chlorophenyl)-5-methyl-7- [(E,4S)-4-(2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (12.4 mg, 26.28 μmol, 30.87% yield, 100% purity) were obtained as a white solid.

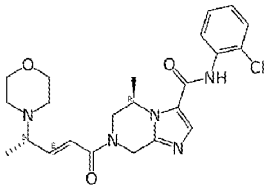
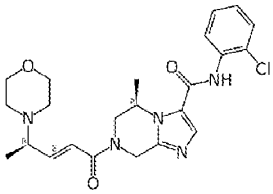
[01230] LCMS: m/z 470.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.79-6.74 (m, 1H), 6.62-6.54 (m, 1H), 5.27-5.20 (m, 1H), 5.05 (s, 1H), 4.70-4.56 (m, 1H), 4.33-4.26 (m, 2H), 3.93 (d, J = 6.0 Hz, 1H), 3.72-3.66 (m, 1H), 3.46 (s, 2H), 2.89-2.87 (m, 1H), 2.39-2.38 (m, 2H), 1.74-1.69 (m, 1H), 1.57-1.56 (m, 1H), 1.30-1.24 (m, 3H), 1.12 (s, 3H).

[01231] LCMS: m/z 470.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.91 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.39-7.36 (m, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.76-6.69 (m, 1H), 6.63-6.56 (m, 1H), 5.29-5.19 (m, 1H), 5.05 (s, 1H), 4.74-4.53 (m, 1H), 4.35-4.25 (m, 2H), 3.83 (d, J = 7.2 Hz, 1H), 3.71-3.65 (m, 1H), 3.60 (s, 1H), 3.51 (d, J = 6.4 Hz, 1H), 2.82-2.76 (m, 1H), 2.38-2.32 (m, 2H), 1.75-1.70 (m, 1H), 1.62-1.58 (m, 1H), 1.29-1.24 (m, 3H), 1.10 (d, J = 6.4 Hz, 3H).

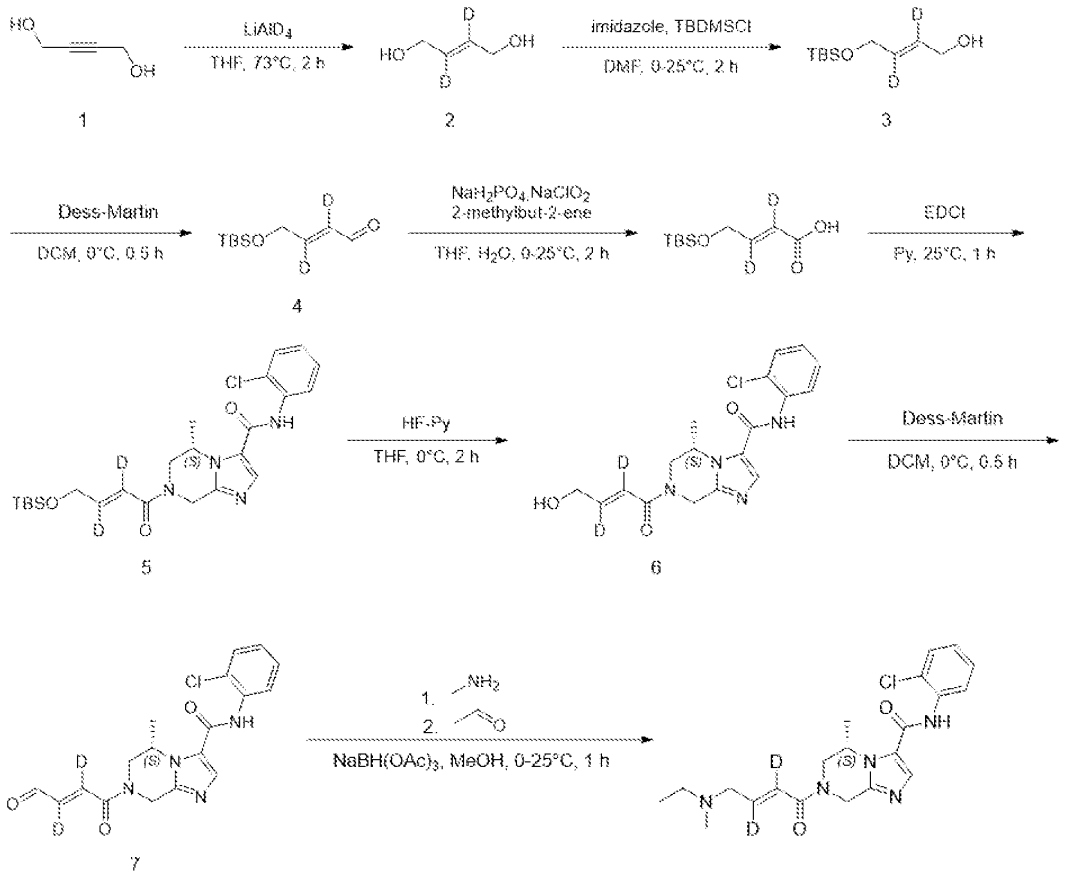
[01232] Compounds in Table V were synthesized following the procedure for (5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table V

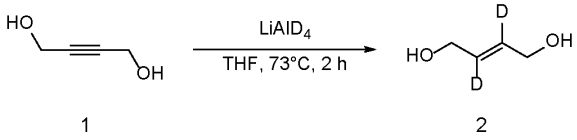
Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-4-morpholinopent-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.72-6.67 (m, 2H), 5.27-5.23 (m, 1H), 5.05-5.04 (m, 1H), 4.70-4.57 (m, 1H), 4.29 (t, J = 11.6 Hz, 1H), 3.70 (q, J = 9.2 Hz, 1H), 3.57 (t, J = 3.2 Hz, 4H), 3.17-3.11 (m, 1H), 2.41-2.40 (m, 4H), 1.28 (t, J = 5.2 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H).	LCMS: m/z 458.2 $[M+H]^+$	
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-(2-oxa-5-azabicyclo[2.2.1] heptan-5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 6.8 Hz, 1H), 7.31-7.27 (m, 1H), 6.79-6.70 (m, 1H), 6.61-6.49 (m, 1H), 5.31-5.19 (m, 1H), 5.04-5.03 (m, 1H), 4.70-4.56 (m, 1H), 4.32-4.24 (m, 2H), 3.94 (d, J = 8.0 Hz, 1H), 3.70 (d, J = 15.2 Hz, 0.5H), 3.46-3.36 (m, 3H), 3.26-3.25 (s, 0.5H), 2.88 (d, J = 9.6 Hz, 1H), 2.42-2.32 (m, 1H), 1.69-1.67 (m, 1H), 1.56 (s, 1H), 1.25-1.24 (m, 3H), 1.13-1.11 (m, 3H).	LCMS: m/z 470.2 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-MeOH (0.1% NH_3H_2O)] ; B%: 35%, isocratic elution mode
(5S)-N-(2-chlorophenyl)-5-methyl-7-[(E,4R)-4-(2-oxa-5-azabicyclo[2.2.1]heptan -5-yl)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.56-7.51 (m, 2H), 7.39-7.35 (m, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.69 (m, 1H), 6.63-6.57 (m, 1H), 5.26-5.22 (m, 1H), 5.04 (s, 1H), 4.69-4.53 (m, 1H), 4.33-4.31 (m, 2H), 3.83-3.82 (m, 1H), 3.73-3.66 (m, 0.5H), 3.60 (s, 1H), 3.54-3.50 (m, 1H), 3.29 (s, 1H), 3.27 (s, 0.5H), 2.80 (d, J = 10.0 Hz, 1H), 2.37-2.32 (m, 1H), 1.73-1.70 (m, 1H), 1.59-1.57 (m, 1H), 1.29-1.23 (m, 3H), 1.10-1.08(m, 3H).	LCMS: m/z 470.2 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-MeOH (0.1% NH_3H_2O)] ; B%: 35%, isocratic elution mode

Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E,4S)-4-morpholinopent-2-enoyl] -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.72-6.63 (m, 2H), 5.27-5.21 (m, 1H), 5.05 (s, 1H), 4.72-4.55 (m, 1H), 4.37-4.23 (m, 1H), 3.75-3.63 (m, 1H), 3.56-3.55 (m, 4H), 3.17-3.14 (m, 1H), 2.41-2.40 (m, 4H), 1.30-1.24 (m, 3H), 1.14 (d, J = 6.8 Hz, 3H).	LCMS: m/z 458.2 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH(0.1 % NH_3H_2O)] ; B%: 50%, isocratic elution mode)
(5R)-N-(2-chlorophenyl) -5-methyl-7-[(E,4R)-4-morpholinopent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.62 (m, 2H), 5.27-5.23 (m, 1H), 5.04 (s, 1H), 4.73-4.54 (m, 1H), 4.36-4.24 (m, 1H), 3.76-3.65 (m, 1H), 3.57 (t, J = 4.4 Hz, 4H), 3.20-3.14 (m, 1H), 2.41-2.40 (m, 4H), 1.30-1.26 (m, 3H), 1.13 (d, J = 6.4 Hz, 3H).	LCMS: m/z 458.2 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH(0.1 % NH_3H_2O)] ; B%: 50%, isocratic elution mode)

Example 197: Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

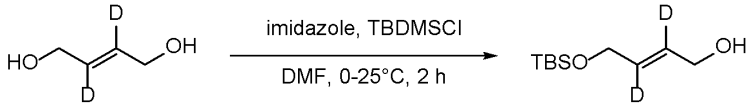


Step 1.1 Synthesis of (E)-2,3-dideuteriobut-2-ene-1,4-diol



[01233] To a solution of but-2-yne-1,4-diol (23 g, 267.17 mmol, 1 *eq*) in THF (500 mL) was slowly added lithium;tetradeuterioalumanuide (20.28 g, 534.33 mmol, 27.55 mL, 2 *eq*) at 25°C. The reaction mixture was heated to 73°C and stirred at 73°C for 2 h. The reaction mixture was cooled down to 0°C and D_2O (100 mL) was added dropwise to reaction mixture, and filtered and the filter cake was washed with ethyl acetate and MeOH. The colorless filtrate solution was dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound (E)-2,3-dideuteriobut-2-ene-1,4-diol (21.5 g, 238.58 mmol, 89.30% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.63 (t, J = 5.2 Hz, 2H), 3.91 (d, J = 4.8 Hz, 4H).

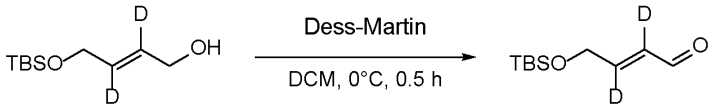
Step 1.2 Synthesis of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-en-1-ol



2 3

[01234] To a solution of (E)-2,3-dideuteriobut-2-ene-1,4-diol (21.5 g, 238.58 mmol, 1 *eq*) in DMF (300 mL) was added imidazole (24.36 g, 357.87 mmol, 1.5 *eq*). The mixture was stirred at 25°C for 1 h, then TBDMSCl (39.55 g, 262.44 mmol, 1.1 *eq*) was added to the mixture at 0°C, the mixture was stirred at 0°C for 1 h. The reaction mixture was quenched by addition of water (300 mL) at 0°C, and then extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-en-1-ol (24.5 g, 119.88 mmol, 50.25% yield) was obtained as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20 (s, 2H), 4.17 (s, 2H), 0.92 (s, 9H), 0.09 (s, 6H).

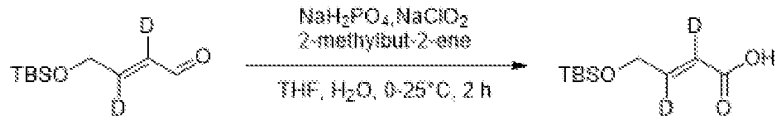
Step 1.3 Synthesis of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enal



3 4

[01235] To a solution of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-en-1-ol (15 g, 73.39 mmol, 1 *eq*) in DCM (300 mL) was added Dess-Martin (32.69 g, 77.06 mmol, 1.05 *eq*) at 0°C. The mixture was stirred at 0°C for 0.5 h. The reaction mixture was quenched by addition of sat.aq. $NaHCO_3$ (100 mL) at 0°C, and then extracted with DCM (100 mL x 2). The combined organic layers were washed with brine (100 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enal (13 g, 64.24 mmol, 87.53% yield) was obtained as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.62 (s, 1H), 4.46 (s, 2H), 0.94 (s, 9H), 0.10 (s, 6H).

Step 1.4 Synthesis of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoic acid



4

[01236] To a solution of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enal (13 g, 64.24 mmol, 1 *eq*) in THF (150 mL) were added sodium;dihydrogen phosphate (15.41 g, 128.48 mmol, 2 *eq*), 2-methylbut-2-ene (25.82 g, 368.10 mmol, 39.00 mL, 5.73 *eq*) at 25°C, then the solution of sodium;chlorite (17.43 g, 192.72 mmol, 3 *eq*) in H_2O (50 mL) was added dropwise into the reaction mixture at 0°C. The reaction mixture was warmed to 25°C and stirred for 2 h. The reaction mixture was quenched by addition of water (100 mL) at 0 °C, and then extracted with EtOAc (80 mL x 2). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoic acid (13 g, crude) was obtained as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.38 (s, 2H), 0.94 (s, 9H), 0.10 (s, 6H).

Step 1.5 Synthesis of (5S)-7-[(E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoyl] -N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

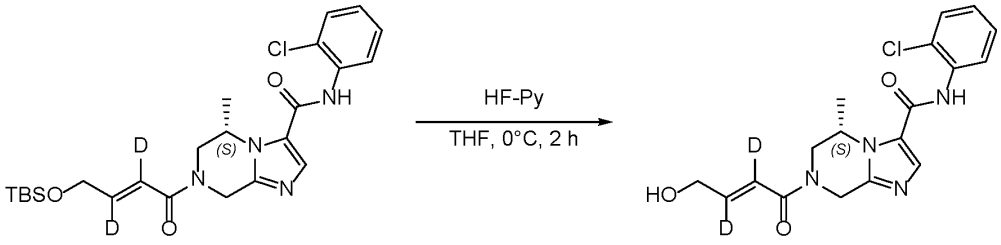


5

[01237] A mixture of (E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoic acid (413.07 mg, 1.89 mmol, 1.1 *eq*), (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.5 g, 1.72 mmol, 1 *eq*) and EDCI (659.34 mg, 3.44 mmol, 2 *eq*)in Py (10 mL) was stirred at 25°C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage ®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~100 % Ethyl acetate/Petroleum ether gradient @ 36 mL/min). Compound (5S)-7-[(E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-

a]pyrazine-3-carboxamide (0.8 g, 1.63 mmol, 94.73% yield) was obtained as brown gum. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.39 (td, J = 8.0 Hz, 1.6 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.07 (d, J = 4.4 Hz, 1H), 4.73-4.58 (m, 1H), 4.36 (s, 2H), 4.31-4.12 (m, 1H), 3.79-3.69 (m, 0.5H), 3.28-3.21 (m, 0.5H), 1.28 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

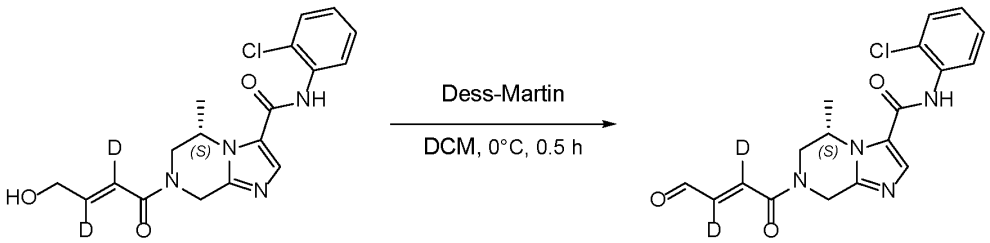
Step 1.6 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-hydroxy-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



5 6

[01238] To a solution of (5S)-7-[(E)-4-[tert-butyl(dimethyl)silyl]oxy-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.6 g, 1.22 mmol, 1 *eq*) in THF (6 mL) was added pyridine;hydrofluoride (1.10 g, 11.10 mmol, 1 mL, 9.08 *eq*) at 0°C. The mixture was stirred at 0°C for 2 h. The reaction mixture was quenched by addition of water (5 mL) at 0°C, and then adjusted pH=8 with sat.aq. $NaHCO_3$ and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/MeOH gradient @ 36 mL/min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-hydroxy-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (250 mg, 663.42 μmol, 54.30% yield) was obtained as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.4 Hz, 1.6 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 5.34-5.09 (m, 1H), 5.06 (s, 2H), 4.75-4.53 (m, 1H), 4.34-4.21 (m, 1H), 4.16 (d, J = 6.0 Hz, 2H), 3.77-3.65 (m, 0.5H), 3.30-3.19 (m, 0.5H), 1.34-1.21 (m, 3H).

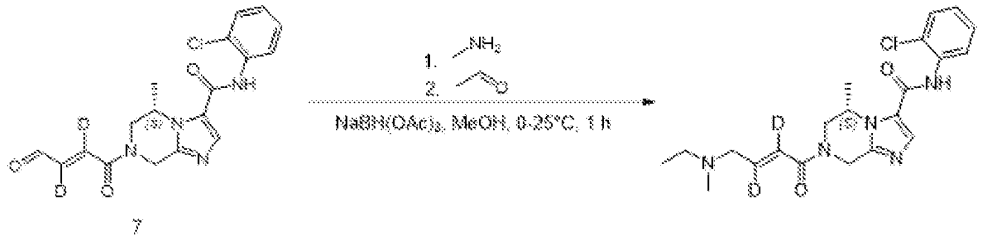
Step 1.7 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-oxo-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide -



6 7

[01239] To a solution of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-hydroxy-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (250 mg, 663.42 μmol, 1 *eq*) in DCM (5 mL) was added Dess-Martin (337.66 mg, 796.11 μmol, 1.2 *eq*) at 0°C. The mixture was stirred at 0°C for 0.5 h. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ (5 mL) at 0°C, and then extracted with DCM (5 mL x 2). The combined organic layers were washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/MeOH gradient @ 36 mL/min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-oxo-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (220 mg, 586.95 μmol, 88.47% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (d, J = 8.8 Hz, 1H), 9.78 (d, J = 2.8 Hz, 1H), 7.91 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 5.32-5.24 (m, 1H), 5.11 (d, J = 1.6 Hz, 1H), 4.79-4.59 (m, 1H), 4.42-4.32(m, 1H), 3.82 (dd, J = 14.4 Hz, 3.2 Hz,1H), 1.30 (dd, J = 20.4 Hz, 2.4 Hz, 3H).

Step 1.8 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



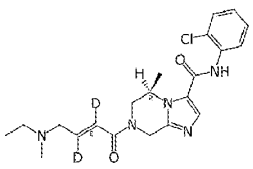
7

[01240] To a solution of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-oxo-but-2-enoyl]-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (180 mg, 480.23 μmol, 1 *eq*), methanamine;hydrochloride (38.91 mg, 576.28 μmol, 1.2 *eq*) and HOAc (28.84 mg, 480.23

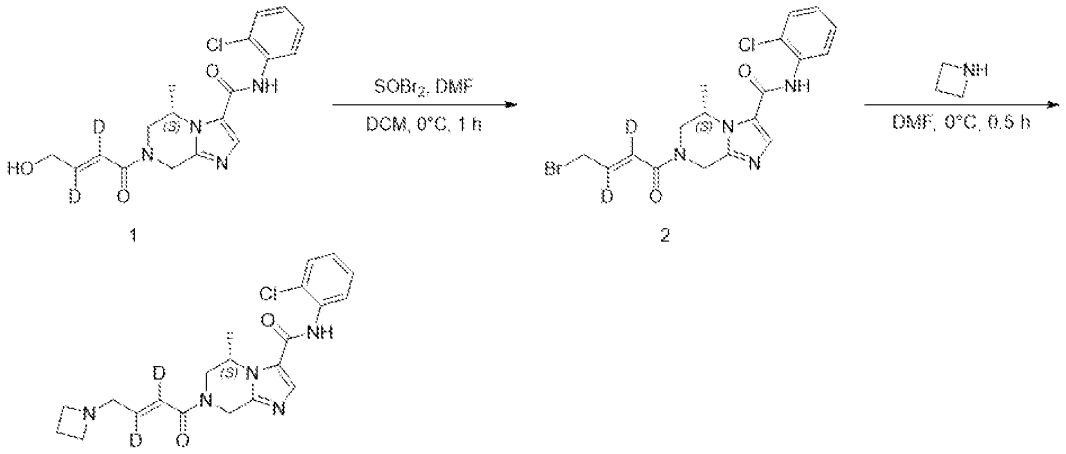
μmol, 27.49 μL, 1 *eq*) in MeOH (4 mL) was added $NaBH(OAc)_3$ (254.45 mg, 1.20 mmol, 2.5 *eq*) at 0°C, the mixture was stirred at 0°C for 0.5 h. Then acetaldehyde (5 M, 192.09 μL, 2 *eq*) was added to the mixture, and then $NaBH(OAc)_3$ (254.45 mg, 1.20 mmol, 2.5 *eq*) was added to the mixture, the mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 50% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (29.5 mg, 69.76 μmol, 14.53% yield, 98.83% purity) was obtained as an off-white solid. LCMS: m/z 418.2 [M+H]. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.40-7.36 (m, 1H), 7.33-7.29 (m, 1H), 5.29- 5.18 (m, 1H), 5.11-5.00 (m, 1H), 4.74-4.54 (m, 1H), 4.36-4.22 (m, 1H), 3.70 (d, *J* = 14.0 Hz, 0.5H), 3.28-3.21 (m, 0.5H), 3.14 (s, 2H), 2.43-2.31 (m, 2H), 2.14 (s, 3H), 1.29-1.25 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

[01241] Compounds in Table W were synthesized following the procedure for (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table W

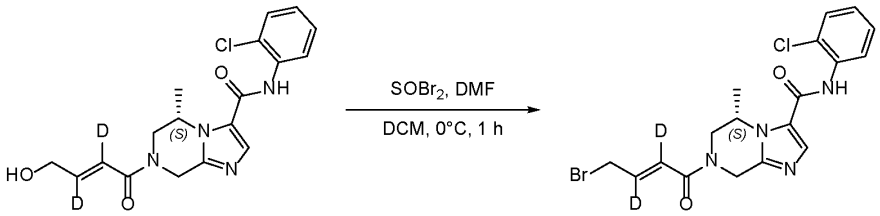
Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, *J* = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 5.28-5.18 (m, 1H), 5.04 (br.s, 1H), 4.70-4.57 (m, 1H), 4.30-4.28 (m, 1H), 3.70 (d, *J* = 14.0 Hz, 0.5H), 3.27-3.23 (m, 0.5H), 3.14 (s, 2H), 2.37 (q, *J* = 6.8 Hz, 2H), 2.14 (s, 3H), 1.29-1.28 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 418.2 $[M+H]^+$

Example 198: Synthesis of (5S)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



1 2

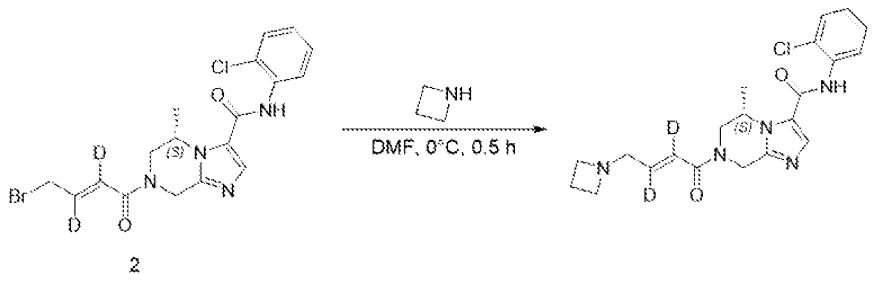
Step 1.1 Synthesis of (5S)-7-[(E)-4-bromo-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



1 2

[01242] To a solution of (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-hydroxy-but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.45 g, 1.19 mmol, 1 *eq*) and DMF (87.29 mg, 1.19 mmol, 91.88 µL, 1 *eq*) in DCM (10 mL) was added sulfurous dibromide (322.70 mg, 1.55 mmol, 120.28 µL, 1.3 *eq*) at 0°C. The mixture was stirred at 0°C for 1 h. LCMS showed the reaction was completed, one new peak with desired MS was formed. The reaction mixture was quenched by addition of water (5 mL) at 0°C, and then extracted with DCM (5 mL x 2). The combined organic layers were washed with brine (15 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound (5S)-7-[(E)-4-bromo-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.6 g, crude) was obtained as brown oil. LCMS: m/z 439.0/441.0 $[M+H]^+$.

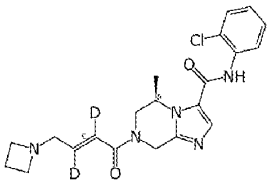
Step 1.2 Synthesis of (5S)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01243] To a solution of (5S)-7-[(E)-4-bromo-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.35 g, 795.94 μmol, 1 *eq*) in DMF (3 mL) was added azetidine (40.90 mg, 716.35 μmol, 48.34 μL, 0.9 *eq*) at 0°C, then the mixture was stirred at 0°C for 0.5h. The reaction mixture was adjusted pH = 6 with 4 N HCl, the residue was directly purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 70 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 17%- 55% B over 8.0 min). Compound (5S)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (21.9 mg, 49.77 μmol, 6.25% yield, 94.52% purity) was obtained as a white solid. LCMS: m/z 416.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 5.27-5.14 (m, 1H), 5.06 (s, 1H), 4.71-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.74-3.63 (m, 0.5H), 3.28-3.13 (m, 0.5H), 3.12 (s, 6H), 2.02-1.95 (m, 2H), 1.29-1.25 (m, 3H).

[01244] Compounds in Table WA were synthesized following the procedure for (5S)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2- chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

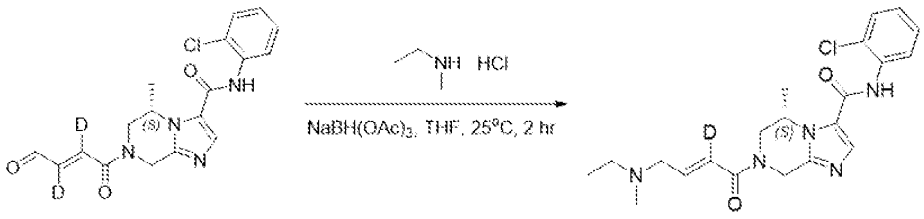
Table WA

Name	Structure	NMR	LCMS
(5R)-7-[(E)-4-(azetidin-1-yl)-2,3-dideuterio-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.40-7.36 (m, 1H), 7.31-7.27 (m, 1H), 5.29-5.13 (m, 1H), 5.05-5.02 (m, 1H), 4.70-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.69 (d, *J* = 12.8 Hz, 0.5H), 3.29-3.24 (m, 0.5H), 3.15-3.12 (m,	LCMS: m/z 416.1 $[M+H]^+$

Name	Structure	NMR	LCMS
		6H), 1.99 (q, *J* = 6.8 Hz, 2H), 1.29-1.24 (m, 3H).	

Example 199: Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2-deuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

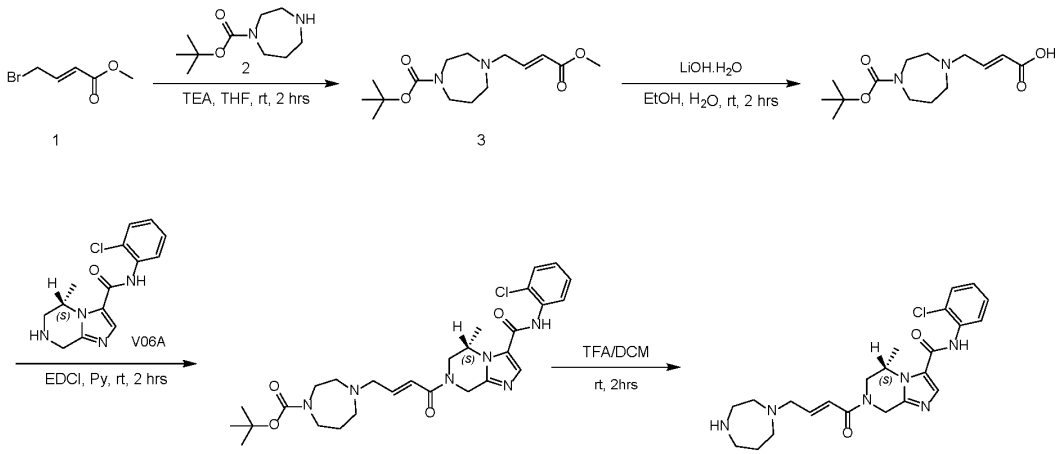
Step 1.1 Synthesis of (5S)-N-(2-chlorophenyl)-7-[(E)-2-deuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



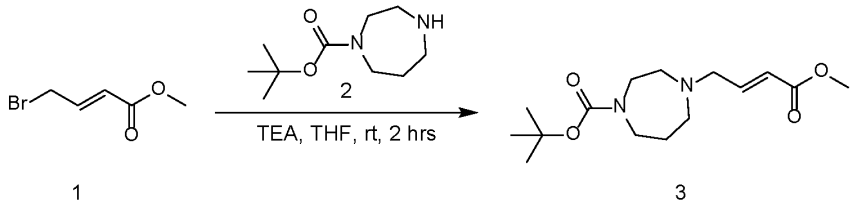
1

[01245] To a solution of N-methylethanamine (15.30 mg, 160.08 μmol, 22.24 μL, 1.2 eq, HCl) in THF (1 mL) was added TEA (16.20 mg, 160.08 μmol, 22.28 μL, 1.2 eq) at 25°C, then (5S)-N-(2-chlorophenyl)-7-[(E)-2,3-dideuterio-4-oxo-but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.05 g, 133.40 μmol, 1 eq), CH_3COOH (801.08 μg, 13.34 μmol, 7.64e-1 μL, 0.1 eq), $NaBH(OAc)_3$ (70.68 mg, 333.50 μmol, 2.5 eq) were added into the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2hr. The reaction mixture was quenched by addition H_2O (1 mL) at 25°C, and then concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18}150* 40* 7um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-2-deuterio-4-[ethyl(methyl)amino]but-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (3.4 mg, 8.16 μmol, 6.11% yield) was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.72 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.74-6.73 (m, 1H), 5.28-5.16 (m, 1H), 5.05-5.04 (m, 1H), 4.70-4.57 (m, 1H), 4.31-4.26 (m, 1H), 3.72-3.68 (m, 0.5H), 3.27-3.22 (m, 0.5H), 3.14 (d, *J* = 6.0 Hz, 2H), 2.39-2.34 (m, 2H), 2.14 (s, 3H), 1.29-1.26 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

Example 200: Synthesis of tert-butyl 4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate.

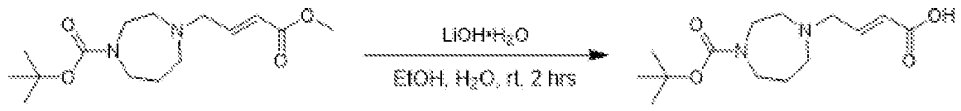


Step 1.1 Synthesis of tert-butyl 4-[(E)-4-methoxy-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate



[01246] To a solution of tert-butyl 1,4-diazepane-1-carboxylate (9 g, 44.94 mmol, 8.86 mL, 1.2 *eq*) in THF (100 mL) was added TEA (11.37 g, 112.34 mmol, 15.64 mL, 3 *eq*) at 20°C. Then methyl (E)-4-bromobut-2-enoate (6.70 g, 37.45 mmol, 4.40 mL, 1 *eq*) was added to the mixture dropwise at 20°C. The reaction mixture was stirred at 20°C for 2 hrs. The reaction mixture was filtered and the filter cake was washed with THF (100 mL x 3). Then the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl 4-[(E)-4-methoxy-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (10 g, 33.51 mmol, 89.50% yield) was obtained as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.82 (dt, J = 6.0 Hz, 1H), 6.01 (d, J = 15.6 Hz, 1H), 3.65 (s, 3H), 3.35-3.32 (m, 4H), 3.26 (d, J = 5.6 Hz, 2H), 2.58-2.56 (m, 2H), 2.54-2.53 (m, 2H), 1.70 (s, 2H), 1.39 (s, 9H).

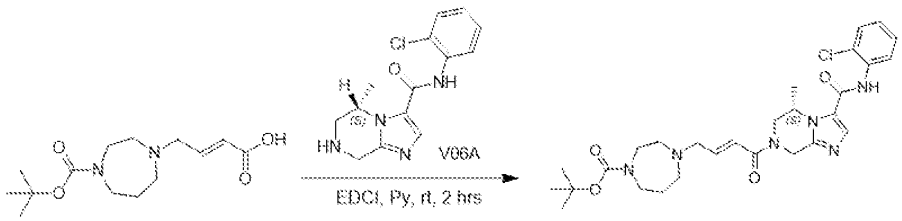
Step 1.2 Synthesis of (E)-4-(4-tert-butoxycarbonyl-1,4-diazepan-1-yl)but-2-enoic acid



3

[01247] To a solution of tert-butyl 4-[(E)-4-methoxy-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (10.3 g, 34.52 mmol, 1 *eq*) in EtOH (80 mL) and H_2O (40 mL) was added $LiOH•H_2O$ (3.62 g, 86.30 mmol, 2.5 *eq*) at 20°C. The reaction mixture was stirred at 20°C for 2 hrs. LCMS indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04%HCl)-ACN]; gradient: 10%-40% B over 20.0 min). Compound (E)-4-(4-tert-butoxycarbonyl-1,4-diazepan-1-yl)but-2-enoic acid (8 g, 28.13 mmol, 81.50% yield) was obtained as a yellow solid. LCMS: m/z 285.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.81 (dt, J = 6.4 Hz, 1H), 6.03 (d, J = 15.6 Hz, 1H), 3.57-3.38 (m, 6H), 2.88 (s, 4H), 1.90 (s, 2H), 1.40 (s, 9H).

Step 1.3 Synthesis of tert-butyl 4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate

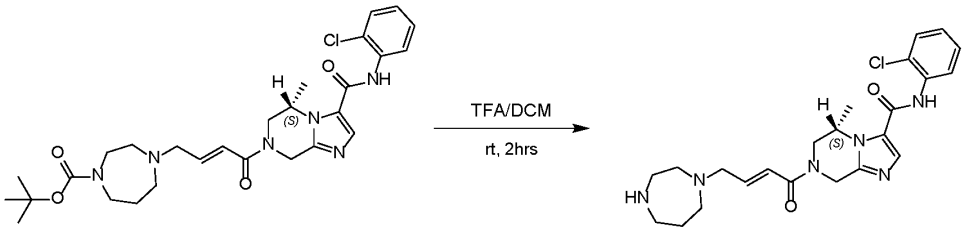


[01248] To a solution of (E)-4-(4-tert-butoxycarbonyl-1,4-diazepan-1-yl)but-2-enoic acid (293.40 mg, 1.03 mmol, 1.2 *eq*) and (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.25 g, 859.85 μmol, 1.00 *eq*) in pyridine (5 mL) was added EDCI (329.67 mg, 1.72 mmol, 2 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~15% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Then the crude product was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 35%-65% B over 8.0 min). Compound tert-butyl 4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-

dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (0.0593 g, 106.32 µmol, 98.71% yield, 99.878% purity) was obtained as a white solid. LCMS: m/z 557.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.71 (m, 2H), 5.28-5.18 (m, 1H), 5.05 (s, 1H), 4.70-4.58 (m, 1H), 4.28 (d, J = 16.8 Hz, 1H), 3.71 (d, J = 14.0 Hz, 1H), 3.37-3.34 (m, 4H), 3.28 (d, J = 4.0 Hz, 2H), 2.59-2.58 (m, 2H), 1.72-1.71 (m, 2H), 1.39 (s, 10H), 1.30-1.25 (m, 3H).

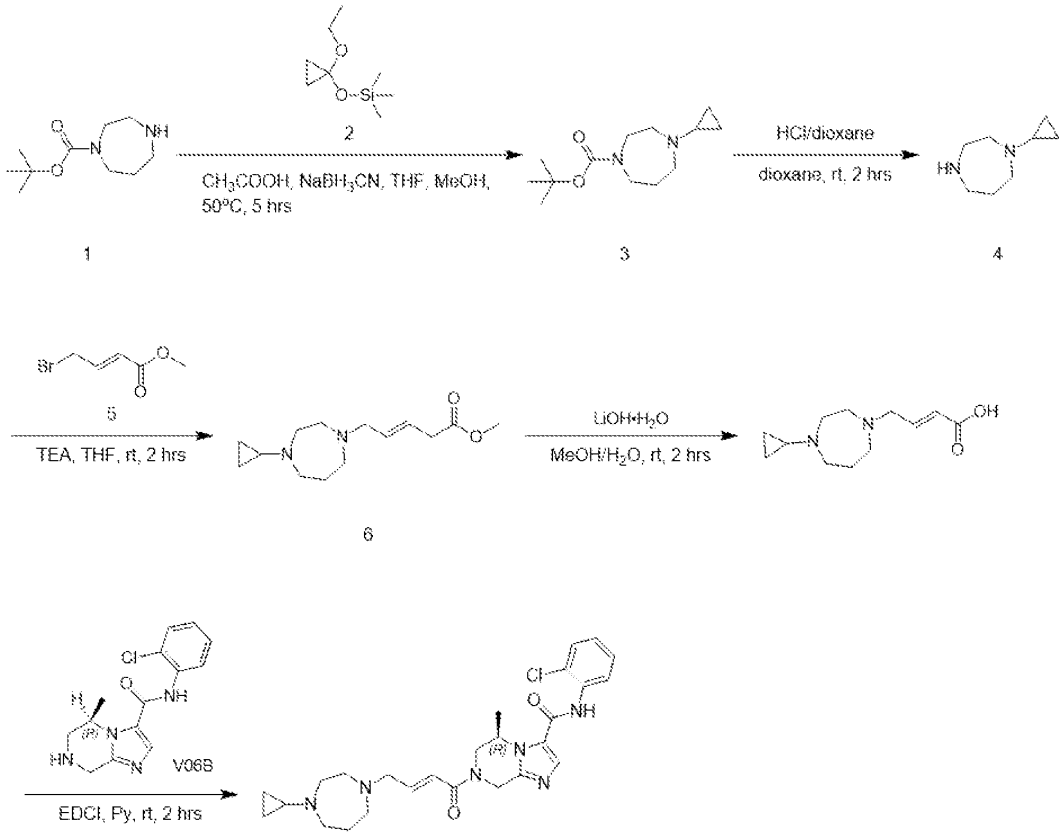
Example 201: Synthesis of (S,E)-7-(4-(1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.

Step 1.1 Synthesis of (S,E)-7-(4-(1,4-diazepan-1-yl)but-2-enoyl)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

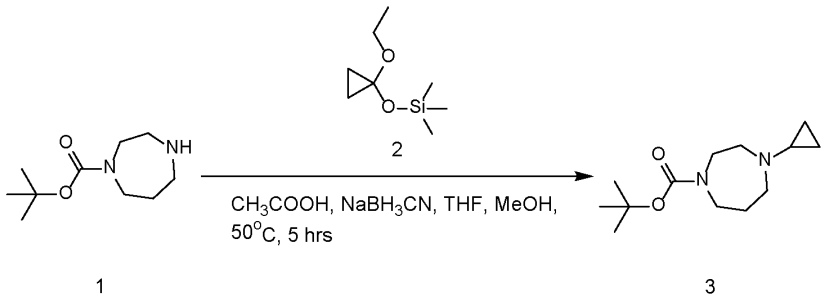


[01249] To a solution of tert-butyl 4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate (0.3 g, 538.52 µmol, 1 *eq*) in DCM (6 mL) was added TFA (184.21 mg, 1.62 mmol, 120.01 µL, 3 *eq*) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 15%-45% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-7-[(E)-4-(1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.0068 g, 14.87 µmol, 6.79% yield, 99.905% purity) was obtained as a white solid. LCMS: m/z 457.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.84 (d, J = 10.4 Hz, 1H), 7.89-7.88 (m, 1H), 7.54 (t, J = 7.2 Hz, 2H), 7.38 (t, J = 6.8 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 5.17-5.04 (m, 2H), 4.64-4.52 (m, 1H), 4.23-4.12 (m, 1H), 3.68-3.60 (m, 1H), 3.49-3.41 (m, 1H), 3.19-3.10 (m, 2H), 3.02-2.64 (m, 9H), 2.33-2.27 (m, 1H), 1.86-1.71 (m, 2H), 1.35-1.23 (m, 3H).

Example 202: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



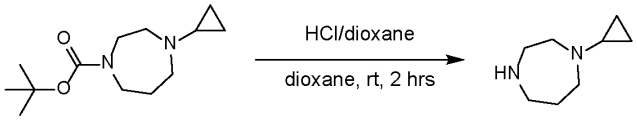
Step 1.1 Synthesis of tert-butyl 4-cyclopropyl-1,4-diazepane-1-carboxylate



[01250] To a solution of tert-butyl 1,4-diazepane-1-carboxylate (4 g, 19.97 mmol, 3.94 mL, 1 eq) and (1-ethoxycyclopropoxy)-trimethyl-silane (6.96 g, 39.94 mmol, 8.03 mL, 2 eq) in THF (40 mL) and MeOH (40 mL) were added CH_3COOH (1.92 g, 31.96 mmol, 1.83 mL, 1.6 eq) and $NaBH_3CN$ (1.88 g, 29.96 mmol, 1.5 eq) at 25°C. The reaction mixture was heated to 50°C

and stirred at 50°C for 5 hrs. The reaction was cooled to 25°C and quenched by addition of H_2O (5 mL) and then 1 N NaOH (20 mL) was added. The mixture was concentrated under reduced pressure. The residue was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound tert-butyl 4-cyclopropyl-1,4-diazepane-1-carboxylate (5.6 g, crude) was obtained as colorless oil. LCMS: m/z 241.3 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.49-3.41 (m, 4H), 2.86-2.74 (m, 4H), 1.85-1.78 (m, 3H), 1.46 (s, 9H), 0.47-0.40 (m, 4H).

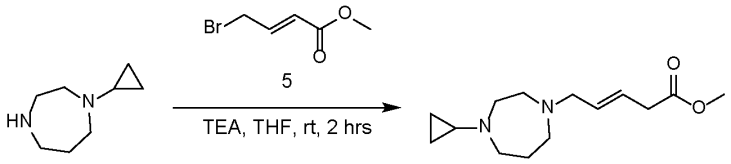
Step 1.2 Synthesis of 1-cyclopropyl-1,4-diazepane



3 4

[01251] To a solution of tert-butyl 4-cyclopropyl-1,4-diazepane-1-carboxylate (5.6 g, 23.30 mmol, 1 eq) in dioxane (60 mL) was added HCl/dioxane (4 M, 5.83 mL, 1 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. Compound 1-cyclopropyl-1,4-diazepane (4.3 g, crude) was obtained as a white solid. LCMS: m/z 141.3 $[M+H]^+$. ^1H NMR (MeOD, 400 MHz) δ 3.60 (d, J = 5.6 Hz, 2H), 3.43 (d, J = 14.4 Hz, 3H), 3.18-3.11 (m, 3H), 2.97-2.95 (m, 1H), 2.77-2.72 (m, 1H), 2.04-1.97 (m, 2H), 0.92-0.88 (m, 2H), 0.69-0.64 (m, 2H).

Step 1.3 Synthesis of methyl (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoate

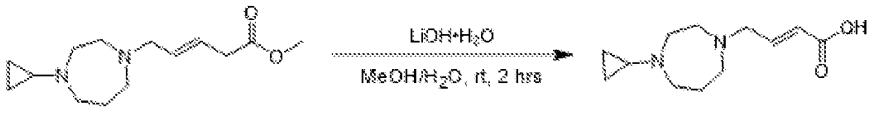


4 6

[01252] To a solution of 1-cyclopropyl-1,4-diazepane (3.8 g, 21.51 mmol, 1 eq, HCl) and methyl (E)-4-bromobut-2-enoate (3.85 g, 21.51 mmol, 2.53 mL, 1 eq) in THF (80 mL) was added TEA (6.53 g, 64.52 mmol, 8.98 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was filtered and the filter cake was washed with THF (50 mL x 3). Then the filtrate was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound methyl (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoate (2.8 g, 11.75 mmol, 54.63% yield) was

obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01-6.94 (m, 1H), 6.00-5.95 (m, 1H), 3.74 (s, 3H), 3.26 (dd, *J* = 6.0 Hz, 1.6 Hz, 2H), 2.86-2.83 (m, 4H), 2.69-2.64 (m, 4H), 1.91-1.86 (m, 1H), 1.77 (q, *J* = 6.0 Hz, 2H), 0.44-0.39 (m, 4H).

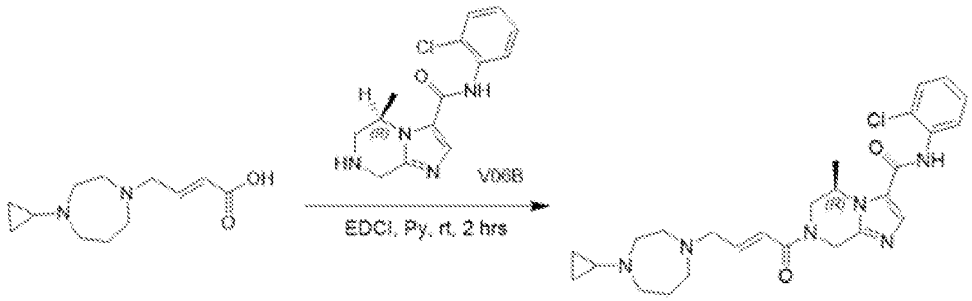
Step 1.4 Synthesis of (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoic acid



s

[01253] To a solution of methyl (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoate (2.8 g, 11.75 mmol, 1 eq) in MeOH (30 mL) and H_2O (10 mL) was added LiOH•H_2O (1.23 g, 29.37 mmol, 2.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} (250 * 70 mm, 15 um); mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1%- 10% B over 20.0 min). Compound (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoic acid (4.7 g, crude) was obtained as colorless oil. LCMS: m/z 225.1 $[M+H]^+$.

Step 1.5 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

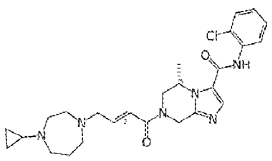


[01254] To a solution of (E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoic acid (92.57 mg, 412.73 μmol, 1.2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.1 g, 343.94 μmol, 1 eq) in pyridine (2 mL) was added EDCI (131.87 mg, 687.88 μmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Genimi NX C_{18} 150 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min). Compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl] -5-methyl-6,8-

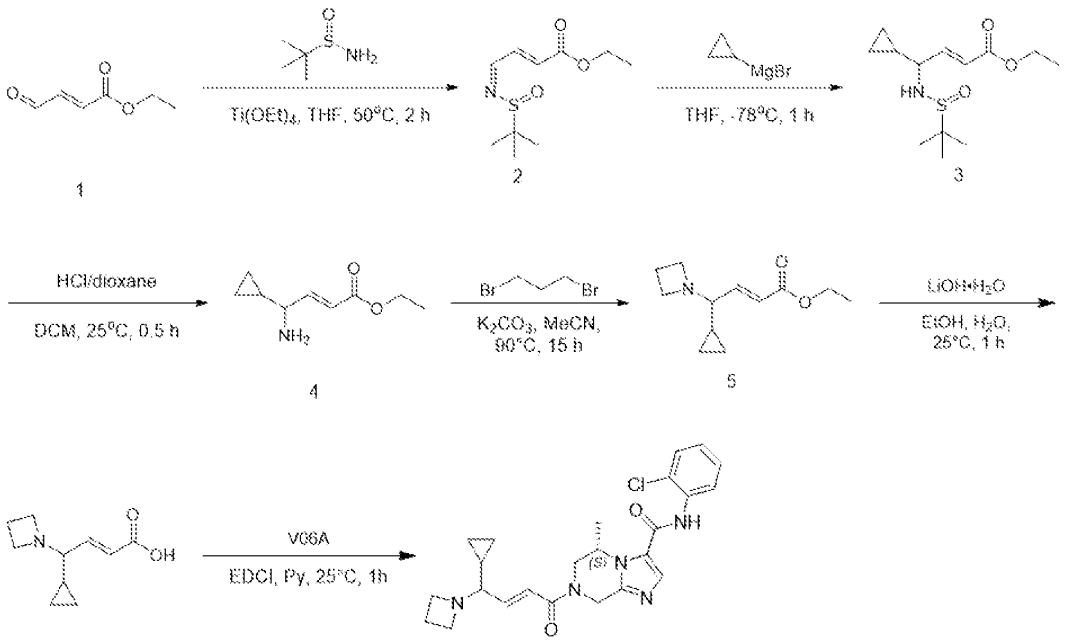
dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.0469 g, 93.90 μmol, 27.30% yield, 99.509% purity) was obtained as a white solid. LCMS: m/z 497.3 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.88 (s, 1H), 7.54 (td, J = 7.6 Hz, 1.2 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.71 (m, 2H), 5.28-5.17 (m, 1H), 5.06 (br.s, 1H), 4.70-4.57 (m, 1H), 4.30-4.26 (m, 1H), 3.70 (d, J = 14.0 Hz, 1H), 3.26 (d, J = 4.4 Hz, 2H), 2.77-2.74 (m, 4H), 2.62-2.60 (m, 4H), 1.95-1.80 (m, 1H), 1.70-1.67 (m, 2H), 1.29-1.25 (m, 3H), 0.40-0.38 (m, 2H), 0.27-0.26 (m, 2H).

[01255] Compounds in Table WB were synthesized following the procedure for (5R)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

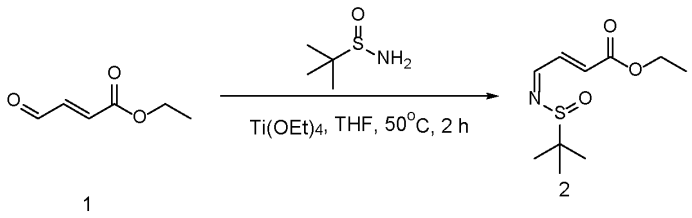
Table WB

Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-7-[(E)-4-(4-cyclopropyl-1,4-diazepan-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br.s, 1H), 7.88 (s, 1H), 7.54 (t, J = 6.4 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.77-6.67 (m, 2H), 5.27-5.14 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.27 (d, J = 16.8 Hz, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.26 (d, J = 4.0 Hz, 2H), 2.76-2.74 (m, 4H), 2.60-2.59 (m, 4H), 1.87 (s, 1H), 1.69-1.66 (m, 2H), 1.29-1.25 (m, 3H), 0.39 (d, J = 4.8 Hz, 2H), 0.26 (s, 2H)	LCMS: m/z 497.2 $[M+H]^+$

Example 203: Synthesis of (5S)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



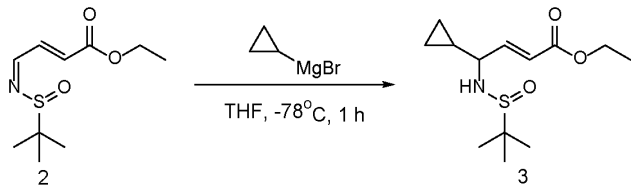
Step 1.1 Synthesis of ethyl (E,4Z)-4-tert-butylsulfinyliminobut-2-enoate



[01256] A mixture of ethyl (E)-4-oxobut-2-enoate (5 g, 39.02 mmol, 1 *eq*), 2-methylpropane-2-sulfinamide (9.46 g, 78.05 mmol, 2 *eq*) and tetraethoxytitanium (17.80 g, 78.05 mmol, 16.18 mL, 2 *eq*) in THF (80 mL) was heated to 50°C and stirred at 50°C for 2 h. The reaction mixture was quenched by addition of NH_4Cl (50 mL) at 0 °C, and then the mixture was filtered and the filtrate was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound ethyl (E,4Z)-4-tert-butylsulfinyliminobut-2-enoate (8.5 g, 36.75 mmol, 94.16% yield) was obtained as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, *J* =

9.6 Hz, 1H), 7.43 (dd, *J* = 16.0 Hz, 9.2 Hz, 1H), 6.50 (d, *J* = 15.6 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.35 (q, *J* = 7.2 Hz, 3H), 1.24 (s, 9H).

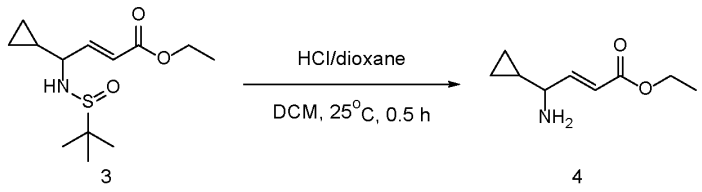
Step 1.2 Synthesis of ethyl (E)-4-(tert-butylsulfinylamino)-4-cyclopropyl-but-2-enoate



2 3

[01257] To a solution of ethyl (E,4Z)-4-tert-butylsulfinyliminobut-2-enoate (2 g, 8.65 mmol, 1 *eq*) in THF (40 mL) was added bromo(cyclopropyl)magnesium (1 M, 9.51 mL, 1.1 *eq*) at -78°C. The mixture was stirred at -78°C for 1 h. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (50 mL) at 0 °C, and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (40 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @80 mL/min). Compound ethyl (E)-4-(tert-butylsulfinylamino)-4-cyclopropyl-but-2-enoate (1.6 g, 5.85 mmol, 67.69% yield) was obtained as brown oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.00-6.85 (m, 1H), 6.07-5.99 (m, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.21-3.16 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 9H), 1.05-0.94 (m, 1H), 0.68-0.62 (m, 2H), 0.50-0.46 (m, 1H), 0.39-0.35 (m, 1H).

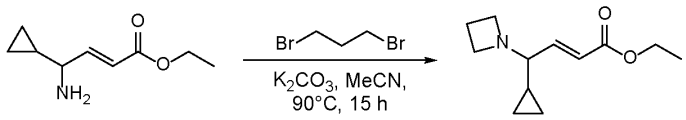
Step 1.3 Synthesis of ethyl (E)-4-amino-4-cyclopropyl-but-2-enoate



3 4

[01258] To a solution of ethyl (E)-4-(tert-butylsulfinylamino)-4-cyclopropyl-but-2-enoate (1.6 g, 5.85 mmol, 1 *eq*) in DCM (10 mL) was added HCl/dioxane (4 M, 10 mL) at 25°C. The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated. Compound ethyl (E)-4-amino-4-cyclopropyl-but-2-enoate (1 g, crude, HCl) was obtained as brown oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.91-8.77 (m, 2H), 7.03 (dd, *J* = 16.0 Hz, 6.0 Hz, 1H), 6.25 (t, *J* = 16.0 Hz, 1H), 4.23-4.17 (m, 2H), 3.33 (br.s, 1H), 1.31-1.26 (m, 4H), 0.86-0.74 (m, 3H), 0.45-0.43 (m, 1H).

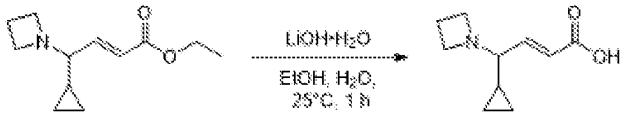
Step 1.4 Synthesis of ethyl (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoate



4 5

[01259] To a solution of ethyl (E)-4-amino-4-cyclopropyl-but-2-enoate (1 g, 4.86 mmol, 1 *eq*, HCl) in MeCN (20 mL) was added 1,3-dibromopropane (981.56 mg, 4.86 mmol, 495.74 μL, 1 *eq*) and K_2CO_3 (1.68 g, 12.15 mmol, 2.5 *eq*) at 25°C. The mixture was heated to 90°C and stirred at 90°C for 15 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @80 mL/min). Compound ethyl (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoate (0.48 g, 2.29 mmol, 47.17% yield) was obtained as brown oil. LCMS: m/z 210.1 $[M+H]^+$.

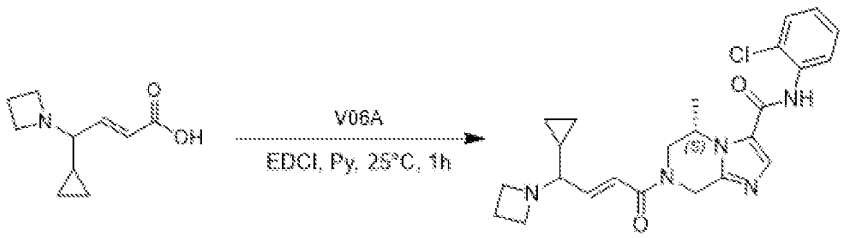
Step 1.5 Synthesis of (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoic acid



5

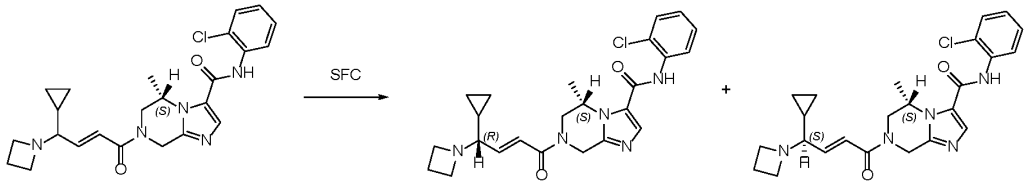
[01260] To a solution of ethyl (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoate (0.48 g, 2.29 mmol, 1 *eq*) in EtOH (5 mL) and H_2O (2 mL) was added $LiOH•H_2O$ (240.61 mg, 5.73 mmol, 2.5 *eq*) at 25°C. The mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated to remove EtOH, the residue was adjusted pH = 6 with 4 N HCl. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 250 * 50 mm * 15 um; mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 1%- 10% B over 10.0 min). Compound (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoic acid (150 mg, 827.67 μmol, 36.09% yield) was obtained as a white solid. LCMS: m/z 182.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 11.71 (s, 1H), 6.65 (dd, *J* = 16.0 Hz, 8.8 Hz, 1H), 6.13 (d, *J* = 16.0 Hz, 1H), 4.26-4.13 (m, 1H), 4.06 (d, *J* = 2.8 Hz, 1H), 4.00-3.80 (m, 2H), 3.41-3.38 (m, 1H), 2.47-2.35 (m, 1H), 2.24-2.09 (m, 1H), 1.12-0.96 (m, 1H), 0.75-0.48 (m, 3H), 0.26-0.14 (m, 1H).

Step 1.6 Synthesis of (5S)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

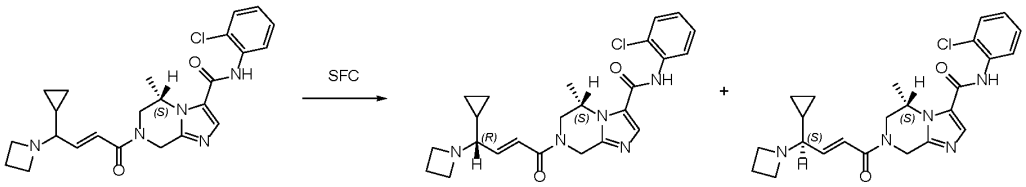


[01261] A mixture of (E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoic acid (74.80 mg, 412.73 μmol, 1 *eq*), (5S)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (120 mg, 412.73 μmol, 1 *eq*) and EDCI (158.24 mg, 825.46 μmol, 2 *eq*) in Py (5 mL) was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20%- 50% B over 8.0 min). Compound (5S)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (105.5 mg, 226.61 μmol, 54.91% yield, 97.51% purity) was obtained as a white solid. LCMS: m/z 454.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 6.64-6.52 (m, 2H), 5.31-5.14 (m, 1H), 5.12-5.00 (m, 1H), 4.74-4.53 (m, 1H), 4.35-4.22 (m, 1H), 3.72-3.68 (m, 0.5H), 3.25-3.20 (m, 0.5H), 3.18-3.01 (m, 4H), 2.15-2.06 (m, 1H), 1.98-1.86 (m, 2H), 1.32-1.17 (m, 3H), 0.70-0.59 (m, 1H), 0.57-0.46 (m, 1H), 0.40-0.21 (m, 2H), 0.12-0.04 (m, 1H).

Example 204: Synthesis of (5S)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.1 Synthesis of (5S)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



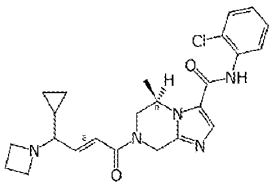
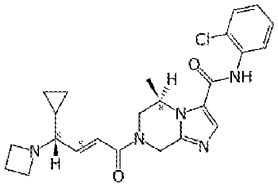
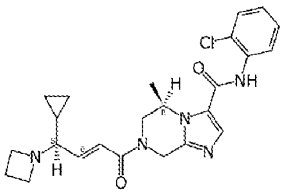
[01262] (5S)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (100 mg, 220.28 μmol, 1 *eq*) was separated by SFC(column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); mobile phase: [CO_2- EtOH (0.1% NH_3H_2O)]; B%: 35%, isocratic elution mode). Compound (5S)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (24 mg, 51.85 μmol, 23.54% yield, 98.08% purity) was obtained as a white solid. Compound (5S)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (22.7 mg, 49.16 μmol, 22.32% yield, 98.31% purity) was obtained as a white solid.

[01263] LCMS: m/z 454.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (t, J = 6.8 Hz, 2H), 7.39-7.35 (m, 1H), 7.31-7.27 (m, 1H), 6.64-6.54 (m, 2H), 5.28-5.21 (m, 1H), 5.06 (s, 1H), 4.70-4.54 (m, 1H), 4.33-4.20 (m, 1H), 3.75-3.66 (m, 0.5H), 3.27-3.20 (m, 0.5H), 3.12-3.05 (m, 4H), 2.10 (t, J = 8.0 Hz, 1H), 1.98-1.86 (m, 2H), 1.32-1.17 (m, 3H), 0.70-0.61 (m, 1H), 0.58-0.46 (m, 1H), 0.40-0.27 (m, 2H), 0.11-0.01 (m, 1H).

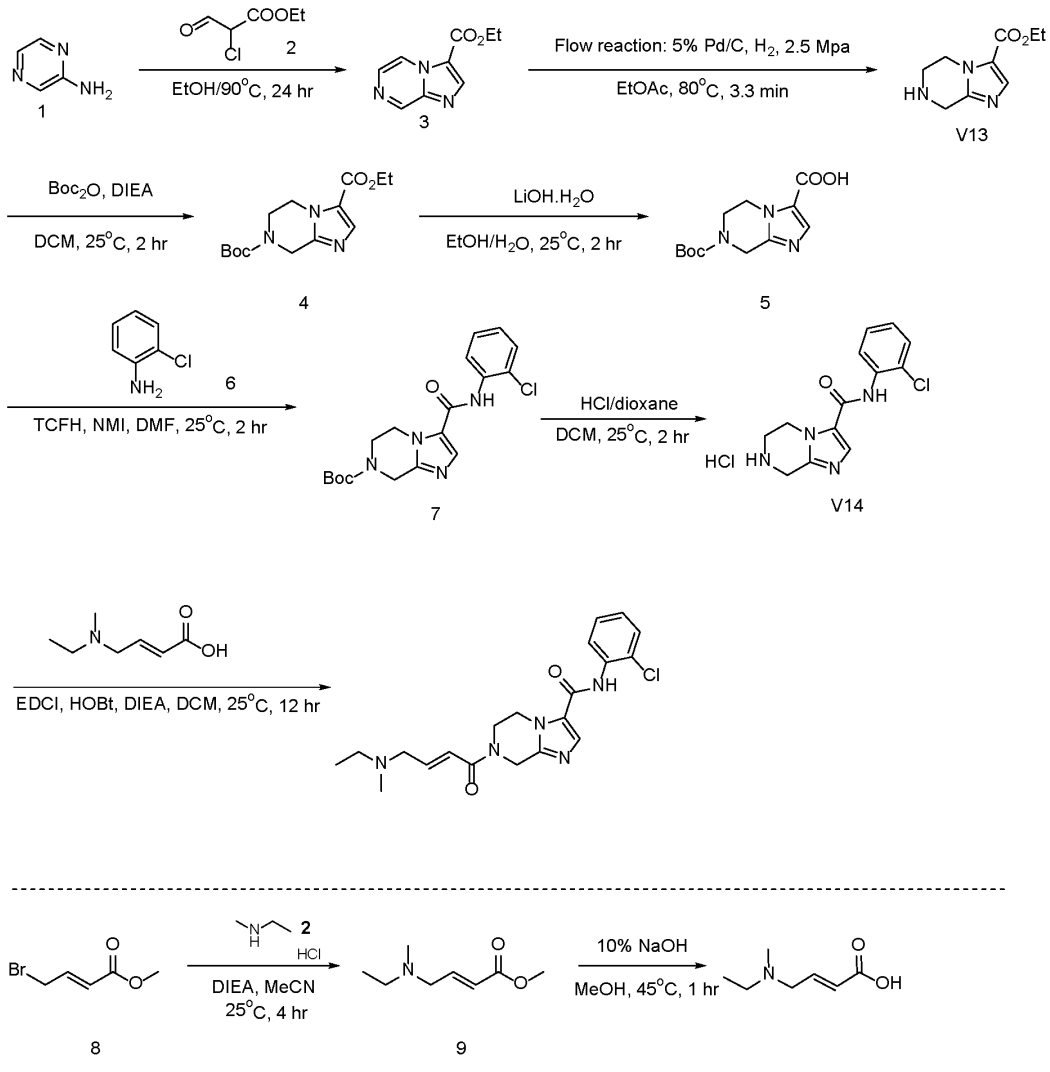
[01264] LCMS: m/z 454.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.56-7.53 (m, 2H), 7.38 (td, J = 8.0 Hz, 1.6Hz, 1H), 7.31-7.27 (m, 1H), 6.67-6.47 (m, 2H), 5.33-5.20 (m, 1H), 5.10-5.01 (m, 1H), 4.71-4.54 (m, 1H), 4.33-4.23 (m, 1H), 3.74-3.66 (m, 0.5H), 3.25-3.23 (m, 0.5H), 3.13 (t, J = 6.4 Hz, 4H), 2.10 (t, J = 8.0 Hz, 1H), 1.99-1.89 (m, 2H), 1.30-1.22 (m, 3H), 0.72-0.59 (m, 1H), 0.58-0.46 (m, 1H), 0.40-0.25 (m, 2H), 0.10-0.01 (m, 1H).

[01265] Compounds in Table X were synthesized following the procedure for synthesis of tert-butyl 4-[(E)-4-[(5S)-3-[(2-chlorophenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-oxo-but-2-enyl]-1,4-diazepane-1-carboxylate and synthesis of (5S)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table X

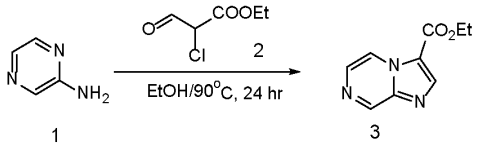
Name	Structure	NMR	LCMS	SFC conditions
(5R)-7-[(E)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.88 (s, 1H), 7.55-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.63-6.50 (m, 2H), 5.28-5.15 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.31-4.24 (m, 1H) , 3.70 (d, J = 14.0 Hz, 1H), 3.26-3.22 (m, 1H), 3.14-3.10 (m, 3H), 2.10 (td, J = 8.0 Hz, 3.2 Hz, 1H), 1.96-1.91 (m, 2H), 1.27-1.24 (m, 3H), 0.69-0.61 (m, 1H), 0.54-0.47 (m, 1H), 0.35-0.27 (m, 2H), 0.04 (s, 1H).	LCMS: m/z 454.1 $[M+H]^+$	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (br s, 1H), 7.88 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.64-6.51 (m, 2H), 5.28-5.15 (m, 1H), 5.05 (s, 1H), 4.70-4.55 (m, 1H), 4.32-4.24 (m, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.15 (s, 4H), 2.15 (s, 1H), 1.98-1.91 (m, 2H), 1.29-1.25 (m, 3H), 0.66 (s, 1H), 0.52 (s, 1H), 0.36-0.31 (m, 2H), 0.057-0.037 (m, 1H).	LCMS: m/z 454.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm × 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% $NH_3 \cdot H_2O$)]; B%: 40%, isocratic elution mode).
(5R)-7-[(E,4S)-4-(azetidin-1-yl)-4-cyclopropyl-but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.88 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.37 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.2 Hz, 1H), 6.67-6.50 (m, 2H), 5.28-5.17 (m, 1H), 5.05 (s, 1H), 4.89-4.55 (m, 1H), 4.31-4.24 (m, 1H), 3.71 (d, J = 13.2 Hz, 1H), 3.16 (s, 4H), 2.16 (s, 1H), 1.95 (d, J = 6.0 Hz, 2H), 1.28-1.27 (m, 3H), 0.71-0.63 (m, 1H), 0.55-0.49 (m, 1H), 0.36-0.28 (m, 2H), 0.098-0.057 (m, 1H).	LCMS: m/z 454.1 $[M+H]^+$	SFC (column: DAICEL CHIRALPAK AD (250 mm × 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% $NH_3 \cdot H_2O$)]; B%: 40%, isocratic elution mode).

Example 205: Synthesis of N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



1 2 3 V13 4 5 6 7 V14 8 9

Step 1.1 Synthesis of ethyl imidazo[1,2-a]pyrazine-3-carboxylate

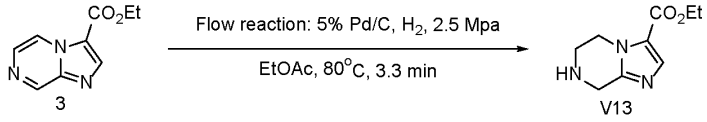


1 3

[01266] To a solution of pyrazin-2-amine (100 g, 1.05 mol, 1 eq) in EtOH (2 L) was added ethyl 2-chloro-3-oxo-propanoate (189.98 g, 1.26 mol, 1.2 eq) at 25°C. The reaction mixture was heated to 90°C and was stirred at 90°C for 24 hr. The reaction mixture was cooled to 25°C and the reaction mixture was concentrated under reduced pressure to give a residue, the residue was diluted with H_2O (500 mL) and adjusted pH = 7 then the reaction mixture was extracted with EtOAc (1000 mL x 3). The combined organic layers were washed with brine (3000 mL x

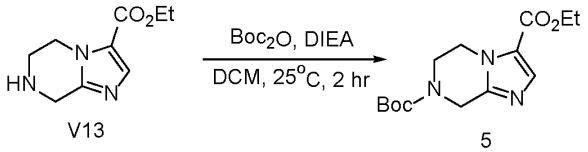
1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g Sepa Flash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 150 mL/min). Compound ethyl imidazo[1,2-a]pyrazine-3-carboxylate (100 g, 523.05 mmol, 49.74% yield) was obtained as a yellow solid. LCMS: m/z 192.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.30 (d, J = 1.6 Hz, 1H), 9.11 (dd, J = 4.4 Hz, 1.2 Hz, 1H), 8.44 (s, 1H), 8.23 (d, J = 4.8 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H).

Step 1.2 Synthesis of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (V13)



[01267] To a solution of ethyl imidazo[1,2-a]pyrazine-3-carboxylate (50 g, 261.53 mmol, 1 eq) in EtOAc (500 mL), then reaction mixture was added Pd/C (5 g, 5% purity) and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 80°C for 3.3 min under H_2 atmosphere. The reaction solution was filtered and the filtration was concentrated to give compound ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (V13) (50 g, 256.12 mmol, 97.93% yield) was obtained as a yellow solid. LCMS: m/z 196.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (s, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.09 (t, J = 5.6 Hz, 2H), 3.88 (s, 2H), 3.05 (t, J = 5.6 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H).

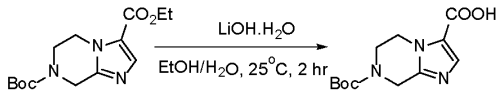
Step 1.3 Synthesis of O7-tert-butyl O3-ethyl 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7 -dicarboxylate



[01268] To a solution of ethyl 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (19.5 g, 99.89 mmol, 1 eq) in DCM (200 mL) were added Boc_2O (26.16 g, 119.87 mmol, 27.54 mL, 1.2 eq) and DIEA (19.36 g, 149.83 mmol, 26.10 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (200 mL) at 25°C, and adjusted the reaction mixture pH = 5 by sat.aq.citric acid and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound O7-tert-butyl O3-ethyl 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (29.5 g, crude) was obtained

as a black oil. LCMS: m/z 296.1 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (s, 1H), 4.73 (s, 2H), 4.36-4.28 (m, 4H), 3.84 (t, J = 5.2 Hz, 2H), 1.49 (s, 9H), 1.36 (t, J = 6.8 Hz, 3H).

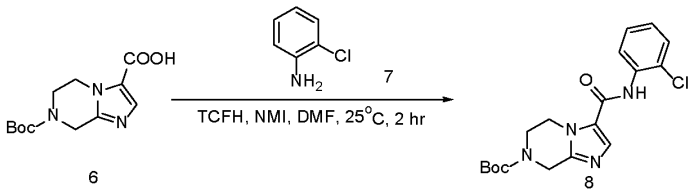
Step 1.4 Synthesis of 7-tert-butoxycarbonyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid



5 6

[01269] To a solution of O7-tert-butyl O3-ethyl 6,8-dihydro-5H-imidazo[1,2-a]pyrazine- 3,7-dicarboxylate (29.50 g, 99.89 mmol, 1 eq) in EtOH (200 mL), H_2O (100 mL) were added $LiOH.H_2O$ (12.58 g, 299.67 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (200 mL) at 25°C, and adjusted the reaction mixture pH = 3 by 1 N HCl and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 7-tert-butoxycarbonyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (18 g, 67.35 mmol, 67.42% yield) was obtained as a white solid. LCMS: m/z 268.2 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 12.76 (s, 1H), 7.57 (s, 1H), 4.58 (s, 2H), 4.23 (t, J = 5.6 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 1.44 (s, 9H).

Step 1.5 Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate

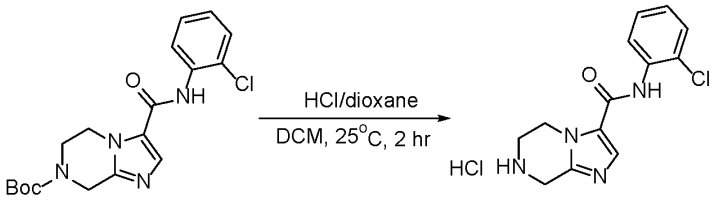


6 8

[01270] To a solution of 7-tert-butoxycarbonyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (18 g, 67.35 mmol, 1 eq) in DMF (180 mL) were added 2-chloroaniline (17.18 g, 134.69 mmol, 14.20 mL, 2 eq), TCFH (56.69 g, 202.04 mmol, 3 eq) and NMI (16.59 g, 202.04 mmol, 16.10 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (300 mL) at 25°C, and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound tert-butyl

3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate (25 g, crude) was obtained as a yellow oil. LCMS: m/z 377.1 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, *J* = 6.8 Hz, 1H), 8.15 (s, 1H), 7.64 (s, 1H), 7.43 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 4.77 (s, 2H), 4.45 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 5.2 Hz, 2H), 1.51 (s, 9H).

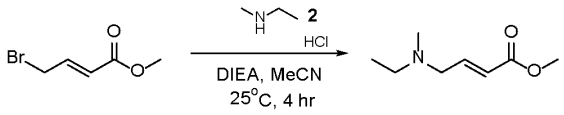
Step 1.6 Synthesis of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V14)



8 V14

[01271] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate (25 g, 66.34 mmol, 1 eq) in DCM (100 mL) was added HCl/dioxane (4 M, 100 mL, 6.03 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give compound N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V14) (25 g, crude) was obtained as a yellow solid. LCMS: m/z 277.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.75 (s, 1H), 8.53 (s, 1H), 7.58 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.40 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.34 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 4.766-4.65 (m, 4H), 3.64 (t, *J* = 5.2 Hz, 2H).

Step 1.7 Synthesis of methyl (E)-4-(ethyl(methyl)amino)but-2-enoate

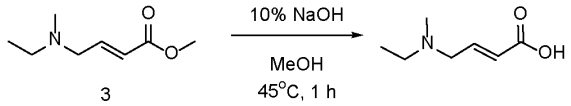


1 3

[01272] To a solution of DIEA (259.91 g, 2.01 mol, 350.28 mL, 3 eq) in MeCN (900 mL) was added N-methylethanamine (76.91 g, 804.71 mmol, 111.78 mL, 1.20 eq, HCl) at 25°C. Then a solution of methyl (E)-4-bromobut-2-enoate (150 g, 670.35 mmol, 98.55 mL, 1 eq) in MeCN (500 mL) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 4 hr. The reaction mixture was concentrated under reduced pressure. To the residue was added water (700 mL) at 25°C and then the aqueous phase was extracted with EtOAc (200 mL x 3). The combined organic phase was washed with brine (200 mL x 1), dried over Na_2SO_4,

filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 660 g Sepa Flash® Silica Flash Column, Eluent of 0~5% Dichloromethane/ Methanol ($NH_3 \cdot H_2O$) gradient @ 150 mL/min). The eluent was removed under reduced pressure to give methyl (E)-4-[ethyl(methyl)amino]but-2-enoate (60 g, 381.66 mmol, 56.93% yield) as brown oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.86-6.80 (m, 1H), 6.03-5.99 (m, 1H), 3.66 (s, 3H), 3.12 (dd, 6.0 Hz, 1.6 Hz, 2H), 2.36 (q, J = 2.8 Hz, 2H), 2.13 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H).

Step 1.8 Synthesis of methyl (E)-4-(ethyl(methyl)amino)but-2-enoate



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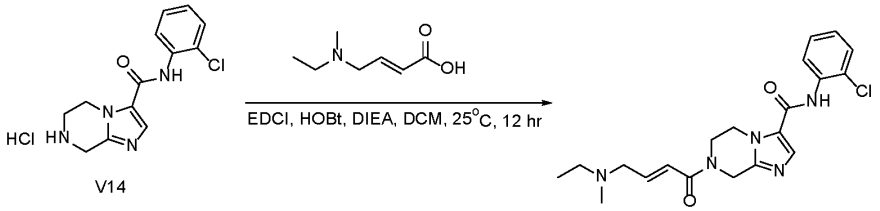
[01273] To a solution of methyl (E)-4-[ethyl(methyl)amino]but-2-enoate (58 g, 368.93 mmol, 1 eq) in MeOH (300 mL) was added NaOH (338.33 g, 845.83 mmol, 150 mL, 10% purity) at 25°C. The reaction mixture was heated to 45°C and stirred at 45°C for 1 hr. The reaction mixture was cooled to 0°C and adjusted pH = 2 with 6 M HCl at 0°C. The reaction mixture was concentrated under reduce pressure. To the residue was added hot EtOH (100 mL), there was solid formed. The reaction mixture was filtrated, the filtrate was concentrated under reduced to give (E)-4-[ethyl(methyl)amino]but-2-enoic acid (38 g, 265.39 mmol, 71.94% yield) as brown oil. LCMS: m/z 144.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.79-6.72 (m, 1H), 5.99 (d, J = 1.6 Hz, 1H), 3.29-3.26 (m, 2H), 2.54 (s, 2H), 2.25 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H).

Step 1.9 Synthesis of N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



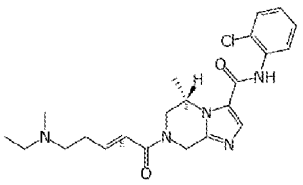
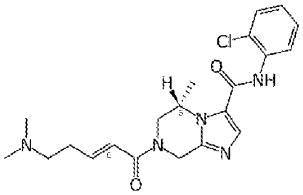
V14

[01274] To a reaction mixture of N-(2-chlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide (18.3 g, 58.43 mmol, 1 eq, HCl), (E)-4-[ethyl(methyl)amino]but-2-enoic acid (13.65 g, 75.96 mmol, 1.3 eq, HCl) in DCM (200 mL) were added EDCI (24.64 g, 128.55 mmol, 2.2 eq), HOBt (17.37 g, 128.55 mmol, 2.2 eq) and DIEA (37.76 g, 292.16 mmol, 50.89 mL, 5 eq) at 25°C, and then reaction mixture was stirred at 25°C for 12 hr. The reaction mixture was quenched by addition H_2O (200 mL) at 25°C, and extracted with DCM

(150 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, the residue was added H_2O (200 mL), the reaction mixture was adjusted pH = 2 by 1 M HCl, and extracted with DCM (150 mL x 3), organic layers discard, water layers adjusted pH = 11 by 10% NaOH, then and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine (300 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters X bridge Prep OBD C_{18} 150 * 40 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 15% - 55% B over 8.0 min). Compound N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (9.45 g, 23.51 mmol, 40.24% yield) was obtained as a yellow solid. LCMS: m/z 402.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.84 (s, 1H), 7.87 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 7.6 Hz, 1.2 Hz, 1H), 6.76-6.66 (m, 2H), 4.91-4.75 (m, 2H), 4.32-4.30 (m, 2H), 4.01-3.96 (m, 2H), 3.14 (d, J = 4.8 Hz, 2H), 2.38 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).

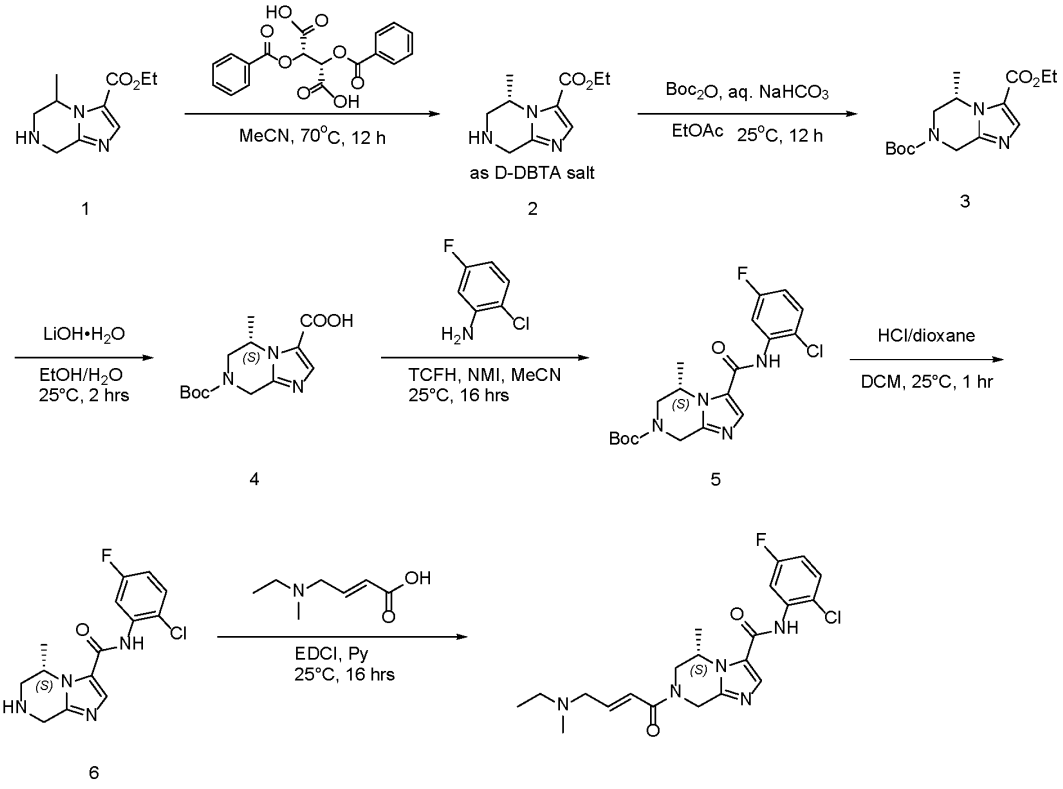
[01275] Compounds in Table Y were synthesized following the procedure for N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table Y

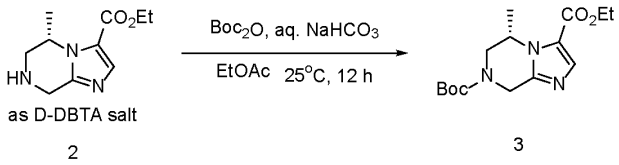
Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-7-[(E)-5-[ethyl(methyl)amino]pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.82-6.62 (m, 2H), 5.26-5.22 (m, 1H), 5.04-5.03 (m, 1H), 4.67-4.55 (m, 1H), 4.34-4.24 (m, 1H), 3.70-3.66 (m, 0.5H), 3.26-3.22 (m, 0.5H), 2.45-2.42 (m, 2H), 2.35 (q, J = 6.8 Hz, 4H), 2.13 (s, 3H), 1.30-1.25 (m, 3H), 0.96 (t, J = 7.2 Hz, 3H).	LCMS: m/z 430.2 $[M+H]^+$
(5S)-N-(2-chlorophenyl)-7-[(E)-5-(dimethylamino)pent-2-enoyl]-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		1H NMR (DMSO-*d6*, 400 MHz) δ 9.88 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.81-6.77 (m, 1H), 6.69-6.62 (m, 1H), 5.24 (d, J = 18.4 Hz, 1H), 5.04 (s, 1H), 4.67-4.57 (m, 1H), 4.34-4.24 (m, 1H), 3.68 (d, J = 14.0 Hz, 1H), 3.28-3.21 (m, 1H),	LCMS: m/z 416.2 $[M+H]^+$

Name	Structure	NMR	LCMS
		2.35 (s, 3H), 2.13-2.07 (m, 6H), 1.30-1.23 (m, 3H).	

Example 206: Synthesis of (5S)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



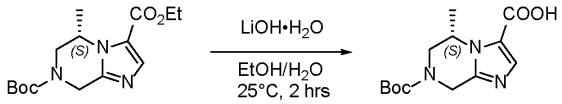
Step 1.2 Synthesis of O7-tert-butyl O3-ethyl (5S)-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3,7-dicarboxylate



[01276] To the reaction mixture of ethyl (5S)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxylate (34.00 g, 81.24 mmol, 1 eq) in $NaHCO_3$ (200 mL) and EtOAc (100 mL) was added Boc_2O (17.73 g, 81.24 mmol, 18.66 mL, 1 eq) at 25°C. The reaction mixture was stirred at 25°C for 12 hours. To the reaction mixture was added water (150 mL). The organic phase was separated, the aqueous phase was extracted with EtOAc (120 mL x 3), the

combined organic phase was washed with brine (120 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 120 g SepaFlash® Silica Flash Column, Eluent of 20~40% Petroleum ether: Ethyl acetate gradient @ 100 mL/min). The eluent was removed under reduced pressure to give compound O7-tert-butyl O3-ethyl (5S)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (12 g, 36.02 mmol, 44.33% yield, 92.85% purity) as yellow oil. LCMS: m/z 310.2 $[M+H]^{+}$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.64 (s, 1H), 4.95-4.89 (m, 2H), 4.28-4.10 (m, 4H), 3.40-3.39 (m, 1H), 1.44 (s, 9H), 1.30-1.26 (m, 6H).

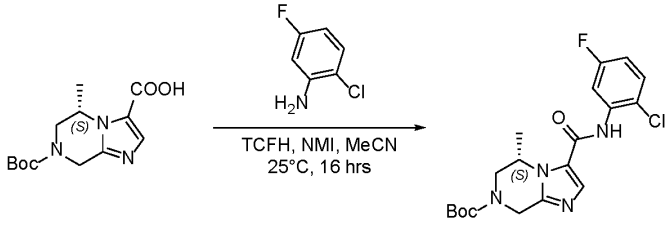
Step 1.3 Synthesis of (5S)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



1 2

[01277] To a solution of O7-tert-butyl O3-ethyl (5S)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate (8 g, 25.86 mmol, 1 eq) in EtOH (60 mL) and H_2O (20 mL) was added LiOH•H_2O (2.71 g, 64.65 mmol, 2.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to give the water layer. And then the water layer was adjusted pH = 5 by 3 M HCl at 0°C, and the precipitate was formed. The precipitate was collected through filtration. The filter liquor was extracted with DCM: i-PrOH (3:1) (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the product. Compound (5S)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (2.9 g, 10.31 mmol, 39.86% yield) was obtained as a pale yellow solid. LCMS: m/z 282.2 $[M+H]^{+}$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.59 (s, 1H), 4.90 (s, 2H), 4.40-4.10 (m, 2H), 3.52 (s, 1H), 1.44 (s, 9H), 1.28 (d, J = 5.6 Hz, 3H).

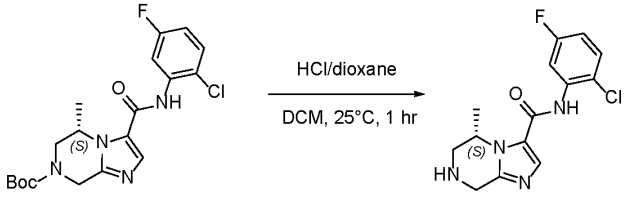
Step 1.4 Synthesis of tert-butyl (5S)-3-[(2-chloro-5-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



2 3

[01278] To a solution of (5S)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (600.00 mg, 2.13 mmol, 1 eq) and 2-chloro-5-fluoro-aniline (620.94 mg, 4.27 mmol, 2 eq) in MeCN (6 mL) were added NMI (875.59 mg, 10.66 mmol, 850.09 µL, 5 eq) and TCFH (2.39 g, 8.53 mmol, 4 eq) at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage ®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 50 mL/min). Compound tert-butyl (5S)-3-[(2-chloro-5-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (1.24 g, crude) was obtained as yellow oil. LCMS: m/z 409.0 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.39 (s, 1H), 8.28 (s, 1H), 7.63-7.60 (m, 1H), 7.51-7.47 (m, 1H), 7.24-7.19 (m, 1H), 5.11-5.10 (m, 2H), 4.61-4.36 (m, 1H), 4.12-4.09 (m, 1H), 3.38 (s, 1H), 1.45 (s, 9H), 1.35 (d, J = 5.6 Hz, 3H).

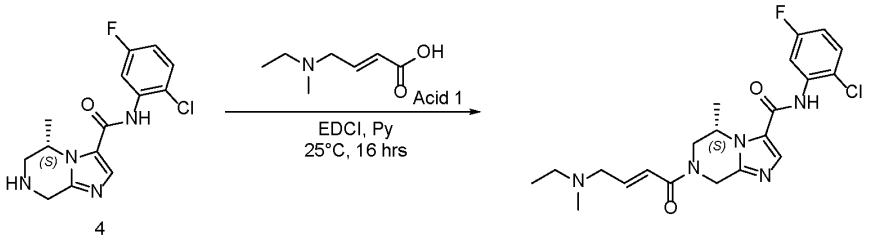
Step 1.5 Synthesis of (5S)-N-(2-chloro-5-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide



3 4

[01279] To a solution of tert-butyl (5S)-3-[(2-chloro-5-fluoro-phenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (1.24 g, 3.03 mmol, 1 eq) in DCM (10 mL) was added HCl/dioxane (4 M, 1.00 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. Compound (5S)-N-(2-chloro-5-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (1.2 g, crude, HCl) was obtained as yellow oil. LCMS: m/z 309.0 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.66 (s, 1H), 8.38 (s, 1H), 7.64-7.60 (m, 1H), 7.48 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 7.26-7.21 (m, 1H), 5.26-5.23 (m, 2H), 4.57 (q, J = 15.6 Hz, 2H), 3.66-3.60 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H).

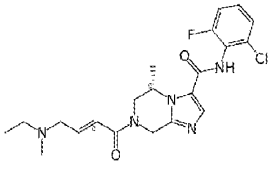
Step 1.6 Synthesis of (5S)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

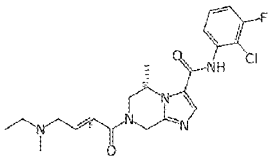
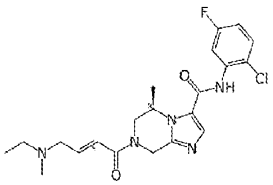
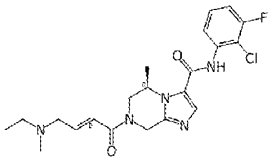
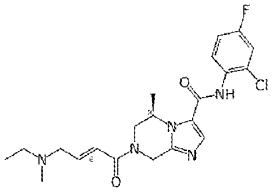
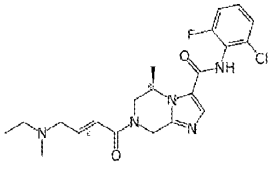


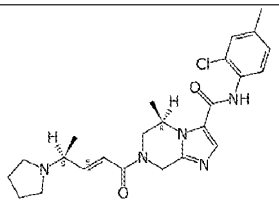
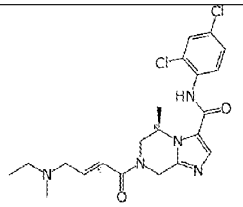
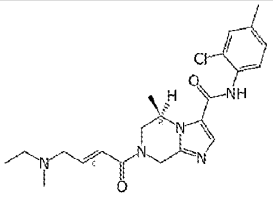
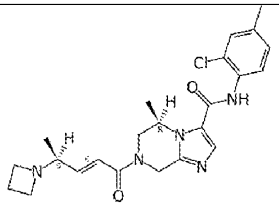
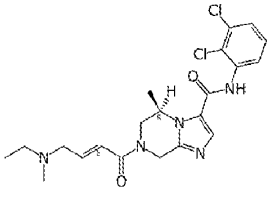
[01280] To a solution of (5S)-N-(2-chloro-5-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (1.1 g, 3.19 mmol, 1 eq, HCl) and (E)-4-[ethyl(methyl)amino]but-2 -enoic acid (456.26 mg, 3.19 mmol, 1 eq) in Pyridine (11 mL) was added EDCI (1.22 g, 6.37 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 250 * 50 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 50% B over 10.0 min). Compound (5S)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (145 mg, 334.17 μmol, 10.49% yield) was obtained as a light brown solid. LCMS: m/z 434.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.92 (s, 1H), 7.62-7.58 (m, 1H), 7.51 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 7.20-7.15 (m, 1H), 6.73-6.72 (m, 2H), 5.28-5.22 (m, 1H), 5.07-5.04 (m, 1H), 4.71-4.58 (m, 1H), 4.31-4.26 (m, 1H), 3.69 (d, J = 12.4 Hz, 0.5H), 3.27-3.25 (m, 0.5H), 3.14 (d, J = 4.0 Hz, 2H), 2.39-2.34 (m, 2H), 2.14 (s, 3H), 1.30-1.28 (m, 3H), 0.99 (t, J = 6.8 Hz, 3H).

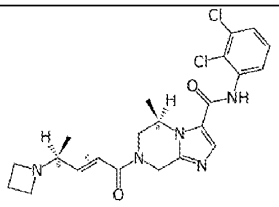
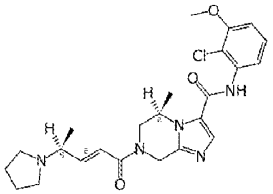
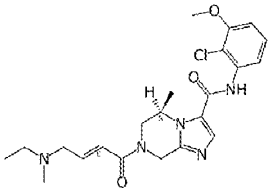
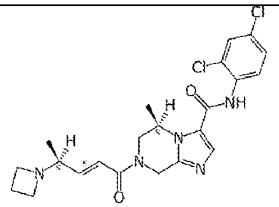
[01281] Compounds in Table Z were synthesized following the procedure for (5S)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

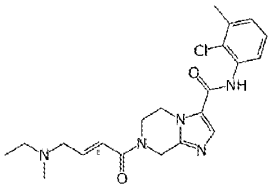
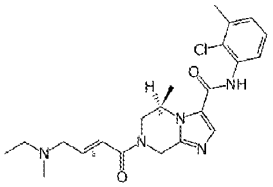
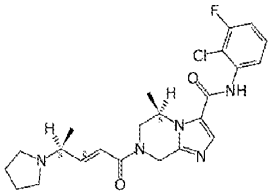
Table Z

Name	Structure	NMR	LCMS
(5S)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.99 (s, 1H), 7.90 (s, 1H), 7.45-7.40 (m, 2H), 7.37-7.36 (m, 1H), 6.79-6.73 (m, 2H), 5.29-5.18 (m, 1H), 5.02 (s, 1H), 4.66-4.56 (m, 1H), 4.30-4.23 (m, 1H), 3.73-3.69 (m, 0.5H), 3.27-3.23 (m, 0.5H), 3.18-3.14 (m, 2H), 2.37-2.34 (m, 2H), 2.14 (s, 3H), 1.27-1.23 (m, 3H), 0.99 (d, J = 7.2 Hz, 3H).	LCMS: m/z 434.1 $[M+H]^+$

Name	Structure	NMR	LCMS
(5S)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.63-10.47 (m, 1H), 8.39-8.28 (m, 1H), 7.48-7.38 (m, 3H), 7.16-7.02 (m, 1H), 6.86-6.74 (m, 1H), 5.48-5.35 (m, 1H), 5.18 (s, 1H), 4.86-4.37 (m, 2H), 3.98-3.94 (m, 2H), 3.35 (d, J = 12.8 Hz, 1H), 3.10-3.03 (m, 2H), 2.70-2.67 (m, 3H), 1.40-1.30 (m, 3H), 1.26 (d, J = 4.0 Hz, 3H). ^{19}F NMR (DMSO-d_6, 400 MHz) δ -113.38 (s, 1F).	LCMS: m/z 434.1 $[M+H]^+$
(5R)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.88 (s, 1H), 7.92 (s, 1H), 7.60 (dd, J = 7.2 Hz, 6.0 Hz, 1H), 7.51 (dd, J = 10.0 Hz, 3.2 Hz, 1H), 7.18 (td, J = 8.0 Hz, 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 5.29-5.18 (m, 1H), 5.05 (s, 1H), 4.71-4.56 (m, 1H), 4.32-4.26 (m, 1H), 3.70 (d, J = 13.6 Hz, 0.5H), 3.24-3.22 (m, 0.5H), 3.14 (d, J = 3.6 Hz, 2H), 2.40-2.34 (m, 2H), 2.14 (s, 3H), 1.30-1.27 (m, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 434.1 $[M+H]^+$
(5R)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) 10.02 (s, 1H), 7.91 (s, 1H), 7.43-7.39 (m, 2H), 7.36-7.31 (m, 1H), 6.74-6.73 (m, 2H), 5.29-5.18 (m, 1H), 5.04-5.01 (m, 1H), 4.70-4.58 (m, 1H), 4.32-4.26 (m, 1H), 3.72-3.68 (m, 0.5H), 3.27-3.25 (m, 0.5H), 3.14 (d, J = 4.0 Hz, 2H), 2.39-2.35 (m, 2H), 2.14 (s, 3H), 1.29-1.23 (m, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 434.0 $[M+H]^+$
(5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.90 (s, 1H), 7.87 (s, 1H), 7.57-7.51 (m, 2H), 7.27 (td, J = 8.4 Hz, 1.2 Hz, 1H), 6.77-6.68 (m, 2H), 5.28-5.18 (m, 1H), 5.04 (s, 1H), 4.71-4.57 (m, 1H), 4.34-4.24 (m, 1H), 3.71-3.68 (m, 1H), 3.14 (d, J = 4.4 Hz, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.29-1.25 (m, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 434.2 $[M+H]^+$
(5R)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.55-10.40 (m, 1H), 8.35-8.24 (m, 1H), 7.48-7.35 (m, 3H), 7.15-7.12 (m, 1H), 6.85-6.78 (m, 1H), 5.47-5.33 (m, 1H), 5.15-5.14 (m, 1H), 4.85-4.35 (m, 2H), 3.97-3.83 (m, 2.5H), 3.37-3.34 (m, 0.5H),	LCMS: m/z 434.1 $[M+H]^+$

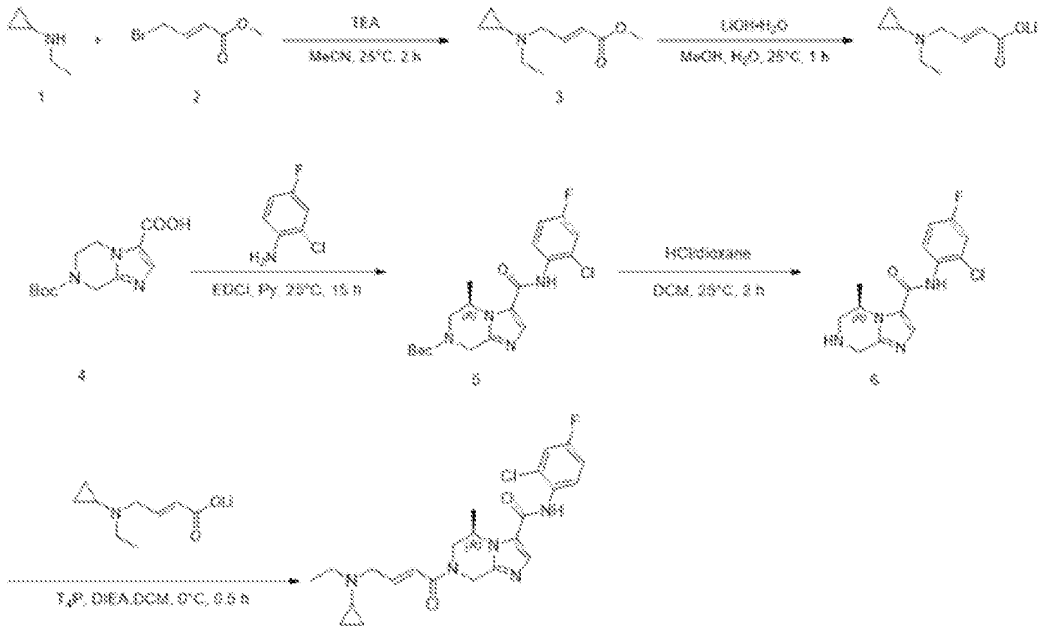
Name	Structure	NMR	LCMS
		3.16-3.04 (m, 2H), 2.69-2.68 (m, 3H), 1.38-1.24 (m, 6H).	
(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.78 (s, 1H), 7.87 (s, 1H), 7.38-7.37 (m, 2H), 7.18 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 6.69-6.67 (m, 2H), 5.26-5.18 (m, 1H), 5.04 (br.s, 1H), 4.70-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.69 (d, *J* = 11.2 Hz, 0.5H), 3.27-3.21 (m, 0.5H), 3.05-3.00 (m, 1H), 2.43-2.41 (m, 4H), 2.32 (s, 3H), 1.66 (br. s, 4H), 1.29-1.23 (m, 3H), 1.15 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 456.2 $[M+H]^+$
(5R)-N-(2,4-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.90 (s, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.79-6.69 (m, 2H), 5.28-5.18 (m, 1H), 5.04 (s, 1H), 4.69-4.57 (m, 1H), 4.30-4.26 (m, 1H), 3.71-3.67 (m, 0.5H), 3.32-3.27 (m, 0.5H), 3.14 (d, *J* = 4.0 Hz, 2H), 2.36-2.77 (q, *J* = 6.8 Hz, 2H), 2.14 (s, 3H), 1.29-1.26 (m, 3H), 0.99 (d, *J* = 7.2 Hz, 3H).	LCMS: m/z 450.1/452.1 $[M+H]^+$
(5R)-N-(2-chloro-4-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.78 (s, 1H), 7.87 (s, 1H), 7.39-7.37 (m, 2H), 7.18 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 6.73 (d, *J* = 4.0 Hz, 2H), 5.28-5.17 (m, 1H), 5.05 (br.s, 1H), 4.69-4.57 (m, 1H), 4.31-4.25 (m, 1H), 3.69 (d, *J* = 13.2 Hz, 0.5H), 3.27-3.22 (m, 0.5H), 3.14 (d, *J* = 4.0 Hz, 2H), 2.39-2.32 (m, 5H), 2.14 (s, 3H), 1.29-1.25 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 430.0 $[M+H]^+$
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-4-methyl- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.78 (s, 1H), 7.86 (s, 1H), 7.39-7.37 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.66-6.49 (m, 2H), 5.26-5.15 (m, 1H), 5.04 (s, 1H), 4.69-4.55 (m, 1H), 4.31-4.24 (m, 1H), 3.68 (d, *J* = 13.6 Hz, 0.5H), 3.27-3.25 (m, 0.5H), 3.08 (t, *J* = 7.2 Hz, 4H), 2.96-2.89 (m, 1H), 2.32 (s. 3H), 1.91 (q, *J* = 7.2 Hz, 2H), 1.28-1.24 (m, 3H), 0.95 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 442.2 $[M+H]^+$
(5R)-N-(2,3-dichlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.02 (s, 1H), 7.90 (s, 1H), 7.58-7.51 (m, 2H), 7.40 (t, *J* = 8.4 Hz, 1H), 6.73-6.71 (m, 2H), 5.29-5.18 (m, 1H), 5.04 (s, 1H), 4.71-4.56 (m, 1H), 4.32-4.26 (m, 1H), 3.70 (d, *J* = 15.2 Hz, 0.5H), 3.27-3.23 (m, 0.5H), 3.15	LCMS: m/z 450.1/452.1 $[M+H]^+$

Name	Structure	NMR	LCMS
		(d, J = 4.4 Hz, 2H), 2.39-2.32 (m, 2H), 2.14 (s, 3H), 1.29-1.24 (m, 3H), 0.99 (t, J = 6.8 Hz, 3H).	
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,3-dichlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.02 (s, 1H), 7.90 (s, 1H), 7.57-7.52 (m, 2H), 7.40 (t, J = 8.4 Hz, 1H), 6.64-6.61 (m, 1H), 6.55-6.50 (m, 1H), 5.27-5.17 (m, 1H), 5.04 (s, 1H), 4.62 (dd, J = 45.2 Hz, 16.4 Hz, 1H), 4.29 (t, J = 12.0 Hz, 1H), 3.69 (d, J = 12.8 Hz, 0.5H), 3.26-3.22 (m, 0.5H), 3.08 (t, J = 6.8 Hz, 4H), 2.96-2.90 (m, 1H), 1.91 (q, J = 6.8 Hz, 2H), 1.29-1.24 (m, 3H), 0.96 (t, J = 6.0 Hz, 3H).	LCMS: m/z 462.1/464.1 $[M+H]^+$
(5R)-N-(2-chloro-3-methoxy-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1-ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.77 (s, 1H), 7.88 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.06 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 6.69-6.67 (m, 2H), 5.26-5.16 (m, 1H), 5.03 (s, 1H), 4.68-4.55 (m, 1H), 4.31-4.24 (m, 1H), 3.87 (s, 3H), 3.71-3.67 (m, 0.5H), 3.23-3.19 (m, 0.5H), 3.05-3.00 (m, 1H), 2.42-2.41 (m, 4H), 1.66 (s, 4H), 1.28-1.25 (m, 3H), 1.15 (t, J = 6.0 Hz, 3H).	LCMS: m/z 472.2 $[M+H]^+$
(5R)-N-(2-chloro-3-methoxy-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.75 (s, 1H), 7.88 (s, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 4.8 Hz, 1H), 6.72-6.70 (m, 2H), 5.28-5.16 (m, 1H), 5.04 (s, 1H), 4.72-4.53 (m, 1H), 4.30-4.25 (m, 1H), 3.88 (s, 3H), 3.72-3.66 (m, 1H), 3.14 (d, J = 4.0 Hz, 2H), 2.37 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.27 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H).	LCMS: m/z 446.0 $[M+H]^+$
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2,4-dichlorophenyl)-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.92 (s, 1H), 7.88 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.64-6.60 (m, 1H), 6.55-6.51 (m, 1H), 5.26-5.16 (m, 1H), 5.05 (s, 1H), 4.70-4.58 (m, 1H), 4.32-4.24 (m, 1H), 3.70-3.67 (m, 0.5H), 3.25-3.24 (m, 0.5H), 3.08 (t, J = 6.8 Hz, 4H), 2.94-2.91 (m, 1H), 1.94-1.87 (m, 2H), 1.29-1.23 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H).	LCMS: m/z 462.1/464.1 $[M+H]^+$

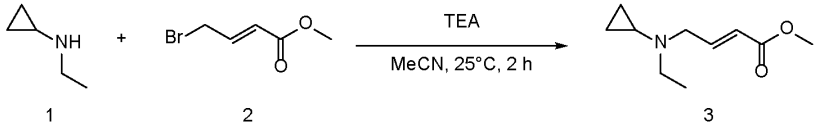
Name	Structure	NMR	LCMS
N-(2-chloro-3-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.78 (s, 1H), 7.86 (s, 1H), 7.37 (t, *J* = 4.0 Hz, 1H), 7.15 (d, *J* = 4.0 Hz, 2H), 6.75-6.71 (m, 2H), 4.91-4.74 (m, 2H), 4.31 (s, 2H), 4.00 (s, 2H), 3.13 (d, *J* = 2.4 Hz, 2H), 2.37-2.33 (m, 5H), 2.13 (s, 3H), 1.01-0.97 (m, 3H).	LCMS: m/z 416.1 $[M+H]^+$
(5R)-N-(2-chloro-3-methyl-phenyl)-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.82 (s, 1H), 7.88 (s, 1H), 7.37-7.35 (m, 1H), 7.27-7.24 (m, 2H), 6.73-6.69 (m, 2H), 5.28-5.21 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.31-4.25 (m, 1H), 3.71-3.68 (m, 0.5H), 3.28-3.22 (m, 0.5H), 3.14-3.13 (m, 2H), 2.37-2.34 (m, 5H), 2.14 (s, 3H), 1.29-1.25 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).	LCMS: m/z 430.2 $[M+H]^+$
(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E,4S)-4-pyrrolidin-1- ylpent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) 10.01 (s, 1H), 7.91 (s, 1H), 7.43-7.39 (m, 2H), 7.36-7.31 (m, 1H), 6.74-6.73 (m, 2H), 5.29-5.18 (m, 1H), 5.04 (s, 1H), 4.70-4.58 (m, 1H), 4.32-4.26 (m, 1H), 3.69 (d, *J* = 13.2 Hz, 0.5H), 3.27-3.25 (m, 0.5H), 3..04-3.01 (m, 1H), 2.50-2.43 (m, 4H), 1.66 (s, 4H), 1.30-1.26 (m, 3H), 1.15 (d, *J* = 6.0 Hz, 3H).	LCMS: m/z 460.1 $[M+H]^+$

Example 208a: Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-

a]pyrazine-3-carboxamide.

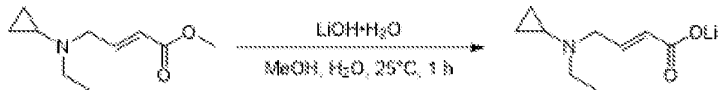


Step 1.1 Synthesis of methyl (E)-4-[cyclopropyl(ethyl)amino]but-2-enoate



[01282] To a solution of methyl (E)-4-bromobut-2-enoate (10 g, 55.86 mmol, 6.57 mL, 1 *eq*) in MeCN (200 mL) was added TEA (16.96 g, 167.59 mmol, 23.33 mL, 3 *eq*) and N-ethylcyclopropanamine (8.15 g, 67.03 mmol, 1.2 *eq*, HCl) at 25°C. The mixture was stirred at 25°C for 2 h. TLC (Petroleum ether: Ethyl acetate=1:1) showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (Biotage®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound methyl (E)-4-[cyclopropyl(ethyl)amino]but-2-enoate (7.5 g, 40.93 mmol, 73.27% yield) was obtained as brown oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.93-6.85 (m, 1H), 6.00 (dt, J = 15.6 Hz, 1.6 Hz, 1H), 3.65 (s, 3H), 3.34 (d, J = 1.6 Hz, 2H), 2.56 (q, J = 7.2 Hz, 2H), 1.82-1.78 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.45-0.42 (m, 2H), 0.30-0.29 (m, 2H).

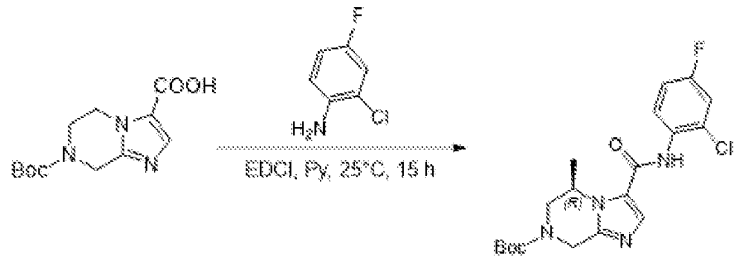
Step 1.2 Synthesis of [(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]oxylithium



3

[01283] To a solution of methyl (E)-4-[cyclopropyl(ethyl)amino]but-2-enoate (7.5 g, 40.93 mmol, 1 *eq*) in MeOH (50 mL) and H_2O (10 mL) was added LiOH•H_2O (4.29 g, 102.32 mmol, 2.5 *eq*) at 25°C. The mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated to give a residue. The crude product was triturated with MeCN at 25°C for 30 min. Compound [(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl] oxylithium (5.7 g, 32.54 mmol, 79.51% yield) was obtained as a white solid. LCMS: m/z 170.1 $[M+H]^+$.

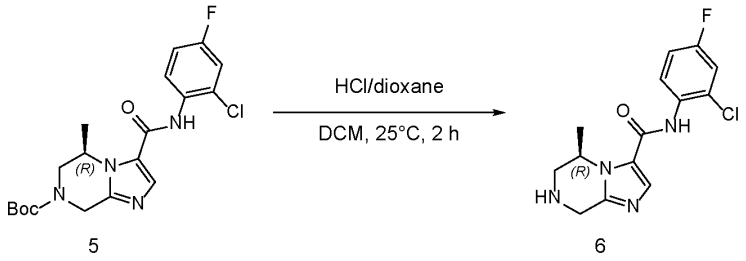
Step 1.3 Synthesis of tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



4 5

[01284] A mixture of (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine- 3-carboxylic acid (0.5 g, 1.78 mmol, 1 *eq*), 2-chloro-4-fluoro-aniline (310.47 mg, 2.13 mmol, 1.2 *eq*) and EDCI (681.47 mg, 3.55 mmol, 2 *eq*) in Py (10 mL) was stirred at 25°C for 15 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 45 mL/min). Compound tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (0.35 g, 856.05 μmol, 48.16% yield) was obtained as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 8.4 Hz, 2.8 Hz, 1H), 5.00-4.91 (m, 2H), 4.41-4.26 (m, 1H), 4.15-4.05 (m, 1H), 1.44 (s, 9H), 1.27 (d, J = 6.0 Hz, 3H).

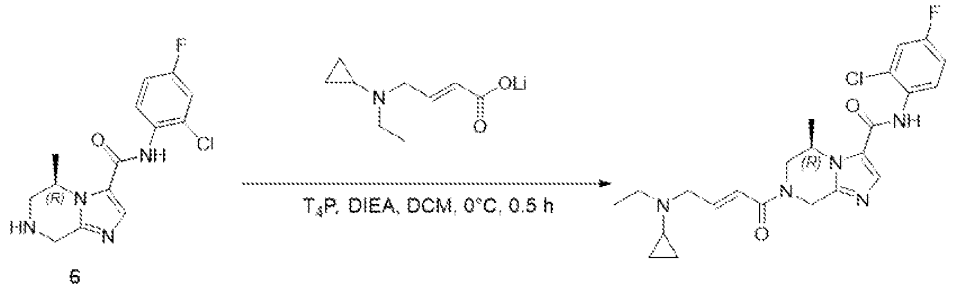
Step 1.4 Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide



5 6

[01285] To a solution of tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (0.35 g, 856.05 μmol, 1 *eq*) in DCM (2 mL) was added HCl/dioxane (4 M, 5 mL) at 25°C. The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated. Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.3 g, crude, HCl) was obtained as a red solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.45 (s, 1H), 8.19 (s, 1H), 7.59-7.52 (m, 2H), 7.50-7.29 (m, 1H), 5.19 (s, 1H), 4.53-4.43 (m, 2H), 3.66-3.54 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H).

Step 1.5 Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



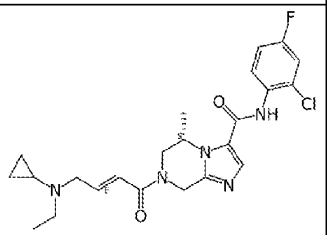
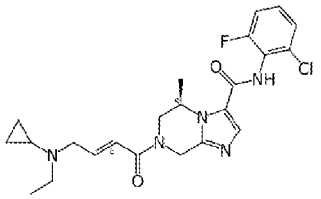
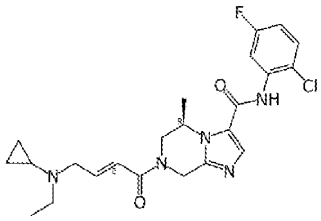
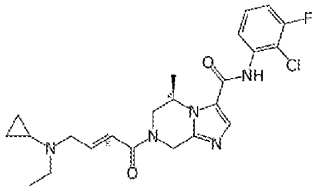
6

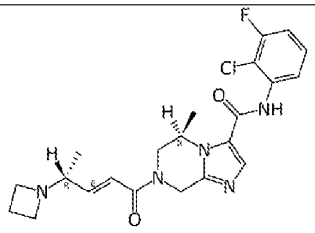
[01286] To a solution of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (100 mg, 289.69 μmol, 1 *eq*, HCl) and [(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]oxylithium (126.85 mg, 724.22 μmol, 2.5 *eq*) in DCM (4 mL) was added DIEA (149.76 mg, 1.16 mmol, 201.83 μL, 4 *eq*) at 25°C, and then T_4P (417.45 mg, 579.38 μmol, 50% purity, 2 *eq*) was added at 0°C. The mixture was stirred at 0°C for 0.5 h. The reaction mixture was quenched with 0.5 mL water, then concentrated under reduced pressure. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 50% B over 8.0 min). Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-

carboxamide (49.5 mg, 106.84 μmol, 36.88% yield, 99.27% purity) was obtained as a white solid. LCMS: m/z 460.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.89 (s, 1H), 7.87 (s, 1H), 7.57-7.51 (m, 2H), 7.27 (td, J = 8.4 Hz, 2.8 Hz, 1H), 6.79-6.74 (m, 2H), 5.29-5.18 (m, 1H), 5.04 (s, 1H), 4.71-4.54 (m, 1H), 4.36-4.25 (m, 1H), 3.71-3.68 (m, 0.5H), 3.37-3.26 (m, 2H), 3.26-3.17 (m, 0.5H), 2.59 (q, J = 7.2 Hz, 2H), 1.80 (s, 1H), 1.28-1.21 (m, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.44-0.43 (m, 2H), 0.32-0.31 (m, 2H).

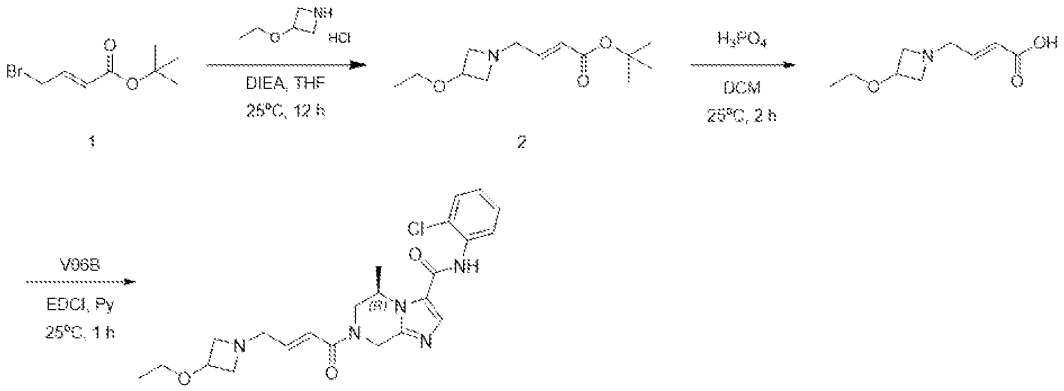
[01287] Compounds in Table ZA were synthesized following the procedure for (5R)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

Table ZA

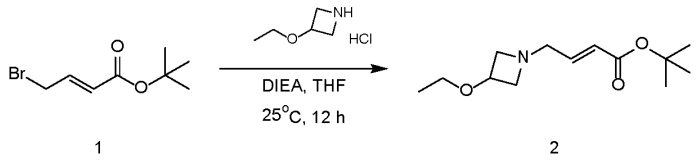
Name	Structure	NMR	LCMS
(5S)-N-(2-chloro-4-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.88 (s, 1H), 7.57-7.51 (m, 2H), 7.27 (td, J = 8.4 Hz, 2.8 Hz, 1H), 6.83-6.70 (m, 2H), 5.30-5.17 (m, 1H), 5.04 (br.s, 1H), 4.69-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.70 (d, J = 14.0 Hz, 0.5H), 3.36 (d, J = 5.6 Hz, 2H), 3.29 (s, 0.5H), 2.59 (q, J = 7.2 Hz, 2H), 1.81-1.80 (m, 1H), 1.28-1.27 (m, 3H), 1.01 (t, J = 8.0 Hz, 3H), 0.46-0.43 (m, 2H), 0.32-0.31 (m, 2H).	LCMS: m/z 460.1 $[M+H]^+$
(5R)-N-(2-chloro-6-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino]but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-$d6$, 400 MHz) δ 9.99 (m, 1H), 7.89 (s, 1H), 7.44-7.34 (m, 3H), 6.79-6.69 (m, 2H), 5.29-5.18 (m, 1H), 5.02-5.01 (m, 1H), 4.62 (dd, J = 40.0 Hz, 17.2 Hz, 1H), 4.32-4.25 (m, 1H), 3.73 (m, 0.5H), 3.48-3.44 (m, 0.5H), 3.36 (m, 1H), 2.60 (q, J = 7.2 Hz, 2H), 1.80 (s, 1H), 1.27-1.23 (m, 3H), 1.01 (t, J = 6.8 Hz, 3H), 0.44-0.43 (m, 2H), 0.31-0.30 (m, 2H).	LCMS: m/z 460.1 $[M+H]^+$
(5R)-N-(2-chloro-5-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.92 (s, 1H), 7.61-7.58 (m, 1H), 7.51 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 7.17 (td, J = 8.0 Hz, 2.8 Hz, 1H), 6.80-6.70 (m, 2H), 5.30-5.19 (m, 1H), 5.05 (s, 1H), 4.70-4.58 (m, 1H), 4.30 (t, J = 17.2 Hz, 1H), 3.70 (d, J = 12.4 Hz, 0.5H), 3.37-3.36 (m, 2H), 3.28-3.22 (m, 0.5H), 2.59 (q, J = 7.2 Hz, 2H), 1.81-1.79 (m, 1H), 1.30-1.27 (m, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.46-0.42 (m, 2H), 0.32-0.31 (m, 2H).	LCMS: m/z 460.1 $[M+H]^+$
(5R)-N-(2-chloro-3-fluoro-phenyl)-7-[(E)-4-[cyclopropyl(ethyl)amino] but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-		^1H NMR (DMSO-$d6$, 400 MHz) δ 10.00 (s, 1H), 7.90 (s, 1H), 7.44-7.38 (m, 2H), 7.35-7.30 (m, 1H), 6.83-6.70 (m, 2H), 5.29-5.15 (m, 1H), 5.04 (s, 1H), 4.72-4.52 (m, 1H), 4.36-4.25 (m, 1H), 3.77-3.63 (m, 0.6H), 3.37-3.35 (m, 2H), 3.25-3.22 (m, 0.4H), 2.58 (q, J = 7.2 Hz, 2H), 1.80 (s, 1H), 1.31-1.20 (m, 3H), 1.01 (t, J = 7.2	LCMS: m/z 460.2 [M+H]

Name	Structure	NMR	LCMS
a]pyrazine-3-carboxamide		Hz, 3H), 0.44-0.43 (m, 2H), 0.32-0.31 (m, 2H).	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chloro-3-fluoro- phenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.00 (s, 1H), 7.90 (s, 1H), 7.45-7.38 (m, 2H), 7.36-7.31 (m, 1H), 6.66-6.47 (m, 2H), 5.28-5.18 (m, 1H), 5.04 (s, 1H), 4.70-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.70 (d, *J* = 13.6 Hz, 0.5H), 3.26-3.21 (m, 0.5H), 3.08-3.04 (m, 4H), 2.95-2.89 (m, 1H), 1.92-1.89 (m, 2H), 1.29-1.25 (m, 3H), 0.96 (d, *J* = 6.4 Hz, 3H).	LCMS: m/z 446.1 [M+H]$^+$

Example 208b: Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-ethoxyazetidin-1-yl)but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



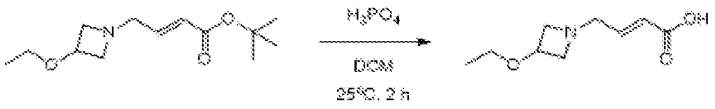
Step 1.1 Synthesis of tert-butyl (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoate



[01288] To the reaction mixture of tert-butyl (E)-4-bromobut-2-enoate (1.4 g, 6.33 mmol, 1 eq), 3-ethoxyazetidine;hydrochloride (958.50 mg, 6.97 mmol, 1.1 eq) in THF (15 mL) was added DIEA (1.23 g, 9.50 mmol, 1.65 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 25%~40% Petroleum ether: Ethyl acetate gradient @ 60 mL/min). The eluent was removed under reduced pressure to give compound tert-butyl (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoate (0.9 g, 3.73 mmol, 58.90% yield) as yellow oil. LCMS: m/z 242.1 [M+H]$^+$. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 6.64 (dt, *J* = 16.0 Hz, 5.6 Hz, 1H), 5.78 (dt,

J = 15.6 Hz, 2.0 Hz, 1H), 4.05-4.01 (m, 1H), 3.51-3.49 (m, 2H), 3.34-3.32 (m, 2H), 3.16 (dd, *J* = 5.6 Hz, 2.0 Hz, 2H), 2.81-2.79 (m, 2H), 1.42 (s, 9H), 1.08 (t, *J* = 7.2 Hz, 3H).

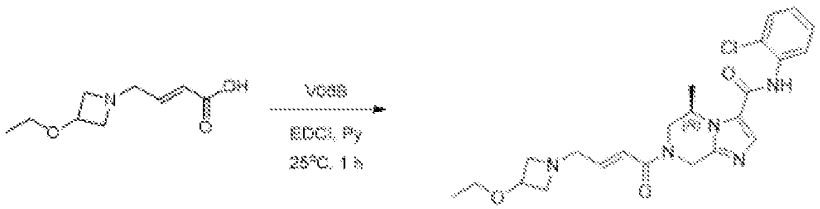
Step 1.2 Synthesis of (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoic acid



2

[01289] To a solution of tert-butyl (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoate (0.8 g, 3.32 mmol, 1 eq) in DCM (6 mL) was added H_3PO_4 (1.5 mL) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. The reaction mixture was cooled to 0°C and adjusted pH = 6 with sat. aq. Na_2CO_3 at 0°C. The crude product was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-10% B over 8.0 min). The residue was dried over lyophilization to give compound (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoic acid (0.5 g, 2.70 mmol, 81.43% yield) as a white oil. LCMS: m/z 186.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.65 (dt, *J* = 15.6 Hz, 5.6 Hz, 1H), 6.02 (d, *J* = 15.6 Hz, 1H), 4.22-4.16 (m, 1H), 3.99-3.96 (m, 2H), 3.68-3.65 (m, 2H), 3.50-3.32 (m, 4H), 1.11 (t, *J* = 7.2 Hz, 3H).

Step 1.3 Synthesis of (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-ethoxyazetidin-1-yl)but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

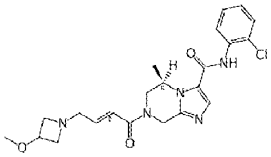
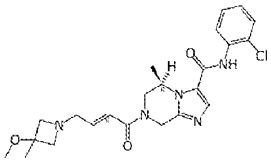
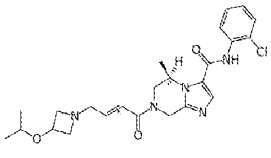


[01290] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.15 g, 458.42 μmol, 1 eq, HCl) in Pyridine (1 mL) was added (E)-4-(3-ethoxyazetidin-1-yl)but-2-enoic acid (101.89 mg, 550.11 μmol, 1.2 eq) at 25°C. And then EDCI (175.76 mg, 916.85 μmol, 2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 25%-55% B over 8.0 min). The residue was dried over lyophilization to give compound (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-ethoxyazetidin-1-yl)but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (75.2 mg, 163.01 μmol, 35.56% yield, 99.27% purity)

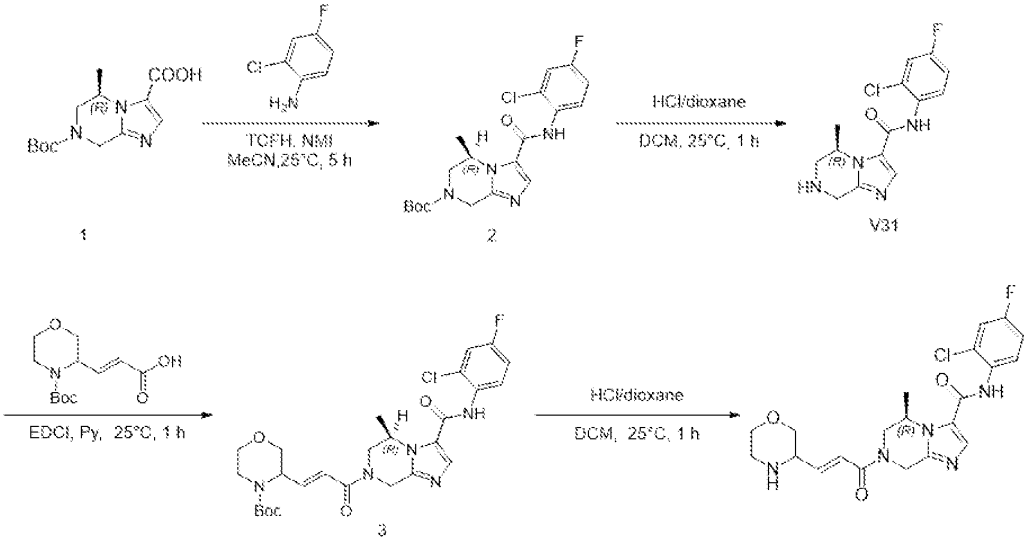
as a yellow solid. LCMS: m/z 458.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.64-6.59 (m, 2H), 5.28-5.16 (m, 1H), 5.05 (s, 1H), 4.70-4.56 (m, 1H), 4.29-4.25 (m, 1H), 4.06-4.03 (m, 1H), 3.72-3.68 (m, 0.5H), 3.55-3.53 (m, 2H), 3.37-3.34 (m, 2H), 3.25-3.24 (m, 0.5H), 3.22-3.21 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 1.29-1.25 (m, 3H), 1.09 (t, J = 6.8 Hz, 3H).

[01291] Compounds in Table AA were synthesized following the procedure for (5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-ethoxyazetidin-1-yl)but-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

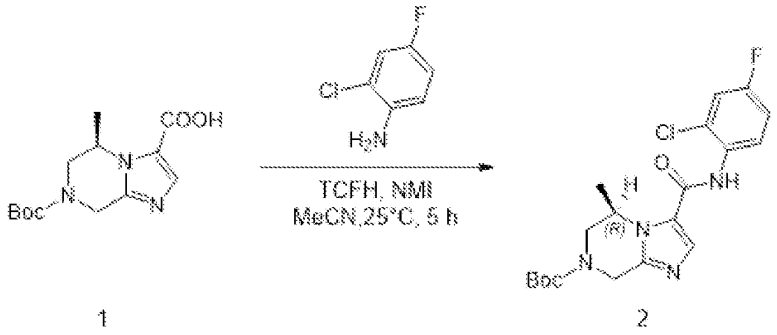
Table AA

Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-methoxyazetidin-1-yl)but-2-enoyl]- 5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (MeOD, 400 MHz) δ 7.84 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 6.8 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 6.81-6.77 (m, 1H), 6.67-6.63 (m, 1H), 5.45 (d, J = 18.8 Hz, 0.5H), 5.22 (s, 1H), 4.78-4.73 (m, 0.5H), 4.57 (s, 1H), 4.40-4.34 (m, 1H), 4.09-4.05 (m, 1H), 3.79-3.59 (m, 0.5H), 3.65 (s, 2H), 3.51-3.40 (m, 0.5H), 3.36 (d, J = 4.4 Hz, 2H), 3.26 (s, 3H), 3.08 (s, 2H), 1.45-1.41 (m, 3H).	LCMS: m/z 444.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-methoxy-3-methyl-azetidin-1-yl) but-2-enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (400 MHz, DMSO-$d6$) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.6 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.64-6.63 (m, 2H), 5.27-5.16 (m, 1H), 5.06 (d, J = 3.2 Hz, 1H), 4.70-4.56 (m, 1H), 4.29-4.25 (m, 1H), 3.72-3.68 (m, 0.5H), 3.29-3.28 (m, 0.5H), 3.23-3.20 (m, 2H), 3.15-3.13 (m, 2H), 3.09 (s, 3H), 2.97-2.96 (m, 2H), 1.38 (s, 3H), 1.29-1.24 (m, 3H).	LCMS: m/z 458.2 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(3-isopropoxyazetidin-1-yl)but-2- enoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 8.0 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 1.26 Hz, 1H), 6.67-6.60 (m, 2H), 5.28-5.16 (m, 1H), 5.06 (s, 1H), 4.71-4.56 (m, 1H), 4.31-4.25 (m, 1H), 4.10 (t, J = 2.0 Hz, 1H), 3.72-3.68 (m, 0.5H), 3.58-3.52 (m, 3H), 3.30-3.24 (m, 0.5H), 3.20 (d, J = 3.2 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 1.29-1.24 (m, 3H), 1.05 (d, J = 3.0 Hz, 6H).	LCMS: m/z 472.2 $[M+H]^+$

Example 209: Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3- ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



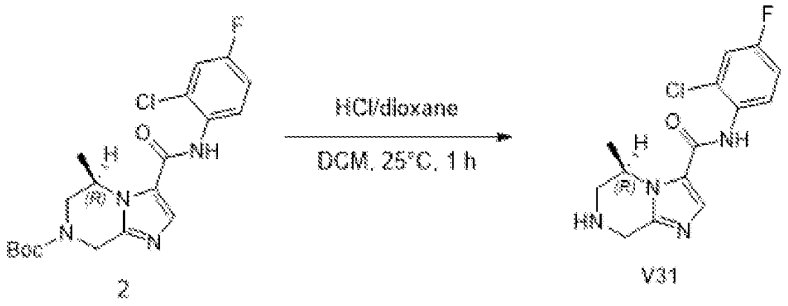
Step 1.1 Synthesis of tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



[01292] To a solution of (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (2 g, 7.11 mmol, 1 *eq*) and 2-chloro-4-fluoro-aniline (1.55 g, 10.66 mmol, 1.5 *eq*) in MeCN (30 mL) were added NMI (2.92 g, 35.55 mmol, 2.83 mL, 5 *eq*) and TCFH (7.98 g, 28.44 mmol, 4 *eq*) at 25°C. The mixture was stirred at 25°C for 5 h. The reaction mixture was quenched by addition of water (20 mL) at 25°C, and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-

imidazo[1,2-a]pyrazine-7-carboxylate (5 g, crude) was obtained as brown gum. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.29 (s, 1H), 8.21 (s, 1H), 7.61-7.53 (m, 2H), 7.33-7.28 (m, 1H), 5.18-5.07 (m, 2H), 4.55-4.43 (m, 1H), 4.17-4.12 (m, 1H), 3.52-3.38 (m, 1H), 1.45 (s, 9H), 1.35 (d, J = 5.2 Hz, 3H).

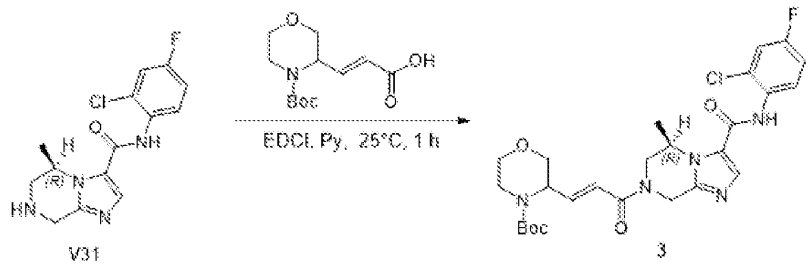
Step 1.2 Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (V31)



2 V31

[01293] To a solution of tert-butyl (5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (5 g, 12.23 mmol, 1 *eq*) in DCM (10 mL) was added HCl/dioxane (4 M, 20 mL) at 25°C. The reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure. Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8- tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V31) (4.5 g, crude) was obtained as brown gum. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.77 (s, 1H), 8.48 (s, 1H), 7.59-7.51 (m, 2H), 7.32-7.27 (m, 1H), 5.29-5.26 (m, 1H), 4.68-4.55 (m, 2H), 3.68-3.58 (m, 2H), 1.59 (d, J = 6.8 Hz, 3H).

Step 1.3 Synthesis of tert-butyl 3-[(E)-3-[(5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate

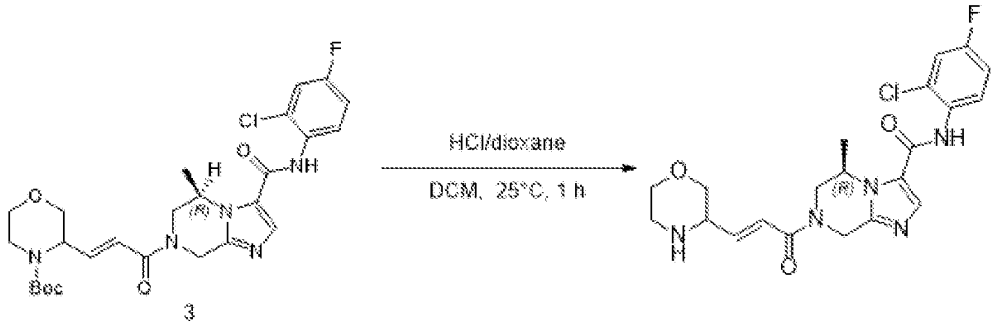


V31 3

[01294] A mixture of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (1 g, 2.90 mmol, 1 *eq*, HCl), (E)-3-(4-tert-butoxycarbonylmorpholin- 3-yl)prop-2-enoic acid (745.32 mg, 2.90 mmol, 1 *eq*), EDCI (1.11 g, 5.79 mmol, 2 *eq*) in Py (15 mL) was stirred at 25°C for 1 h. The reaction mixture was

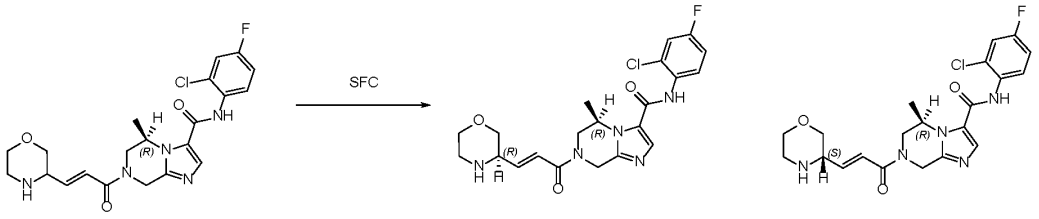
concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage ®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound tert-butyl 3-[(E)-3-[(5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (0.48 g, 875.90 μmol, 30.24% yield) was obtained as a light brown solid. LCMS: m/z 548.1 $[M+H]^+$

Step 1.4 Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01295] To a solution of tert-butyl 3-[(E)-3-[(5R)-3-[(2-chloro-4-fluoro-phenyl)carbamoyl]-5-methyl- 6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-3-oxo-prop-1-enyl]morpholine-4-carboxylate (0.48 g, 875.90 μmol, 1 *eq*) in DCM (5 mL) was added HCl/dioxane (4 M, 5 mL) at 25°C. The mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 18%-48% B over 8.0 min). Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (140.1 mg, 302.17 μmol, 34.50% yield, 96.60% purity) was obtained as a white solid. LCMS: m/z 448.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.89 (s, 1H), 7.88 (s, 1H), 7.57-7.51 (m, 2H), 7.29-7.24 (m, 1H), 6.75-6.60 (m, 2H), 5.23 (d, J = 17.6 Hz, 1H), 5.04 (s, 1H), 4.69-4.56 (m, 1H), 4.34-4.25 (m, 1H), 3.77-3.65 (m, 2H), 3.46-3.38 (m, 3H), 3.30-3.22 (m, 1H), 3.10-3.04 (m, 1H), 2.84-2.70 (m, 2H), 1.29-1.23 (m, 3H).

Example 210: Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3- yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-N- (2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.1 Synthesis of (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-N- (2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

[01296] (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (200 mg, 446.54 μmol, 1 eq) was separated by SFC (column: DAICEL CHIRALPAK IF (250 mm * 30 mm, 10 um); mobile phase: [Heptane-EtOH: ACN= 4:1 (0.1% NH3H2O)]; B%: 50%, isocratic elution mode). Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (66.4 mg, 126.01 μmol, 28.22% yield, 93.73% purity, FA) was obtained as a white solid. Compound (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (63.7 mg, 124.91 μmol, 27.97% yield, 96.85% purity, FA) was obtained as a white solid.

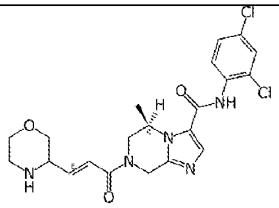
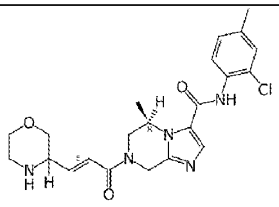
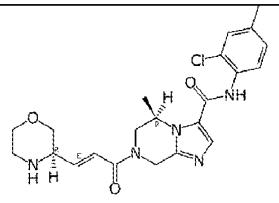
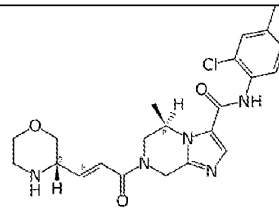
[01297] LCMS: m/z 448.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.91 (s, 1H), 8.25 (s, 2H), 7.88 (s, 1H), 7.57-7.51 (m, 2H), 7.29-7.24 (m, 1H), 6.73-6.59 (m, 2H), 5.23 (d, J = 17.6 Hz, 1H), 5.04 (s, 1H), 4.69-4.56 (m, 1H), 4.32-4.25 (m, 1H), 3.79-3.74 (m, 1H), 3.68-3.65 (m, 1H), 3.48-3.43 (m, 1H), 3.39-3.33 (m, 1H), 3.24 (d, J = 14.0 Hz, 1H), 3.10-3.06 (m, 1H), 2.79-2.76 (m, 2H), 1.30-1.21 (m, 3H).

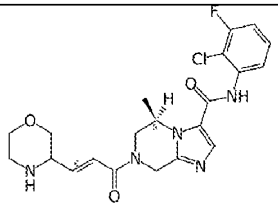
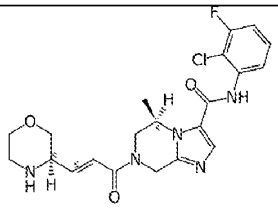
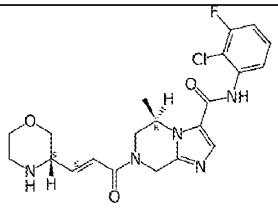
[01298] LCMS: m/z 448.1 $[M+H]^+$ ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 8.32 (s, 2H), 7.89 (s, 1H), 7.58-7.52 (m, 2H), 7.30-7.25 (m, 1H), 6.76-6.62 (m, 2H), 5.25 (d, J = 17.2 Hz, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.32-4.26 (m, 1H), 3.79-3.66 (m, 2H), 3.68-3.65 (m, 1H), 3.47-3.45 (m, 1H), 3.39-3.33 (m, 1H), 3.27-3.24 (m, 1H), 3.12-3.06 (m, 1H), 2.86-2.74 (m, 2H), 1.30-1.25 (m, 3H).

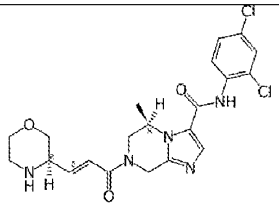
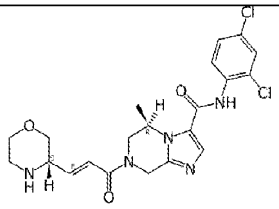
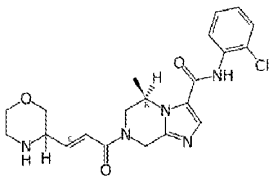
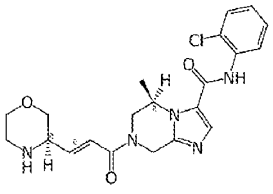
[01299] Compounds in Table AB were synthesized following the procedure for (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and procedure for (5R)-N-(2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3- yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-

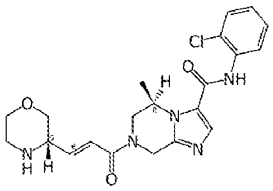
a]pyrazine-3-carboxamide and (5R)-N- (2-chloro-4-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table AB

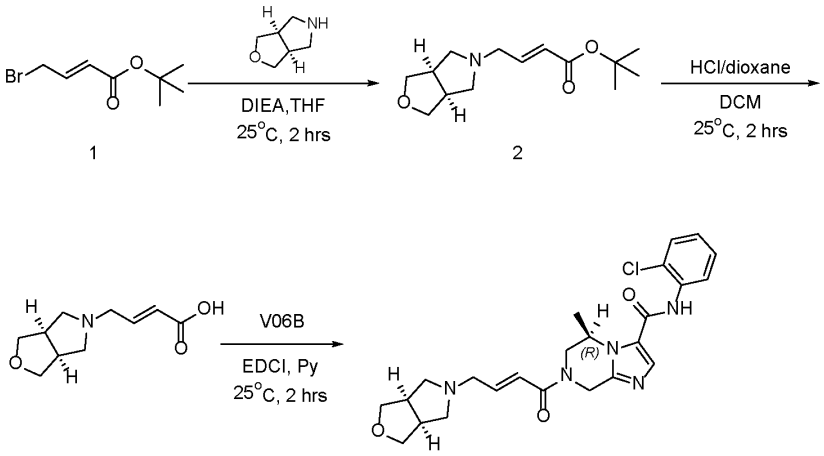
Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) 9.91 (s, 1H), 7.89 (s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.75-6.68 (m, 1H), 6.64-6.59 (m, 1H), 5.24 (d, J = 18.4 Hz, 1H), 5.05-5.00 (m, 1H), 4.70-4.55 (m, 1H), 4.31-4.25 (m, 1H), 3.77-3.65 (m, 4H), 3.47-3.43 (m, 2H), 3.11-3.04 (m, 2H), 2.78 (s, 1H), 1.29-1.22 (m, 3H).	LCMS: m/z 464.1/ 466.1 $[M+H]^+$	
(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.78 (s, 1H), 7.86 (s, 1H), 7.38-7.36 (m, 2H), 7.17 (dd, = 8.0 Hz, 1.2 Hz, 1H), 6.74-6.59 (m, 2H), 5.23 (d, J = 17.2 Hz, 1H), 5.04 (s, 1H), 4.61 (dd, J = 35.2 Hz, 16.8 Hz, 1H), 4.30-4.25 (m, 1H), 3.76-3.65 (m, 3H), 3.31-3.15 (m, 2H), 3.10-3.04 (m, 1H), 2.78-2.66 (m, 3H), 2.31 (s, 3H), 1.29-1.22 (m, 3H).	LCMS: m/z 444.2 $[M+H]^+$	
(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin- 3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.78 (s, 1H), 7.87 (s, 1H), 7.38-7.36 (m, 2H), 7.18-7.16 (m, 1H), 6.75-6.59 (m, 2H), 5.23 (d, J = 18.0 Hz, 1H), 5.08-5.02 (m, 1H), 4.60 (dd, J = 35.2 Hz, 16.8 Hz, 1H), 4.28 (t, J = 10.8 Hz, 1H), 3.79-3.65 (m, 3H), 3.46-3.42 (m, 1H), 3.38-3.35 (m, 1H), 3.28-3.19 (m, 0.5H), 3.07 (t, J = 10.4 Hz, 1H), 2.78-2.75 (m, 2.5H), 2.32 (s, 3H), 1.30-1.21 (m, 3H).	LCMS: m/z 444.1 $[M+H]^+$	SFC (condition: column: DAICEL CHIRALP AK AY-H (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%:55%, isocratic elution mode)
(5R)-N-(2-chloro-4-methyl-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.78 (s, 1H), 7.87 (s, 1H), 7.39-7.36 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.75-6.60 (m, 2H), 5.23 (d, J = 17.6 Hz, 1H), 5.04 (s, 1H), 4.62 (dd, J = 36.4 Hz, 17.2Hz, 1H), 4.31-4.25 (m, 1H), 3.77-3.65 (m, 3H), 3.45-3.43 (m, 1H), 3.37-3.34 (m, 1H), 3.26-3.19 (m, 0.5H), 3.09-2.99	LCMS: m/z 444.1 $[M+H]^+$	SFC (condition: column: DAICEL CHIRALP AK AY-H (250 mm * 30 mm, 10 um); mobile

Name	Structure	NMR	LCMS	SFC conditions
a]pyrazine-3-carboxamide		(m, 1H), 2.81-2.73 (m, 2.5H), 2.32 (s, 3H), 1.28-1.23 (m, 3H).		phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%:55%, isocratic elution mode)
(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.02 (s, 1H), 7.91 (s, 1H), 7.43-7.31 (m, 3H), 6.75-6.60 (m, 2H), 5.27-5.22 (m, 1H), 5.04 (s, 1H), 4.70-4.57 (m, 1H), 4.33-4.26 (m, 1H), 3.77-3.71 (m, 1H), 3.67 (d, J = 10.4 Hz, 1H), 3.46-3.37 (m, 2H), 3.27-3.23 (m, 1H), 3.10-3.04 (m, 1H), 2.79-2.72 (m, 2H), 1.31-1.23 (m, 3H).	LCMS: m/z 448.1 $[M+H]^+$	
(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin- 3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 10.04-9.89 (m, 1H), 7.91 (s, 1H), 7.45-7.39 (m, 2H), 7.35-7.31 (m, 1H), 6.75-6.60 (m, 2H), 5.24 (d, J = 18.0 Hz, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.33-4.26 (m, 1H), 3.79-3.65 (m, 2H), 3.47-3.42 (m, 1H), 3.39-3.38 (m, 1H), 3.29-3.23 (m, 1H), 3.07 (t, J = 10.4 Hz, 1H), 2.78-2.76 (m, 2H), 1.31-1.22 (m, 3H).	LCMS: m/z 448.1 $[M+H]^+$	prep-HPLC (column: DAICEL CHIRALP AK IF (250 mm * 30 mm, 10 um); mobile phase: [Heptane-EtOH: ACN= 4:1 (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
(5R)-N-(2-chloro-3-fluoro-phenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.94-9.88 (m, 1H), 7.90 (s, 1H), 7.44-7.38 (m, 2H), 7.36-7.30 (m, 1H), 6.76-6.61 (m, 2H), 5.25 (d, J = 17.6 Hz, 1H), 5.06 (s, 1H), 4.69-4.57 (m, 1H), 4.32-4.26 (m, 1H), 3.78-3.68 (m, 2H), 3.46-3.43 (m, 1H), 3.38-3.37 (m, 1H), 3.27-3.23 (m, 1H), 3.10-3.04 (m, 1H), 2.82-2.72 (m, 2H), 1.30-1.23 (m, 3H).	LCMS: m/z 448.1 $[M+H]^+$	prep-HPLC (column: DAICEL CHIRALP AK IF (250 mm * 30 mm, 10 um); mobile phase: [Heptane-EtOH: ACN= 4:1 (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)

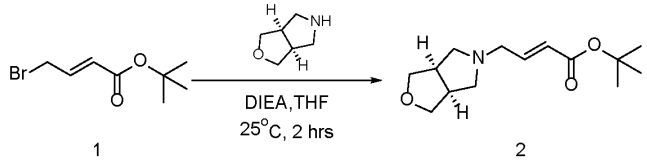
Name	Structure	NMR	LCMS	SFC conditions
(5R)-N-(2,4-dichlorophenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.72-6.60 (m, 2H), 5.24 (d, J = 17.6 Hz, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.32-4.26 (m, 1H), 3.76 (d, J = 10.8 Hz, 2H), 3.67 (d, J = 8.4 Hz, 2H), 3.44-3.42 (m, 2H), 3.09 (t, J = 10.0 Hz, 1H), 2.85-2.79 (m, 2H), 1.41-1.37 (m, 3H).	LCMS: m/z 464.1/466.1 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; gradient: 20%-40% B over 12.0 min)
(5R)-N- (2,4-dichlorophenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.89 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.47 (dd, J = 8.8 Hz, 2.4 Hz, 1H) 6.72-6.60 (m, 2H), 5.24 (d, J = 17.6 Hz, 1H), 5.04 (s, 1H), 4.68-4.56 (m, 1H), 4.30-4.25 (m, 1H), 3.78-3.66 (m, 2H), 3.47-3.46 (m, 1H), 3.38-3.35 (m, 2H), 3.27-3.23 (m, 1H), 3.12-3.05 (m, 1H), 2.83-2.74 (m, 2H), 1.29-1.22 (m, 3H).	LCMS: m/z 464.1/466.1 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OJ (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; gradient: 20%-40% B over 12.0 min)
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-3-morpholin-3-ylprop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.75-6.59 (m, 2H), 5.23 (d, J = 17.2 Hz, 1H), 5.05 (s, 1H), 4.62 (dd, J = 34.8 Hz, 16.8 Hz, 1H), 4.32-4.25 (m, 1H), 3.76-3.65 (m, 2.5H), 3.46-3.43 (m, 1H), 3.38-3.35 (m, 1H), 3.27-3.23 (m, 0.5H), 3.10-3.05 (m, 1H), 2.79-2.75 (m, 3H), 1.30-1.22 (m, 3H).	LCMS: m/z 430.1 $[M+H]^+$	
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-3-[(3R)-morpholin-3-yl]prop -2-enoyl]-6,8-dihydro-5H-		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.2Hz, 1H), 6.75-6.68 (m, 1H), 6.65-6.60 (m, 1H), 5.24 (d, J = 17.6 Hz, 1H), 5.05 (s, 1H), 4.62 (dd, J = 35.6 Hz, 16.4	LCMS: m/z 430.1 $[M+H]^+$	SFC (condition: column: DAICEL CHIRALPAK AY-H(250 mm * 30

Name	Structure	NMR	LCMS	SFC conditions
imidazo[1,2-a]pyrazine-3-carboxamide		Hz, 1H), 4.33-4.30 (m, 1H), 3.77-3.65 (m, 2.5H), 3.46-3.42 (m, 1H), 3.38-3.35 (m, 1H), 3.26-3.23 (m, 0.5H), 3.08 (t, *J* = 10.4 Hz, 1H), 2.79-2.73 (m, 2H), 1.30-1.22 (m, 3H).		mm,10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 60%, isocratic elution mode)
(5R)-N-(2-chlorophenyl)-5-methyl-7-[(E)-3-[(3S)-morpholin-3-yl]prop-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.52 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.2Hz, 1H), 6.72-6.60 (m, 2H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.26-5.22 (m, 1H), 5.05 (s, 1H), 4.62 (dd, *J* = 36.4 Hz, 16.4 Hz, 1H), 4.31-4.28 (m, 1H), 3.77 - 3.65 (m, 2.5H), 3.45-3.43 (m, 1H), 3.37-3.35 (m, 1H), 3.26-3.23 (m, 0.5H), 3.08-3.03 (m, 1H), 2.81-2.72 (m, 2H), 1.29-1.23 (m, 3H).	LCMS: m/z 430.1 $[M+H]^+$	SFC (condition: column: DAICEL CHIRALPAK AY-H(250 mm * 30 mm,10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 60%, isocratic elution mode)

Example 211: Synthesis of (5R)-7-[(E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



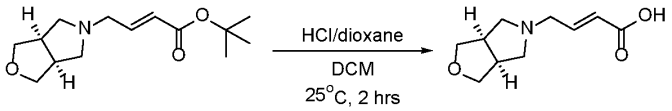
Step 1.1 Synthesis of tert-butyl (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c] pyrrol-5-yl]but-2-enoate.



1 2

[01300] To a solution of (3aR,6aS)-3,3a,4,5,6,6a-hexahydro-1H-furo[3,4-c]pyrrole (500 mg, 3.34 mmol, 1 eq, HCl) and tert-butyl (E)-4-bromobut-2-enoate (738.85 mg, 3.34 mmol, 1 eq) in THF (7 mL) was added DIEA (647.86 mg, 5.01 mmol, 873.13 µL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (Biotage®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 50 mL/min). The eluent was removed under reduced pressure. Compound tert-butyl (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]but-2-enoate (270 mg, 1.07 mmol, 31.89% yield) was obtained as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.73 (dt, J = 15.6 Hz, 6.0 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 3.70 (t, J = 8.4 Hz, 2H), 3.35-3.34 (m, 2H), 3.14 (d, J = 5.2 Hz, 2H), 2.68 (s, 2H), 2.53-2.50 (m, 2H), 2.31 (dd, J = 9.2 Hz, 2.8 Hz, 2H), 1.42 (s, 9H).

Step 1.2 Synthesis of (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] but-2-enoic acid.



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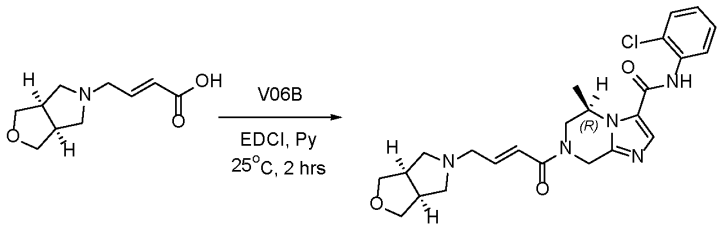
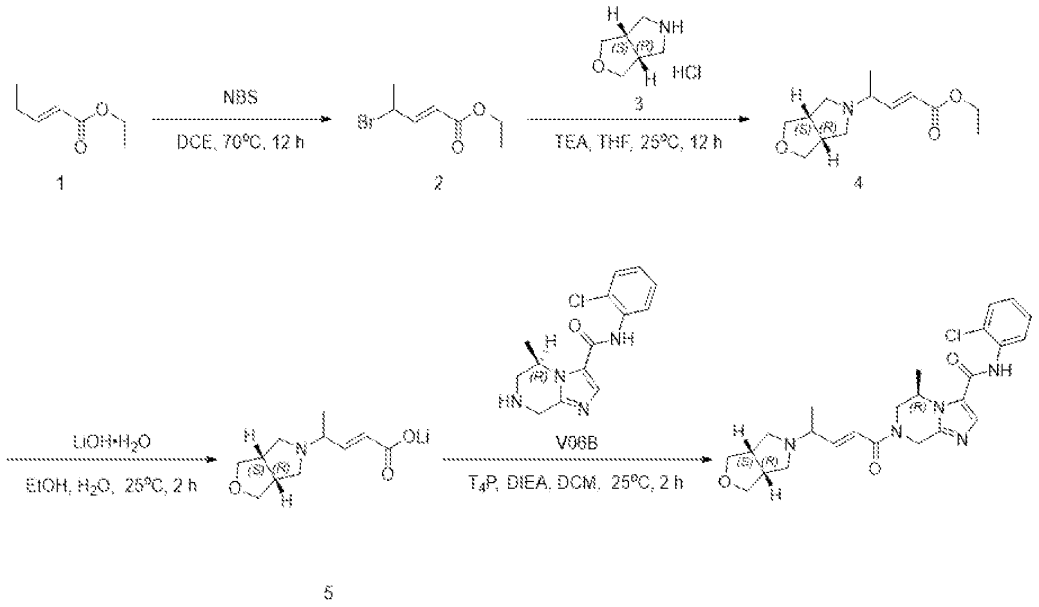
[01301] To a solution of tert-butyl (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] but-2-enoate (270 mg, 1.07 mmol, 1 eq) in DCM (3 mL) was added HCl/dioxane (4 M, 3 mL, 11.26 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed tert-butyl (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]but-2-enoate was consumed. One new peak with desired MS was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. Compound (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]but-2-enoic acid (270 mg, crude) was obtained as a yellow solid. LCMS: m/z 198.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) 11.42-10.87 (m, 1H), 6.87-6.75 (m, 1H), 6.16 (d, J = 15.6 Hz, 1H), 3.97-3.92(m, 2H), 3.74 (t, J = 9.2 Hz, 4H), 3.25-3.24 (m, 2H), 3.07-2.98 (m, 3H), 2.65-2.63 (m, 1H).

Step 1.3 Synthesis of (5R)-7-[(E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

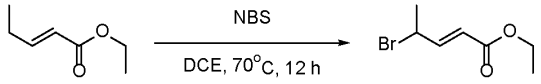


[01302] To a solution of (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (200 mg, 611.23 µmol, 1 eq, HCl) and (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]but-2-enoic acid (180.83 mg, 916.85 µmol, 1.5 eq) in Pyridine (2 mL) was added EDCI (234.35 mg, 1.22 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. LCMS showed (E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]but-2-enoic acid was consumed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 * 40 * 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 10%-60% B over 8.0 min). The residue was dried over lyophilization. Compound (5R)-7-[(E)-4-[(3aR,6aS)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c] pyrrol-5-yl]but-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (135.5 mg, 281.43 µmol, 46.04% yield, 97.61% purity) was obtained as a pale yellow solid. LCMS: m/z 470.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.79-6.68 (m, 2H), 5.27-5.16 (m, 1H), 5.05 (s, 1H), 4.70-4.57 (m, 1H), 4.28 (d, J = 17.6 Hz, 1H), 3.72 (t, J = 7.2 Hz, 3H), 3.40 (dd, J = 8.4 Hz, 2.0 Hz, 2H), 3.22-3.19 (m, 2H), 2.70-2.66 (m, 2H), 2.53 (s, 2H), 2.34-2.32 (m, 2H), 1.30-1.26 (m, 3H).

Example 212: Synthesis of (5R)-7-[(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

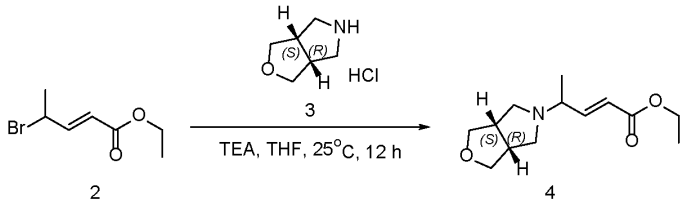


Step 1.1 Synthesis of ethyl (E)-4-bromopent-2-enoate



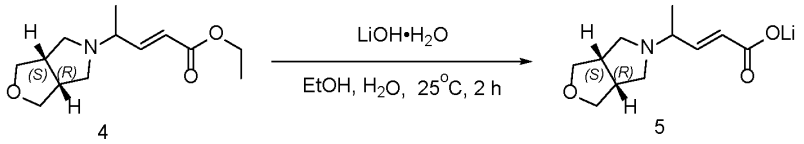
[01303] To a solution of ethyl (E)-pent-2-enoate (5 g, 39.01 mmol, 1 eq) in DCE (50 mL) was added NBS (10.41 g, 58.52 mmol, 1.5 eq) in one portion at 25°C. The reaction mixture was heated to 70°C and stirred at 70°C for 12 h. The reaction mixture was cooled to 0°C and quenched by addition of water (50 mL) at 0°C, then extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~9% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give ethyl (E)-4-bromopent-2-enoate (9 g, crude) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 4.76-4.67 (m, 1H), 4.26-4.19 (m, 2H), 1.83 (d, J = 6.8 Hz, 3H), 1.32-1.29 (m, 3H).

1.2 Synthesis of ethyl (E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl] pent-2-enoate



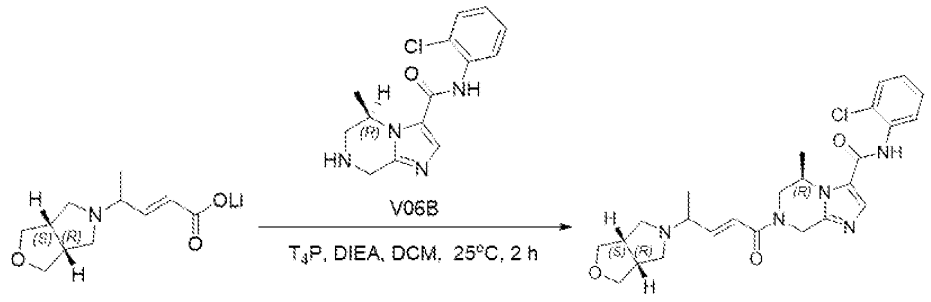
[01304] To a solution of ethyl (E)-4-bromopent-2-enoate (3.5 g, 16.90 mmol, 1 eq) and (3aS,6aR)-3,3a,4,5,6,6a-hexahydro-1H-furo[3,4-c]pyrrole (2.10 g, 18.59 mmol, 1.1 eq) in THF (35 mL) was added TEA (5.13 g, 50.71 mmol, 7.06 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 12 h. The reaction mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 60 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give ethyl (E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoate (1 g, 4.18 mmol, 24.72% yield) as yellow oil. LCMS: m/z 240.2 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.90 (dd, J = 15.6 Hz, 8.0 Hz, 1H), 5.90 (d, J = 16.0 Hz, 1H), 4.19 (q, J = 6.8 Hz, 2H), 3.79-3.75 (m, 2H), 3.6-3.57 (m, 2H), 2.97-2.90 (m, 1H), 2.89-2.73 (m, 4H), 2.33-2.23 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H).

Step 1.3 Synthesis of [(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2- enoyl]oxylithium



[01305] To a solution of ethyl (E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoate (1 g, 4.18 mmol, 1 eq) in EtOH (10 mL) and H_2O (5 mL) was added $LiOH•H_2O$ (350.68 mg, 8.36 mmol, 2 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give [(E)-4-[(3aS,6aR)- 1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoyl]oxylithium (900 mg, 4.14 mmol, 99.17% yield) as a yellow solid.

Step 1.4 Synthesis of (5R)-7-[(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



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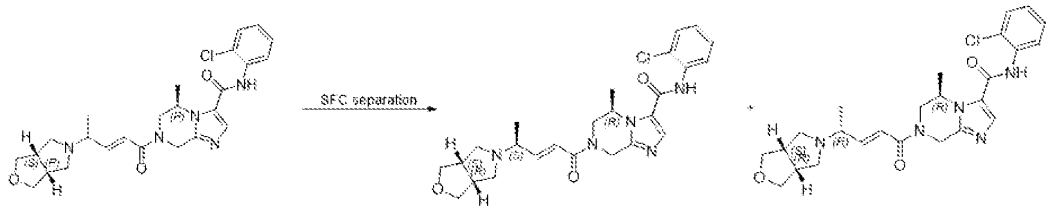
[01306] To a solution of [(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2- enoyl]oxylithium (747.01 mg, 3.44 mmol, 2 eq) and (5R)-N-(2-chlorophenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (500 mg, 1.72 mmol, 1 eq) in DCM (5 mL) were added T_4P (2.48 g, 3.44 mmol, 50% purity, 2 eq) and DIEA (889.02 mg, 6.88 mmol, 1.20 mL, 4 eq) in one portion at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 h. The mixture was cooled to 0°C and concentrated in reduced pressure at 0°C. The residue was poured into water (10 mL) and stirred for 2 min. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 20%- 55% B over 8.0 min) to give (5R)-7-[(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a- hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (125.2 mg, 235.94 μmol, 13.72% yield, 95.16% purity). LCMS: m/z 484.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.73-6.62 (m, 2H), 5.31-5.15 (m, 1H), 5.08-5.05 (m, 1H), 4.69-4.54 (m, 1H), 4.35-4.25 (m, 1H), 3.71-3.68 (m, 2H), 3.40-3.38 (m, 2H), 3.27-3.22 (m, 1H), 3.01 (s, 1H), 2.67-2.66 (m, 2H), 2.62-2.54 (m, 2H), 2.34-2.25 (m, 2H), 1.30-1.26 (m, 3H), 1.16-1.14 (m, J = 6.4 Hz, 3H).

Example 213: Synthesis of (5R)-7-[(E,4S)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-7-[(E,4R)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

1.1 Synthesis of (5R)-7-[(E,4S)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-7-[(E,4R)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01307] (5R)-7-[(E)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (120 mg, 247.94 μmol, 1 eq) was separated by SFC (column: Chiral Pak IH, 250 * 30 mm, 10 um; mobile phase: [CO_2- IPA (0.1% NH_3H_2O)]; B%: 35%, isocratic elution mode) to give (5R)-7-[(E,4S)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (40.1 mg, 82.41 μmol, 33.24% yield, 99.46% purity) as a white solid, and (5R)-7-[(E,4R)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (39.3 mg, 79.46 μmol, 32.05% yield, 97.86% purity) as a white solid.

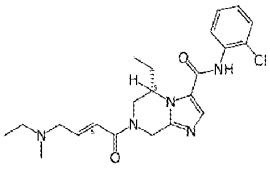
[01308] LCMS: m/z 484.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.73-6.62 (m, 2H), 5.27-5.19 (m, 1H), 5.05 (s, 1H), 4.69-4.54 (m, 1H), 4.31-4.25 (m, 1H), 3.70 (t, J = 6.8 Hz, 2H), 3.40-3.38 (m, 2H), 3.30-3.22 (m, 1H), 3.04-3.00 (m, 1H), 2.68-2.67 (m, 2H), 2.62-2.53 (m, 2H), 2.34-2.25 (m, 2H), 1.30-1.26 (m, 3H), 1.15-1.13 (m, 3H).

[01309] LCMS: m/z 484.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.73-6.62 (m, 2H), 5.28-5.19 (m, 1H), 5.05 (s, 1H), 4.69-4.57 (m, 1H), 4.32-4.25 (m, 1H), 3.71-3.69 (m, 2H), 3.39-3.37 (m, 2H), 3.28-3.22 (m, 1H), 3.00-2.99 (m, 1H), 2.72-2.67 (m, 2H), 2.61-2.52 (m, 2H), 2.34-2.23 (m, 2H), 1.29-1.25 (m, 3H), 1.15 (d, J = 6.8 Hz, 3H).

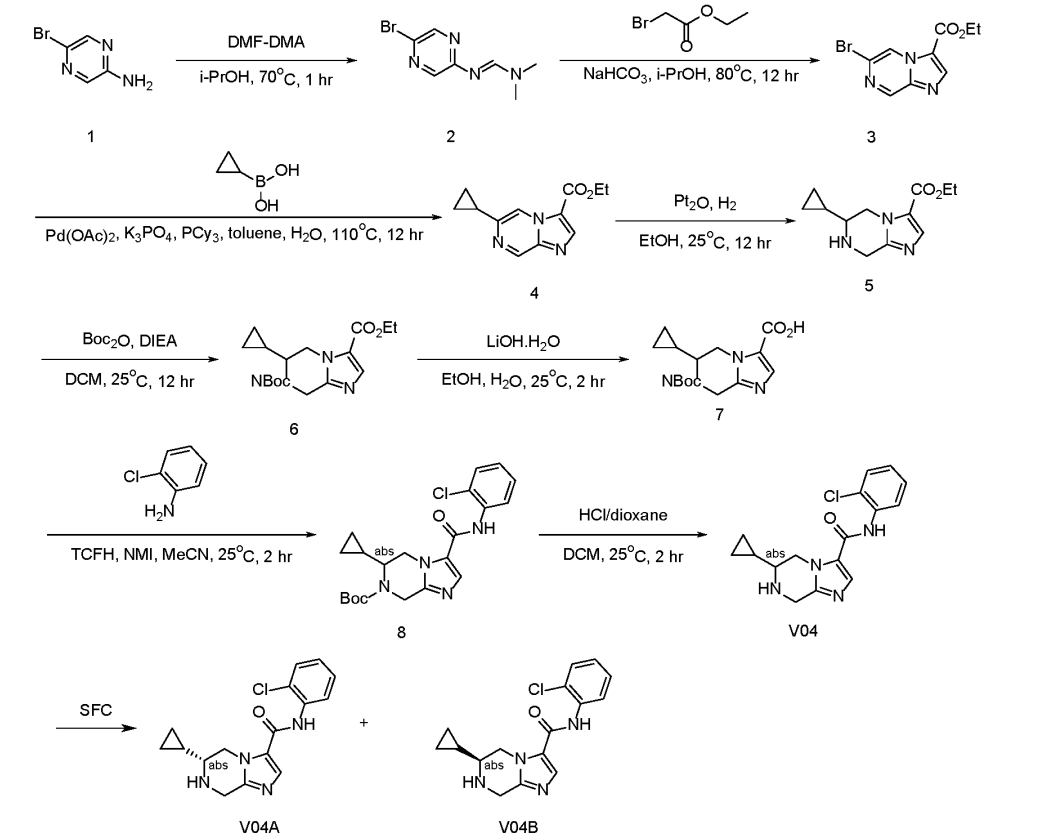
[01310] Compounds in Table AC were synthesized following the procedure for Synthesis of (5R)-7-[(E,4S)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-

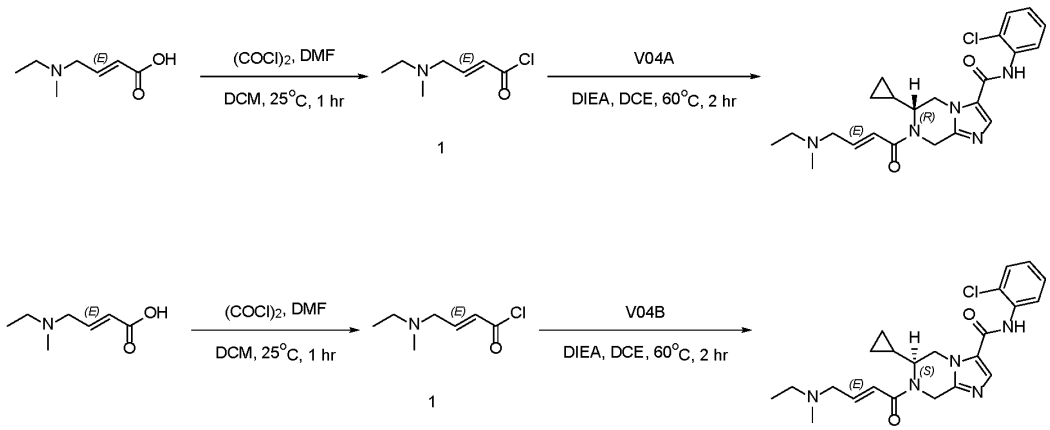
(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5R)-7-[(E,4R)-4-[(3aS,6aR)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol- 5-yl]pent-2-enoyl]-N-(2-chlorophenyl)-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table AC

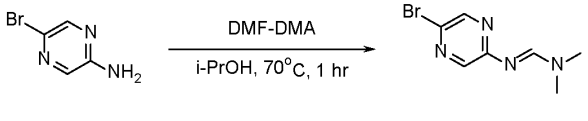
Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.86 (s, 1H), 7.89 (s, 1H), 7.60-7.51 (m, 2H), 7.38 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, J = 1.6 Hz, 1H), 6.79-6.69 (m, 2H), 5.21 (t, J = 19.2 Hz, 1H), 4.84-4.67 (m, 2H), 4.41-4.27 (m, 1H), 3.65 (d, J = 13.6 Hz, 0.5H), 3.18-3.17 (m, 0.5H), 3.14-3.10 (m, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.73-1.68 (m, 1H), 1.48-1.43 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H).	LCMS: m/z 430.1 $[M+H]^+$

Example 214: Synthesis of (6S)-N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide, N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide and (6R)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



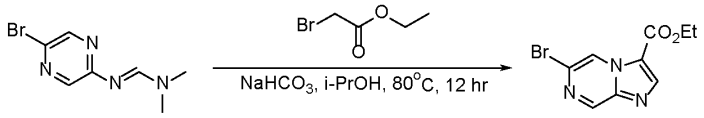


Step 1.1 Synthesis of N'-(5-bromopyrazin-2-yl)-N,N-dimethyl-formamidine



[01311] To a solution of 5-bromopyrazin-2-amine (20 g, 114.94 mmol, 1 eq) in isopropanol (200 mL) was added dropwise DMF-DMA (27.39 g, 229.89 mmol, 30.54 mL, 2 eq) at 20°C. The reaction mixture was heated to 70°C and was stirred at 70°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue trituration with Petroleum ether (10 mL x 1) filtered and concentrated under reduced pressure to give compound N'-(5-bromopyrazin-2-yl)-N,N-dimethyl-formamidine (26 g, 113.50 mmol, 98.74% yield) as a white solid. LCMS: m/z 230.1 $[M+H]^+$.

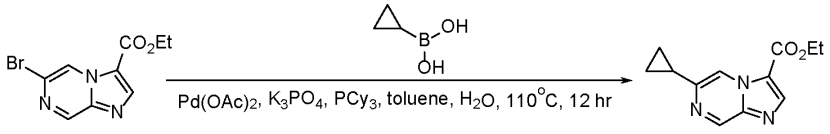
Step 1.2 Synthesis of ethyl 6-bromoimidazo[1,2-a]pyrazine-3-carboxylate



2 3

To a solution of N'-(5-bromopyrazin-2-yl)-N,N-dimethyl-formamidine (26 g, 113.50 mmol, 1 eq) in propan-2-ol (300 mL) were added $NaHCO_3$ (19.07 g, 227.00 mmol, 8.83 mL, 2 eq) and ethyl 2-bromoacetate (56.86 g, 340.50 mmol, 37.68 mL, 3 eq) at 20°C. The reaction mixture was heated to 80°C and was stirred at 80°C for 12 hr. The reaction mixture was cooled to 20°C and the reaction mixture was evaporated to dryness, and the residue was diluted with ethyl acetate and washed with water. The organic phase was dried over anhydrous sodium sulfate and concentrated to obtain crude product. The residue was purified by flash silica gel chromatography (ISCO®; 330 g Sepa Flash ® Silica Flash Column, Eluent of 0 ~ 30% Ethyl acetate/Petroleum ether gradient @ 120 mL/min). Compound ethyl 6-bromoimidazo[1,2-a]pyrazine-3-carboxylate (11 g, 40.73 mmol, 35.88% yield) was obtained as a yellow solid. LCMS: m/z 271.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.19 (s, 2H), 8.46 (s, 1H), 4.41(q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H).

1.3 Synthesis of ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate

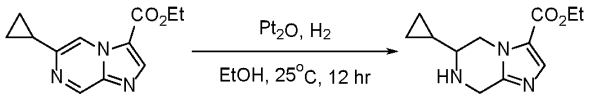


3 4

[01312] To a reaction mixture of ethyl 6-bromoimidazo[1,2-a]pyrazine-3-carboxylate (11 g, 40.73 mmol, 1 eq), cyclopropylboronic acid (5.25 g, 61.09 mmol, 1.5 eq) in toluene (200 mL) and H_2O (10 mL) were added $Pd(OAc)_2$ (1.83 g, 8.15 mmol, 0.2 eq), K_3PO_4 (30.26 g, 142.55 mmol, 3.5 eq), PCy_3 (4.57 g, 16.29 mmol, 5.28 mL, 0.4 eq) at 25°C, and then the reaction mixture was heated to 110°C and was stirred at 110°C for 12 hr under N_2 atmosphere. The

reaction mixture was cooled to 25°C and was quenched by addition H_2O (100 mL) at 25 °C and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (150 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0 ~ 50% Ethyl acetate/Petroleum ether gradient @ 50mL/min). Compound ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (3.8 g, 16.43 mmol, 40.35% yield) was obtained as a white solid. LCMS: m/z 232.2 $[M+H]^+$.

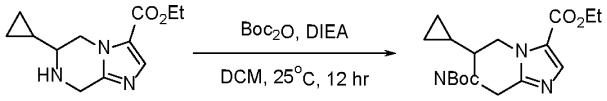
Step 1.4 Synthesis of ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate



4 5

[01313] The PtO_2 (746.28 mg, 3.29 mmol, 0.2 eq) was added into flask stand-up bottom under Ar atmosphere at 25°C, then EtOH (60 mL) was added into flask stand-up bottom, then reaction mixture was added ethyl 6-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (3.8 g, 16.43 mmol, 1 eq) and then the reaction mixture was degassed and purged with H_2 for 3 times, then the reaction mixture was stirred at 25°C for 12 hr under H_2 atmosphere. The reaction solution was filtered and the filtration was concentrated to give compound ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxylate (3.5 g, 14.88 mmol, 90.53% yield) was obtained as a black oil. LCMS: m/z 236.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.58 (s, 1H), 4.43 (dd, J = 13.2 Hz, 3.6 Hz, 1H), 4.25 (q, J = 6.8 Hz, 2H), 4.07-4.02 (m, 1H), 3.90-3.85 (m, 1H), 3.81-3.75 (m, 1H), 2.39-2.33 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.90-0.86 (m, 1H), 0.50-0.48 (m, 2H), 0.37-0.33 (m, 2H).

Step 1.4 Synthesis of O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3,7-dicarboxylate

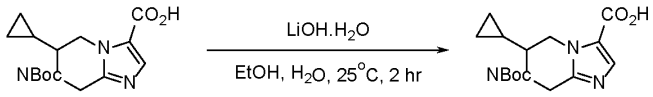


5 6

[01314] To a solution of ethyl 6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (3.5 g, 14.88 mmol, 1 eq) in DCM (40 mL) were added Boc_2O (3.90 g, 17.85 mmol, 4.10 mL, 1.2 eq) and DIEA (2.88 g, 22.31 mmol, 3.89 mL, 1.5 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (5 mL) at 25°C, and adjusted the reaction mixture pH = 5 by sat. aq. citric acid and extracted with

EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (5 g, crude) was obtained as a white solid. LCMS: m/z 336.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.67 (s, 1H), 4.85 (d, J = 17.6 Hz, 1H), 4.62 (d, J = 13.6 Hz, 1H), 4.44 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.11 (dd, J = 13.2 Hz, 4.4 Hz, 1H), 3.86-3.83 (m, 1H), 1.43 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 0.91-0.84 (m, 1H), 0.46-0.33 (m, 4H).

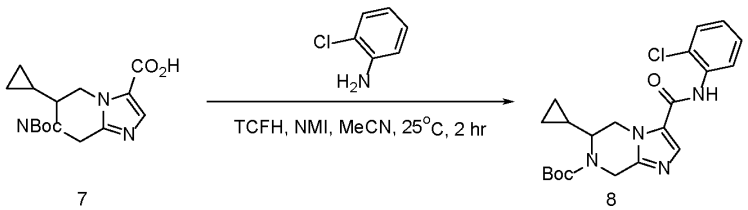
Step 1.5 Synthesis of 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-3-carboxylic acid



6 7

[01315] To a solution of O7-tert-butyl O3-ethyl 6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (5 g, 14.91 mmol, 1 eq) in EtOH (40 mL), H_2O(10 mL) was added LiOH.H_2O (1.88 g, 44.72 mmol, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove EtOH, then the reaction mixture was added H_2O (5 mL) then the reaction mixture was adjusted pH = 3-4 by 1 N HCl and extracted with DCM: isopropanol =3:1 (10 mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (3.5 g, crude) was obtained as a yellow oil. LCMS: m/z 308.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 12.92 (s, 1H), 7.62 (s, 1H), 4.85 (d, J = 9.6 Hz, 1H), 4.62 (d, J = 13.2 Hz, 1H), 4.43 (d, J = 17.6 Hz, 1H), 4.07 (dd, J = 13.6 Hz, 4.4 Hz, 1H), 3.84-3.82 (m, 1H), 1.43 (s, 9H), 0.88-0.85 (m, 1H), 0.46-0.36 (m, 4H).

Step 1.6 Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-7-carboxylate

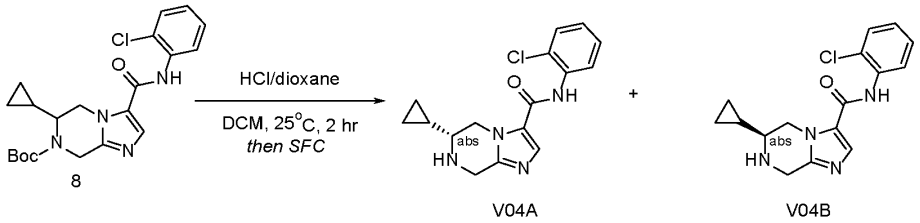


7 8

[01316] To a solution of 7-tert-butoxycarbonyl-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine -3-carboxylic acid (3.5 g, 11.39 mmol, 1 eq) in MeCN (50 mL) were added 2-chloroaniline (2.91 g, 22.78 mmol, 2.40 mL, 2 eq), TCFH (9.59 g, 34.16 mmol, 3 eq) and NMI

(2.80 g, 34.16 mmol, 2.72 mL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (10 mL) at 25°C, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0 ~ 40% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). Compound tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (3.5 g, 8.40 mmol, 73.72% yield) was obtained as a yellow oil. LCMS: m/z 417.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.14 (s, 1H), 8.16 (s, 1H), 7.57 (td, J = 8.0 Hz, 1.2 Hz, 2H), 7.40 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.32 (td, J = 7.6 Hz, 1.6 Hz, 1H), 5.03-4.89 (m, 1H), 5.80-4.77 (m, 1H), 4.57-4.53 (m, 1H), 4.16 (dd, J = 14.0 Hz, 4.4 Hz, 1H), 3.88-3.87 (m, 1H), 1.44 (s, 9H), 1.05-1.02 (m, 1H), 0.49-0.35 (m, 4H).

1.7 Synthesis of (6S)-N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V04B), N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (V04A)



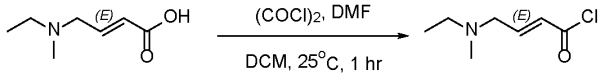
[01317] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-6-cyclopropyl-6,8-dihydro -5H-imidazo[1,2-a]pyrazine-7-carboxylate (3.5 g, 8.40 mmol, 1 eq) in DCM (15 mL) were added HCl/dioxane (4 M, 14.27 mL, 6.80 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was quenched by addition H_2O (10 mL) at 25°C, and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, the residue was trituration with DCM (10 mL x 1) filtered and concentrated under reduced pressure to give a crude, and then the crude was added H_2O (10 mL), the reaction mixture was adjusted pH = 10 by aq. Na_2CO_3, then filtered and concentrated under reduced pressure to give a product. The residue was purified by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm,10 um); mobile phase: [CO_2 – EtOH (0.1% NH_3H_2O)]; B%: 60%, isocratic elution mode). Compound (6S)-N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V04B) (0.41 g, 1.29 mmol, 15.42% yield) was obtained as a yellow solid. Compound N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-

a]pyrazine-3-carboxamide (V04A) (0.415 g, 1.31 mmol, 15.60% yield) was obtained as a yellow solid.

[01318] LCMS: m/z 317.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.74 (s, 1H), 7.80 (s, 1H), 7.56-7.53 (m, 2H), 7.37 (td, J = 8.4 Hz, 1.2 Hz, 1H), 7.27 (td, J = 7.6 Hz, 1.6 Hz, 1H), 4.45 (dd, J = 13.2 Hz, 4.0 Hz, 1H), 4.01-3.97 (m, 1H), 3.85-3.73 (m, 2H), 2.73-2.67 (m, 1H), 2.30-2.24 (m, 1H), 0.87-0.82 (m, 1H), 0.48-0.31 (m, 4H).

[01319] LCMS: m/z 317.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.77 (s, 1H), 7.82 (s, 1H), 7.55-7.53 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.28 (td, J = 8.4 Hz, 1.2 Hz, 1H), 4.45 (dd, J = 13.6 Hz, 4.0 Hz, 1H), 4.07-4.03 (m, 1H), 3.91-3.78 (m, 2H), 2.37-2.33 (m, 2H), 0.89-0.84 (m, 1H), 0.49-0.33 (m, 4H).

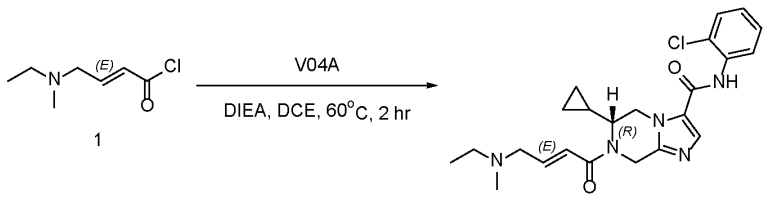
Step 1.8 Synthesis of (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride



1

[01320] To a solution of (E)-4-[ethyl(methyl)amino]but-2-enoic acid (0.15 g, 1.05 mmol, 1 eq) in DCM (2 mL) was added $(COCl)_2$ (531.89 mg, 4.19 mmol, 366.82 µL, 4 eq) and a drop of DMF at 20°C. The reaction mixture was stirred at 20°C for 2 hr. LC-MS showed the reaction was complete (quenched by MeOH). The reaction mixture was concentrated under reduced pressure to give compound (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.15 g, 928.05 µmol, 88.59% yield) was obtained as a red oil. LCMS: m/z 158.2 $[M+MeOH]^+$.

1.9 Synthesis of (6R)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



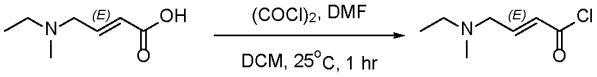
1

[01321] To a reaction mixture of (6S)-N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (147.00 mg, 464.03 µmol, 1 eq) in DCE (3 mL) were added (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.15 g, 928.05 µmol, 2 eq), DIEA (119.94 mg, 928.05 µmol, 161.65 µL, 2 eq) at 25°C and then the reaction mixture was heated to 60°C and was stirred at 60°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 5% - 30% B over 8.0 min). Compound (6S)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-

[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (33.4 mg, 75.57 μmol, 16.29% yield) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.92-10.71 (m, 1H), 10.39-10.12 (m, 1H), 8.36-8.22 (m, 1H), 7.60-7.54 (m, 2H), 7.41-7.40 (m, 1H), 7.36-7.34 (m, 1H), 7.06-7.03 (m, 1H), 6.79-6.77 (m, 1H), 5.45-5.37 (m, 1H), 5.84-4.81 (m, 1H), 4.34-4.11 (m, 1H), 4.11-4.10 (m, 1H), 3.95-3.93 (m, 3H), 3.15-3.04 (m, 2H), 2.70 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H), 1.21-1.17 (m, 1H), 0.50-0.27 (m, 4H).

Example 215: Synthesis of (6S)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

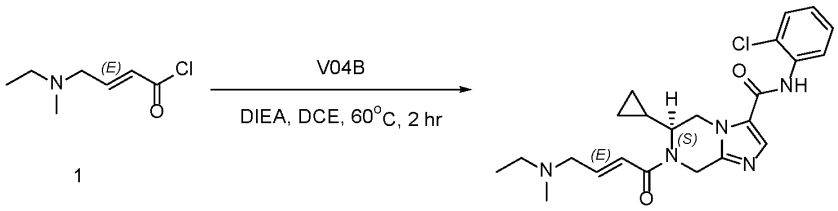
Step 2.0 Synthesis of (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride



1

[01322] To a solution of (E)-4-[ethyl(methyl)amino]but-2-enoic acid (0.2 g, 1.40 mmol, 1 eq) in DCM (2 mL) were added $(COCl)_2$ (709.19 mg, 5.59 mmol, 489.10 μL, 4 eq) and DMF (10.21 mg, 139.68 μmol, 10.75 μL, 0.1 eq) at 20°C. The reaction mixture was stirred at 20° C for 2 hr. LC-MS showed the reaction was complete (quenched by MeOH). The reaction mixture was concentrated under reduced pressure to give compound (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.2 g, 1.24 mmol, 88.59% yield) was obtained as a red oil. LCMS: m/z 158.2 $[M+H]^+$.

Step 2.1 Synthesis of (6S)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

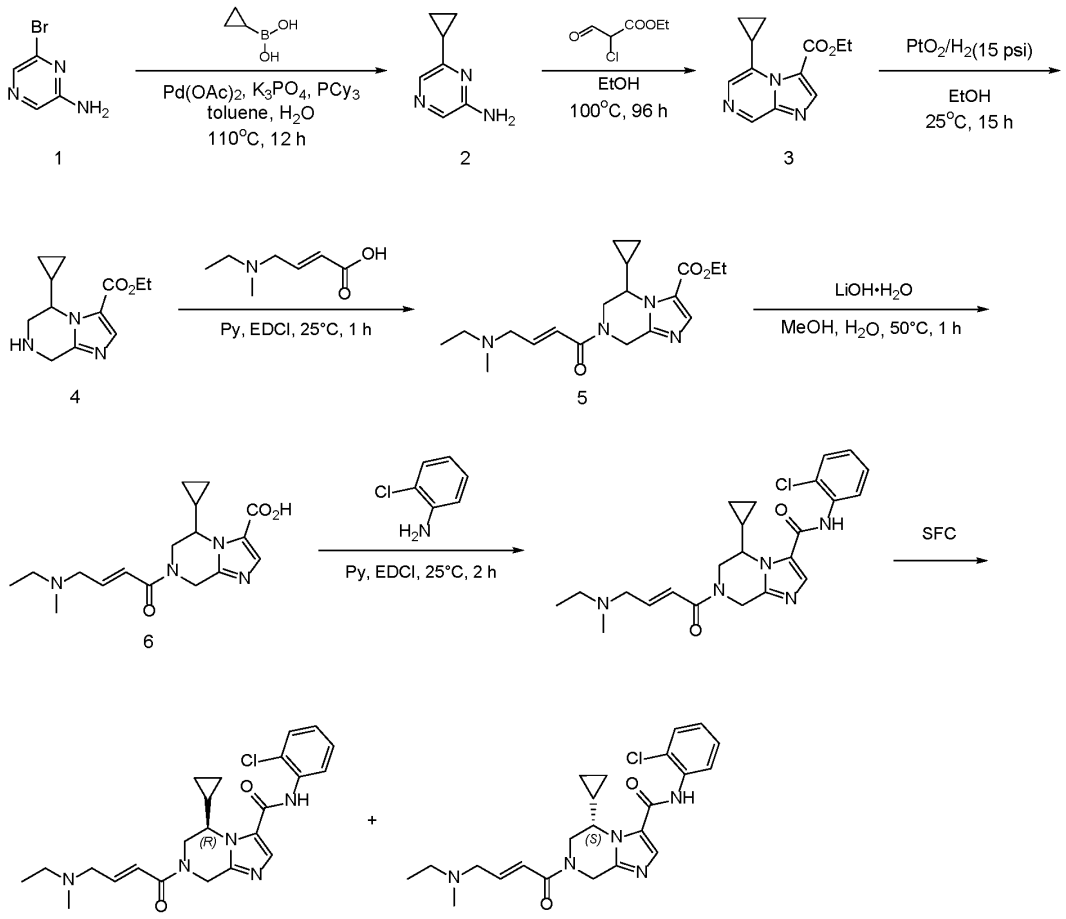


1

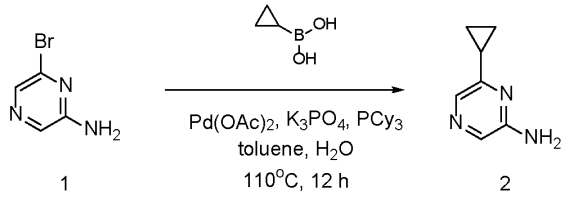
To a reaction mixture of (6R)-N-(2-chlorophenyl)-6-cyclopropyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (196.00 mg, 618.70 μmol, 1 eq) in DCE (5 mL) were added (E)-4-[ethyl(methyl)amino]but-2-enoyl chloride (0.2 g, 1.24 mmol, 2 eq), DIEA (159.92 mg, 1.24 mmol, 215.53 μL, 2 eq) at 25°C, and then the reaction mixture was heated to 60°C and was stirred at 60°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100

* 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)- ACN]; gradient: 5% - 30% B over 8.0 min). Compound (6R)-N-(2-chlorophenyl)-6-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (63 mg, 142.55 μmol, 23.04% yield) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.67 (s, 1H), 8.57 (s, 1H), 7.59-7.52 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.08-7.05 (m, 1H), 6.83-6.56 (m, 1H), 5.53-5.49 (m, 1H), 4.87-4.84 (m, 1H), 4.65-4.60 (m, 1H), 4.38-4.17 (m,2H), 3.91-3.84 (m, 2H), 3.14-3.00 (m, 2H), 3.68-3.67 (m, 3H), 1.28-1.18 (m, 4H), 0.54-0.29 (m, 4H).

Example 216: Synthesis of N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide, (5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-N-(2- chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



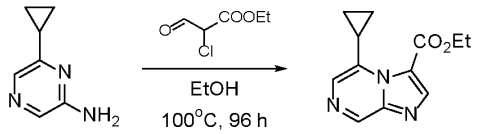
Step 1.1 Synthesis of 6-cyclopropylpyrazin-2-amine



[01323] To the reaction mixture of 6-bromopyrazin-2-amine (10 g, 57.47 mmol, 1 eq), cyclopropylboronic acid (7.40 g, 86.21 mmol, 1.5 eq) in toluene (200 mL) and H_2O (10 mL) were added $Pd(OAc)_2$ (2.58 g, 11.49 mmol, 0.2 eq), K_3PO_4 (42.70 g, 201.15 mmol, 3.5 eq) and PCy_3 (6.45 g, 22.99 mmol, 7.45 mL, 0.4 eq) at 20°C. The reaction mixture was degassed and purged with N_2 for 3 times, then heated to 110°C and stirred at 110°C for 12 hours under N_2 atmosphere. The reaction mixture was cooled to 20°C and filtered through a pad of Clite. To the reaction mixture was added water (400 mL). The reaction mixture was extracted with EtOAc (120 mL x 3), the combined organic phase was washed with brine (120 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by

flash silica gel chromatography (Biotage ®; 120 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Petroleum ether: Ethyl acetate gradient @ 100 mL/min). The eluent was removed under reduced pressure to give 6-cyclopropylpyrazin-2-amine (7.99 g, crude) as a yellow solid. LCMS: m/z 136.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.64 (s, 1H), 7.63 (s, 1H), 6.21 (s, 2H), 1.93-1.88 (m, 1H), 0.87-0.81 (m, 4H).

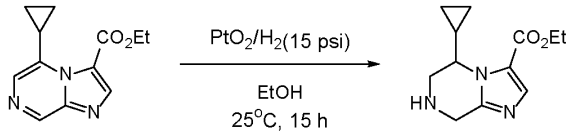
Step 1.2 Synthesis of ethyl 5-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate -



2 3

[01324] To a solution of 6-cyclopropylpyrazin-2-amine (7.8 g, 57.71 mmol, 1 eq), ethyl 2-chloro-3-oxo-propanoate (10.43 g, 69.25 mmol, 1.2 eq) in EtOH (80 mL) was added ethyl 2-chloro-3-oxo-propanoate (10.43 g, 69.25 mmol, 1.2 eq) at 20°C. The reaction mixture was heated to 100°C and stirred at 100°C for 96 hours. The reaction mixture was cooled to 20°C and concentrated under reduced pressure. The reaction mixture was diluted with water (100 mL), adjusted pH = 8 with sat.aq. NaOH at 0°C. The reaction mixture was warmed to 20°C and extracted with EtOAc (30 mL x 3), the combined organic phase was washed with brine (30 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 80 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Petroleum ether: Ethyl acetate gradient @ 100 mL/min). The eluent was removed under reduced pressure to give ethyl 5-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (2.2 g, 8.37 mmol, 14.51% yield, 88% purity) as a yellow solid and ethyl (3E)-2-chloro-3-(6-cyclopropylpyrazin-2-yl)imino-propanoate (4.7 g, 17.56 mmol, 30.42% yield) as a yellow solid. LCMS: m/z 232.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.13 (s, 1H), 8.38 (s, 1H), 8.01 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H), 2.66-2.60 (m, 1H), 1.35 (t, J = 7.2 Hz, 3H), 0.97-0.93 (m, 2H), 0.76-0.74 (m, 2H).

Step 1.3 Synthesis of ethyl 5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate

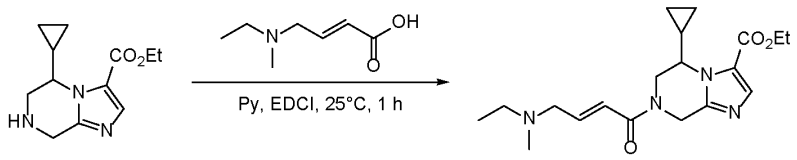


3 4

[01325] To a solution of PtO_2 (216.03 mg, 951.35 μmol, 0.1 *eq*) in EtOH (30 mL) was added ethyl 5-cyclopropylimidazo[1,2-a]pyrazine-3-carboxylate (2.2 g, 9.51 mmol, 1 *eq*) under Ar at

25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. Then the reaction mixture was stirred at 25°C for 15 hr under H_2 (15 Psi). The reaction mixture was filtered through a pad of Clite and the filtrate was concentrated under reduced pressure. Compound ethyl 5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxylate (2.5 g, crude) was obtained as black gum without further purification. LCMS: m/z 236.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.57 (s, 1H), 4.28-4.19 (m, 2H), 4.11-4.03 (m, 1H), 3.94-3.86 (m, 1H), 3.50-3.39 (m, 1H), 3.21-3.00 (m, 2H), 1.42-1.31 (m, 1H), 1.30-1.24 (m, 3H), 0.71-0.63 (m, 1H), 0.48-0.35 (m, 2H), 0.34-0.25 (m, 1H).

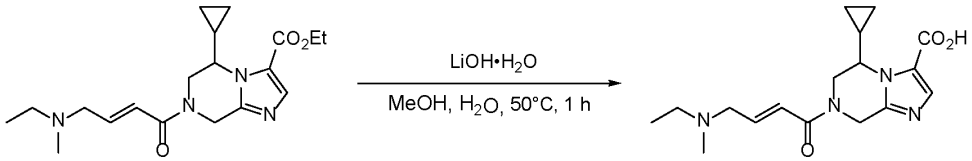
Step 1.4 Synthesis of ethyl 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]- 6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate



4 5

[01326] A mixture of ethyl 5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (2.4 g, 10.20 mmol, 1 *eq*), (E)-4-[ethyl(methyl)amino]but-2-enoic acid (1.75 g, 12.24 mmol, 1.2 *eq*), EDCI (3.91 g, 20.40 mmol, 2 *eq*) in Py (20 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 25°C for 2 hr under N_2 atmosphere. The reaction mixture was concentrated. The residue was purified by flash silica gel chromatography (Biotage ®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/MeOH gradient @ 60 mL/min). Compound ethyl 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate (4 g, crude) was obtained as black gum. LCMS: m/z 361.3 $[M+H]^+$.

Step 1.5 Synthesis of 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid

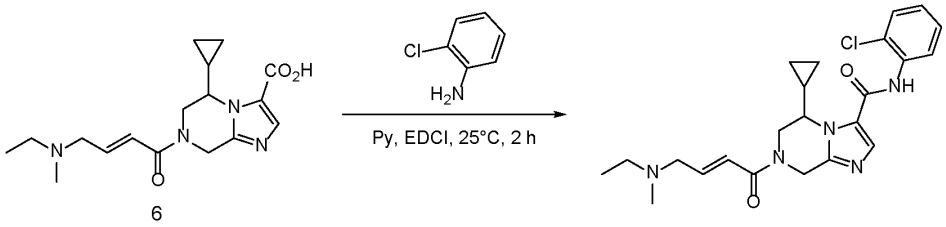


5 6

[01327] To a solution of ethyl 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylate (3.9 g, 10.82 mmol, 1 *eq*) in MeOH (30 mL) and H_2O (15 mL) was added LiOH•H_2O (1.14 g, 27.05 mmol, 2.5 *eq*) at 25°C. The reaction mixture was stirred at 50°C for 1 hr. MeOH was removed under reduced pressure, the residue

was adjusted pH=4 and purified by prep-HPLC (column: Phenomenex luna C_{18} (250 x 70 mm, 15 um); mobile phase: [H_2O (0.04% HCl)-ACN]; gradient:0%-10% B over 18.0 min). Compound 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (0.52 g, 1.56 mmol, 14.46% yield) was obtained as a white solid. LCMS: m/z 333.2 $[M+H]^+$.

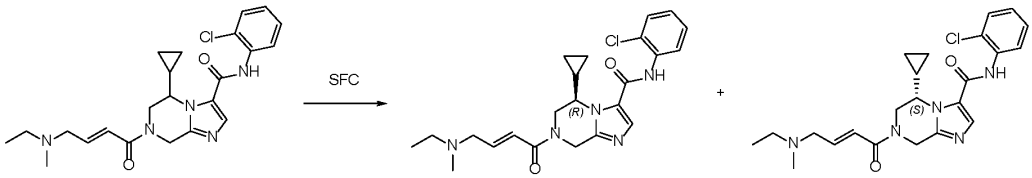
1.6 Synthesis of N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



6

[01328] A mixture of 5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H- imidazo[1,2-a]pyrazine-3-carboxylic acid (0.42 g, 1.26 mmol, 1 *eq*), 2-chloroaniline (177.31 mg, 1.39 mmol, 146.54 µL, 1.1 *eq*) and EDCI (484.45 mg, 2.53 mmol, 2 *eq*) in Py (5 mL) was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: WePure Biotech XP tC_{18} 150 x 40 x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 20% - 50% B over 8.0 min). Compound N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (206.1 mg, 460.88 µmol, 36.48% yield, 98.83% purity) was obtained. LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.84-7.76 (m, 1H), 7.58-7.53 (m, 1H), 7.52-7.46 (m, 1H), 7.41-7.35 (m, 1H), 7.32-7.25 (m, 1H), 6.79-6.65 (m, 2H), 5.35-5.16 (m, 1H), 4.85-4.67 (m, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.48-4.28 (m, 1H), 3.72 (d, J = 13.6 Hz, 0.6H), 3.23 (d, J = 13.2 Hz, 0.4H), 3.14 (s, 2H), 2.41-2.29 (m, 2H), 2.14 (s, 3H), 0.99 (t, J = 7.2 Hz, 3H), 0.97 - 0.86 (m, 1H), 0.65-0.54 (m, 1H), 0.45-0.26 (m, 3H).

Step 1.7 Synthesis of (5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl) amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



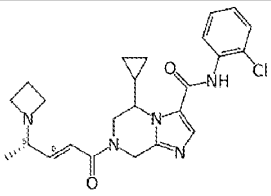
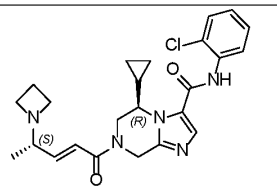
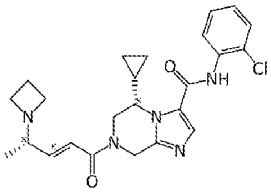
[01329] N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (0.2 g, 452.54 μmol, 1 *eq*) was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm x 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 45%, isocratic elution mode). Compound (5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (82.6 mg, 185.33 μmol, 40.95% yield, 99.16% purity) was obtained as a white solid. LCMS: m/z 442.2 $[M+H]^+$ Compound (5S)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (85.1 mg, 192.25 μmol, 42.48% yield, 99.84% purity) was obtained.

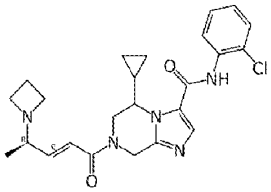
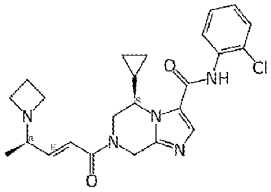
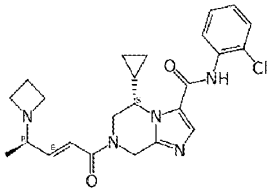
[01330] LCMS: m/z 442.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.95 (s, 1H), 7.84-7.76 (m, 1H), 7.54 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.49 (d, J = 7.2 Hz, 1H), 7.42-7.35 (m, 1H), 7.33-7.26 (m, 1H), 6.82-6.62 (m, 2H), 5.37-5.16 (m, 1H), 4.84-4.68 (m, 1H), 4.61 (d, J = 8.0 Hz, 1H), 4.45-4.30 (m, 1H), 3.77-3.67 (m, 0.6H), 3.23 (d, J = 12.0 Hz, 0.4H), 3.14 (s, 2H), 2.43-2.30 (m, 2H), 2.14 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H), 0.96-0.86 (m, 1H), 0.66-0.55 (m, 1H), 0.46-0.26 (m, 3H).

[01331] ^1H NMR (DMSO-d_6, 400 MHz) δ 9.95 (s, 1H), 7.84-7.76 (m, 1H), 7.56 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.52-7.46 (m, 1H), 7.42-7.33 (m, 1H), 7.33-7.25 (m, 1H), 6.72 (s, 2H), 5.36-5.17 (m, 1H), 4.86-4.68 (m, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.45-4.30 (m, 1H), 3.78-3.66 (m, 0.6H), 3.23 (d, J = 12.0 Hz, 0.4H), 3.14 (s, 2H), 2.42 - 2.30 (m, 2H), 2.14 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H), 0.97-0.87 (m, 1H), 0.65-0.55 (m, 1H), 0.46-0.27 (m, 3H).

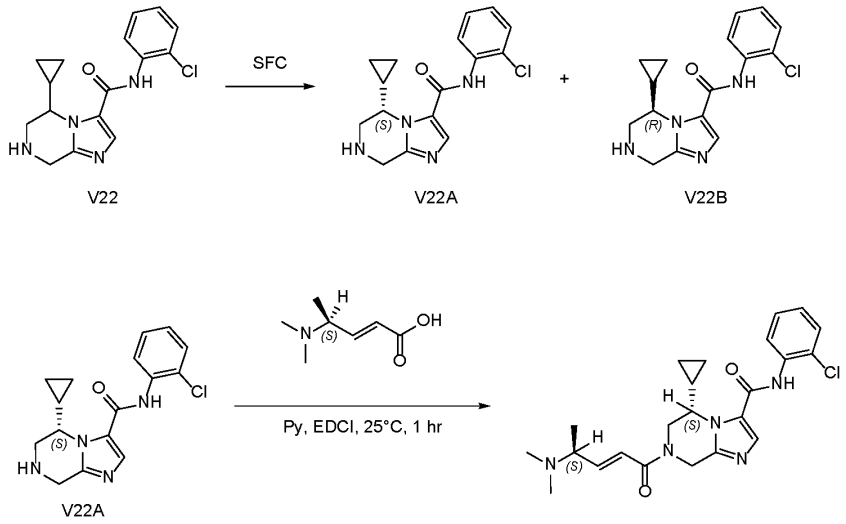
[01332] Compounds in Table AD were synthesized following the procedure for N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table AD

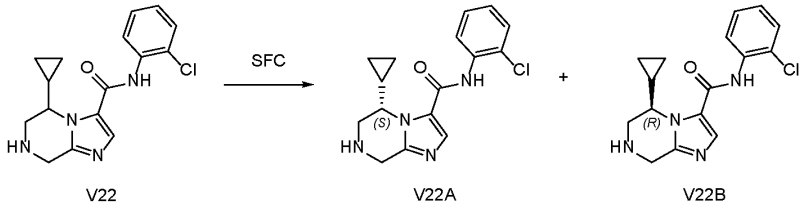
Name	Structure	NMR	LCMS	SFC conditions
7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.96 (s, 1H), 7.88-7.78 (m, 1H), 7.56 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.51 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.39 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 7.31 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.68-6.61 (m, 1H), 6.56-6.48 (m, 1H), 5.36-5.16 (m, 1H), 4.79 (d, J = 12.8 Hz, 0.3H), 4.74 (d, J = 16.8 Hz, 0.3H), 4.68-4.59 (m, 1H), 4.44 (d, J = 14.0 Hz, 0.7H), 4.32 (d, J = 18.0 Hz, 0.7H), 3.72 (d, J = 11.6 Hz, 0.6H), 3.23 (d, J = 11.2 Hz, 0.4H), 3.16-3.01 (m, 4H), 2.99-2.87 (m, 1H), 1.98-1.85 (m, 2H), 1.05-0.85 (m, 4H), 0.69-0.55 (m, 1H), 0.48-0.27 (m, 3H).	LCMS: m/z 454.2 [M+H]	
(5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5 -cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.96 (s, 1H), 7.88-7.78 (m, 1H), 7.56 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.51 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.39 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.31 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.66-6.50 (m, 2H), 5.30-5.21 (m, 1H), 4.79 (d, J = 12.8 Hz, 0.3H), 4.74 (d, J = 16.8 Hz, 0.3H), 4.65-4.60 (m, 1H), 4.44 (d, J = 14.0 Hz, 0.7H), 4.32 (d, J = 18.0 Hz, 0.7H), 3.74-3.70 (m, 0.6H), 3.36-3.20 (m, 0.4H), 3.10 (t, J = 7.2 Hz, 4H), 2.99-2.92 (m, 1H), 1.96-1.89 (m, 2H), 0.99-0.87 (m, 4H), 0.66-0.60 (m, 1H), 0.44-0.32 (m, 3H).	LCMS: m/z 454.2 [M+H]	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um);mobile phase: [CO_2-EtOH (0.1% NH_3•H_2O)]; B%:50%, isocratic elution mode)
(5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.96 (s, 1H), 7.88-7.78 (m, 1H), 7.56 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.51 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.39 (dt, J = 8.4 Hz, 1.2 Hz, 1H), 7.31 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.67-6.47 (m, 2H), 5.29-5.22 (m, 1H), 4.79 (d, J = 13.2 Hz, 0.3H), 4.74 (d, J = 17.2 Hz, 0.3H), 4.62 (d, J = 8.8 Hz, 1H), 4.42 (d, J = 14.8 Hz, 0.7H), 4.32 (d, J = 18.0 Hz, 0.7H), 3.74-3.70 (m, 0.6H), 3.25-3.21 (m, 0.4H), 3.14-3.03 (m, 4H), 2.99-2.92 (m, 1H), 1.94-1.88 (m, 2H), 0.99-0.87 (m, 4H), 0.66-0.60 (m, 1H), 0.44-0.25 (m, 3H).	LCMS: m/z 454.2 [M+H]	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um);mobile phase: [CO_2-EtOH (0.1% NH_3•H_2O)]; B%:50%, isocratic elution mode)

Name	Structure	NMR	LCMS	SFC conditions
7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d6*, 400 MHz) δ 9.96 (s, 1H), 7.82-7.79 (m, 1H), 7.57-7.48 (m, 2H), 7.41-7.28 (m, 2H), 6.67-6.60 (m, 1H), 6.55-6.47 (m, 1H), 5.30-5.21 (m, 1H), 4.80-4.70 (m, 1H), 4.64-4.59 (m, 1H), 4.45-4.29 (m, 1H), 3.73-3.70 (m, 0.6H), 3.25-3.20 (m, 0.4H), 3.11-3.05 (m, 4H), 2.92 (s, 1H), 1.95-1.88 (m, 2H), 0.97-0.91 (m, 4H), 0.61-0.60 (m, 1H), 0.43-0.32 (m, 3H).	LCMS: m/z 454.2 $[M+H]^+$	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d6*, 400 MHz) δ 9.96 (s, 1H), 7.82-7.79 (m, 1H), 7.56-7.48 (m, 2H), 7.41-7.36 (m, 1H), 7.32-7.28 (m, 1H), 6.67-6.61 (m, 1H), 6.52-6.47 (m, 1H), 5.30-5.22 (m, 1H), 4.80-4.70 (m, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.45-4.29 (m, 1H), 4.73-4.70 (m, 0.5H), 3.26-3.21 (m, 0.5H), 3.11-3.05 (m, 4H), 2.95-2.89 (m, 1H), 1.92-1.89 (m, 2H), 1.04-0.91 (m, 4H), 0.61-0.60 (m, 1H), 0.40-0.32 (m, 3H).	LCMS: m/z 454.2 $[M+H]^+$	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)
(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d6*, 400 MHz) δ 9.96 (s, 1H), 7.82-7.79 (m, 1H), 7.56-7.49 (m, 2H), 7.41-7.36 (m, 1H), 7.32-7.28 (m, 1H), 6.66-6.60 (m, 1H), 6.55-6.49 (m, 1H), 5.30-5.20 (m, 1H), 4.80-4.71 (m, 1H), 4.65-4.59 (m, 1H), 4.45-4.29 (m, 1H), 3.73-3.70 (m, 0.5H), 3.24-3.21 (m, 0.5H), 3.09 (t, *J* = 6.8 Hz, 4H), 2.94-2.89 (m, 1H), 1.92 (q, *J* = 6.8 Hz, 2H), 0.98-0.89 (m, 4H), 0.63-0.60 (m, 1H), 0.43-0.30 (m, 3H).	LCMS: m/z 454.2 $[M+H]^+$	SFC (column: Daicel Chiral Pak IM (250 * 25 mm i.d. 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode)

Example 217a: Synthesis of (S)-N-(2-chlorophenyl)-5-cyclopropyl-7-((S,E)-4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.



Step 1.1 Synthesis of (5S)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V22A) and (5R)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V22B)



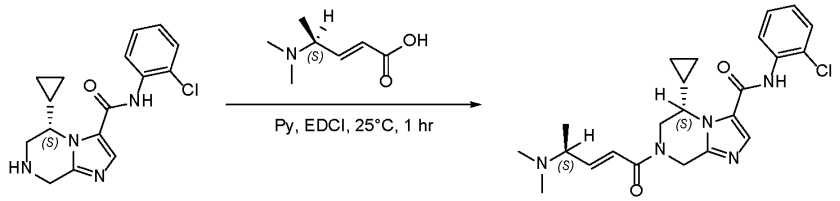
[01333] N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (2 g, 6.31 mmol, 1 *eq*) was separated by SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 um); mobile phase: [CO_2- MeOH(0.1% NH_3H_2O)]; B%: 40%, isocratic elution mode). Compound (5S)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V22A) (0.85 g, 2.68 mmol, 42.50% yield) was obtained as an off-white solid. Compound (5R)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V22B) (0.82 g, 2.59 mmol, 41.00% yield) was obtained as an off-white solid.

[01334] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.66 (s, 1H), 7.55-7.50 (m, 2H), 7.40-7.35 (m, 1H), 7.30-7.26 (m, 1H), 4.23-4.20 (m, 1H), 4.07-4.03 (m, 1H), 3.91-3.86 (m, 1H), 3.17-3.14 (m, 1H), 3.09-3.06 (m, 1H), 1.39-1.34 (m, 1H), 0.73-0.70 (m, 1H), 0.43-0.36 (m, 2H), 0.27-0.25 (m, 1H).

[01335] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.66 (s, 1H), 7.55-7.50 (m, 2H), 7.40-7.37 (m, 1H), 7.30-7.26 (m, 1H), 4.22-4.20 (m, 1H), 4.06-4.02 (m, 1H), 3.89-3.85 (m, 1H),

3.16-3.13 (m, 1H), 3.07-3.03 (m, 1H), 1.39-1.32 (m, 1H), 0.73-0.70 (m, 1H), 0.43-0.36 (m, 2H), 0.28-0.24 (m, 1H).

Step 1.2 Synthesis of (S)-N-(2-chlorophenyl)-5-cyclopropyl-7-((S,E)-4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

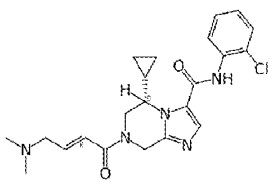


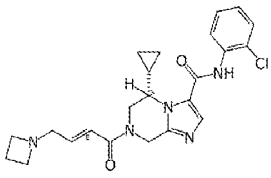
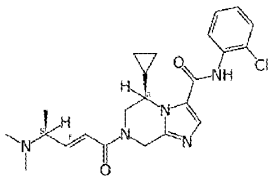
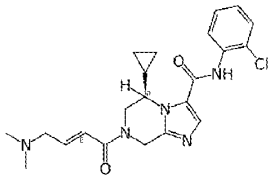
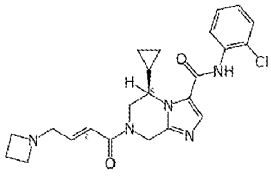
V22A

[01336] A mixture of (5S)-N-(2-chlorophenyl)-5-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (150.00 mg, 473.51 μmol, 1 *eq*), (E,4S)-4-(dimethylamino)pent-2-enoic acid (71.19 mg, 497.18 μmol, 1.05 *eq*), EDCI (181.54 mg, 947.02 μmol, 2 *eq*) in Py (4 mL) was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 25%- 55% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E,4S)-4-(dimethylamino)pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (82.5 mg, 182.30 μmol, 38.50% yield, 97.66% purity) was obtained as an off-white solid. LCMS: m/z 442.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.82-7.80 (m, 1H), 7.56-7.49 (m, 2H), 7.40-7.36 (m, 1H), 7.32-7.28 (m, 1H), 6.74-6.60 (m, 2H), 5.31-5.24 (m, 1H), 4.82-4.78 (m, 0.3H), 4.75-4.71 (m, 0.3H), 4.67-4.61 (m, 1H), 4.47-4.44 (m, 0.7H), 4.35-4.31 (m, 0.7H), 3.73 (d, J = 12.4 Hz, 0.5H), 3.25-3.20 (m, 0.5H), 3.16-3.11 (m, 1H), 2.15 (s, 6H), 1.12-1.10 (m, 3H), 1.06-0.92 (m, 1H), 0.63-0.60 (m, 1H), 0.44-0.39 (m, 3H).

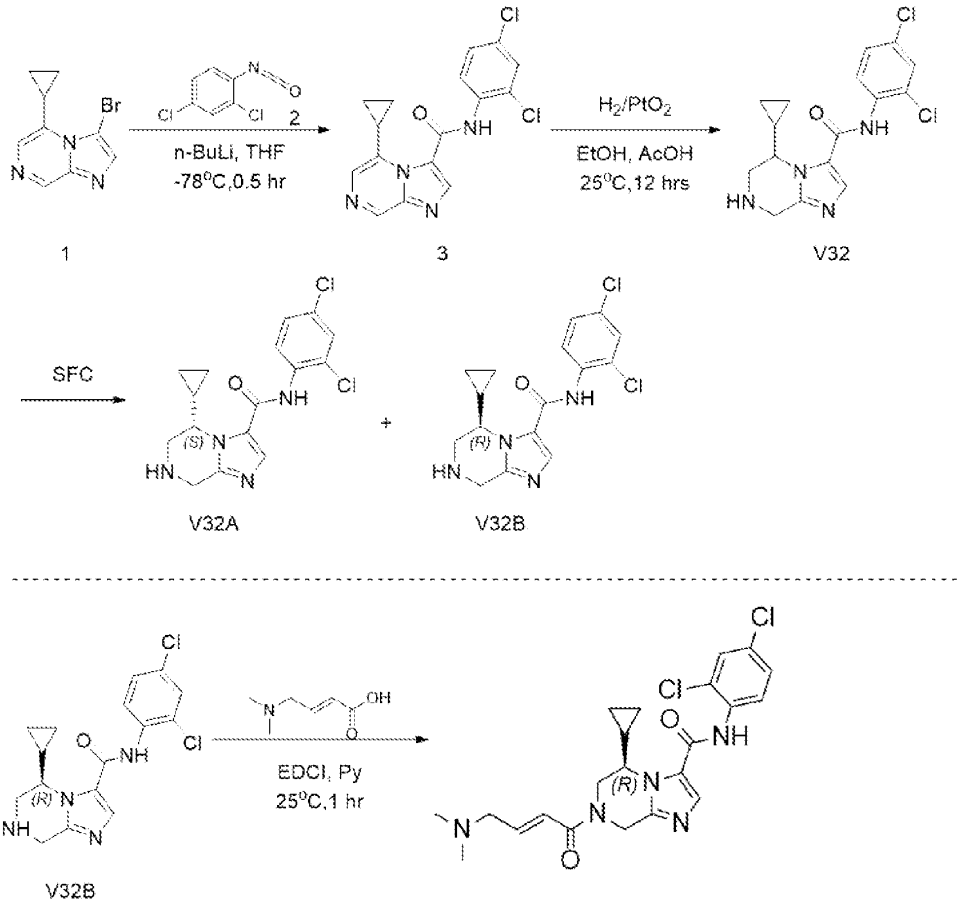
[01337] Compounds in Table AE were synthesized following the procedure for (S)-N-(2-chlorophenyl)-5-cyclopropyl-7-((S,E)-4-(dimethylamino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide.

Table AE

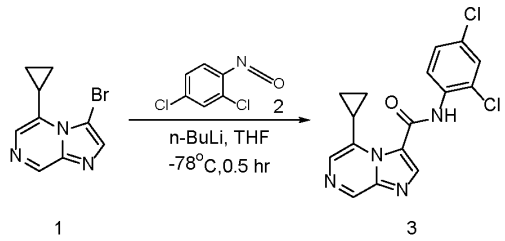
Name	Structure	NMR	LCMS
(5S)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d_6, 400 MHz) 9.95 (s, 1H), 7.81-7.79 (m, 1H), 7.55 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.50 (d, J = 6.4 Hz, 1H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.71 (m, 2H), 5.30-5.21 (m, 1H), 4.82-4.71 (m, 1H), 4.63-4.61 (m, 1H), 4.45-4.31 (m, 1H), 3.74-3.70 (m, 1H), 3.07 (d, J = 2.4	LCMS: m/z 428.1 $[M+H]^+$

Name	Structure	NMR	LCMS
		Hz, 2H), 2.16 (s, 6H), 1.02-0.89 (m, 1H), 0.61-0.59 (m, 1H), 0.43-0.34 (m, 3H).	
(5S)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.96 (s, 1H), 7.82-7.79 (m, 1H), 7.59-7.49 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 6.8 Hz, 1H), 6.66-6.58 (m, 2H), 5.29-5.24 (m, 1H), 4.81-4.76 (m, 1H), 4.63-4.61 (m, 1H), 4.43-4.30 (m, 1H), 3.73-3.70 (m, 0.5H), 3.23-3.20 (m, 0.5H), 3.18-3.15 (m, 6H), 2.03-1.96 (m, 2H), 0.93-0.87 (m, 1H), 0.63-0.57 (m, 1H), 0.43-0.33 (m, 3H).	LCMS: m/z 440.1 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.95 (s, 1H), 7.81-7.79 (m, 1H), 7.56 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.50-7.48 (m, 1H), 7.38 (td, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.32-7.27 (m, 1H), 6.73-6.61 (m, 2H), 5.31-5.24 (m, 1H), 4.81-4.78 (m, 0.3H), 4.75-4.70 (m, 0.3H), 4.61 (d, (td, *J* = 6.0 Hz, 1H), 4.46 (d, *J* = 14.0 Hz, 0.6H), 4.32 (d, *J* = 18.0 Hz, 0.6H), 3.71 (d, *J* = 13.6 Hz, 0.5H), 3.25-3.22 (m, 0.5H), 3.12 (q, *J* = 6.4 Hz, 1H), 2.15-2.14 (m, 6H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.01-0.89 (m, 1H), 0.61-0.60 (m, 1H), 0.43-0.29 (m, 3H).	LCMS: m/z 442.1 $[M+H]^+$
(5R)-N-(2-chlorophenyl)-5-cyclopropyl-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-*d*6) 9.95 (s, 1H), 7.81-7.79 (m, 1H), 7.55 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.72-6.71 (m, 2H), 5.30-5.22 (m, 1H), 4.81-4.71 (m, 1H), 4.63-4.61 (m, 1H), 4.45-4.31 (m, 1H), 3.73-3.70 (m, 0.5H), 3.26-3.21 (m, 0.5H), 3.07 (d, *J* = 2.4 Hz, 2H), 2.16 (s, 6H), 1.00-0.90 (m, 1H), 0.61-0.59 (m, 1H), 0.43-0.33 (m, 3H).	LCMS: m/z 428.0 $[M+H]^+$
(5R)-7-[(E)-4-(azetidin-1-yl)but-2-enoyl]-N-(2-chlorophenyl)-5-cyclopropyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 9.94 (s, 1H), 7.81-7.79 (m, 1H), 7.56-7.53 (m, 1H), 7.51-7.49 (m, 1H), 7.38 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 6.62-6.60 (m, 2H), 5.29-5.19 (m, 1H), 4.81-4.71 (m, 1H), 4.64-4.62 (m, 1H), 4.43-4.30 (m, 1H), 3.74-3.70 (m, 0.5H), 3.24-3.13 (m, 6.5H), 2.03-1.96 (m, 2H), 1.01-0.90 (m, 1H), 0.64-0.59 (m, 1H), 0.43-0.32 (m, 3H).	LCMS: m/z 440.1 $[M+H]^+$

Example 217b: Synthesis of (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



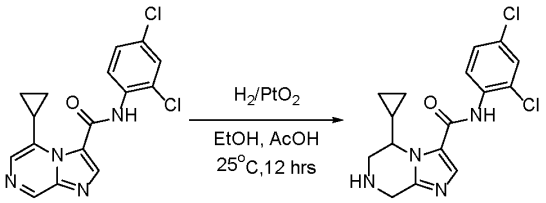
Step 1.1 Synthesis of 5-cyclopropyl-N-(2,4-dichlorophenyl)imidazo[1,2-a]pyrazine-3-carboxamide



[01338] To a solution of 3-bromo-5-cyclopropyl-imidazo[1,2-a]pyrazine (1.5 g, 6.30 mmol, 1 eq) in THF (20 mL) was added n-BuLi (2.5 M, 3.78 mL, 1.5 eq) at -78°C, then 2,4-dichloro-1-isocyanato-benzene (1.78 g, 9.45 mmol, 1.5 eq) in THF (10 mL) was added to the reaction mixture at -78°C. The reaction mixture was stirred at -78°C for 0.5hr. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (20 mL) at -78°C, and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. 2 parallel reactions

were combined to workup. The residue was purified by flash silica gel chromatography (Biotage®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). The eluent was removed under reduced pressure. Compound 5-cyclopropyl-N-(2,4-dichlorophenyl)imidazo[1,2-a]pyrazine-3- carboxamide (0.8 g, 2.30 mmol, 36.57% yield) was obtained as a white solid. LCMS: m/z 347.0 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 9.13 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.25-8.24 (m, 2H), 7.95 (d, J = 1.2 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 2.67-2.60 (m, 1H), 1.04-0.99 (m, 2H), 0.79-0.72 (m, 2H).

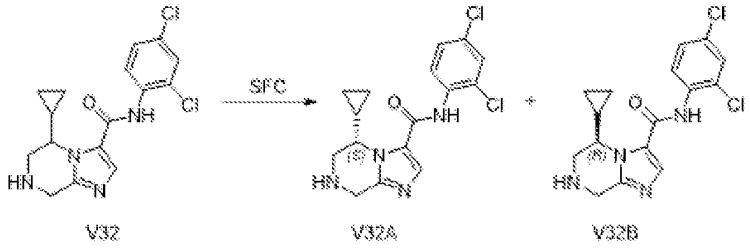
Step 1.2 Synthesis of 5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V32)



3 V32

[01339] To a solution of PtO_2 (0.16 g, 704.61 μmol) in EtOH (32 mL) were added 5-cyclopropyl-N-(2,4-dichlorophenyl)imidazo[1,2-a]pyrazine-3-carboxamide (1.6 g, 4.61 mmol, 1 eq) and AcOH (138.37 mg, 2.30 mmol, 131.91 μL, 0.5 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 12 hrs under H_2 (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give a residue. The crude product was used to the next step. Compound 5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V32) (1.6 g, 4.56 mmol, 98.85% yield) was obtained as a yellow solid. LCMS: m/z 351.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) 9.98-9.93 (m, 1H), 7.71-7.66 (m, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.47 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 4.20 (dd, J = 9.2 Hz, 1.6 Hz, 1H), 4.04 (d, J = 16.4 Hz, 1H), 3.86 (d, J = 16.8 Hz, 1H), 3.15-3.03 (m, 2H), 1.41-1.32 (m, 1H), 0.70-0.65 (m, 1H), 0.47-0.35 (m, 2H), 0.28-0.22 (m, 1H).

Step 1.3 Preparation of (5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide and (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8- tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

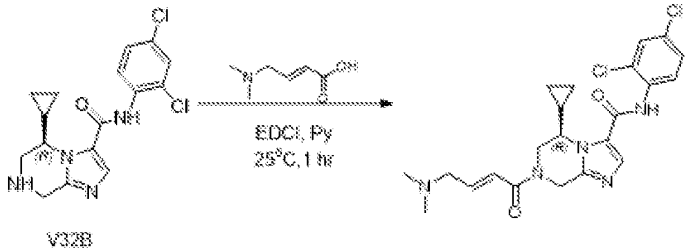


[01340] 5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1.6 g, 4.56 mmol, 1 eq) was separated by SFC (column: Chiral Pak IH, 250 * 30 mm, 10 um; mobile phase: [CO_2- EtOH]; B%: 35%, isocratic elution mode) to give (5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V32A) (600 mg, 1.71 mmol, 37.50% yield) and (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (V32B) (600 mg, 1.71 mmol, 37.50% yield) were obtained as a white solid.

[01341] ^{1}H NMR (400 MHz, DMSO-d_6) 9.92 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.66 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.47 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 4.21-4.18 (m, 1H), 4.04 (d, J = 16.8 Hz, 1H), 3.88 (d, J = 16.8 Hz, 1H), 3.15-3.12 (m, 1H), 3.07-3.03 (m, 1H), 1.38-1.33 (m, 1H), 0.69-0.65 (m, 1H), 0.42-0.35 (m, 2H), 0.28-0.23 (m, 1H).

[01342] ^{1}H NMR (400 MHz, DMSO-d_6) 9.93 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.66 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 4.21-4.19 (m, 1H), 4.03 (d, J = 16.8 Hz, 1H), 3.88 (d, J = 16.4 Hz, 1H), 3.15-3.12 (m, 1H), 3.07-3.03 (m, 1H), 1.40-1.32 (m, 1H), 0.70-0.65 (m, 1H), 0.42-0.37 (m, 2H), 0.28-0.23 (m, 1H).

Step 1.4 Preparation of (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



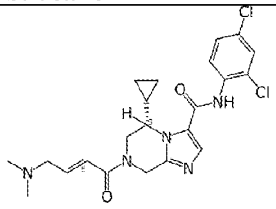
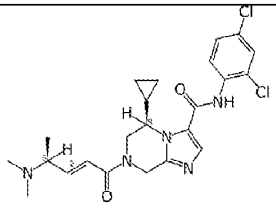
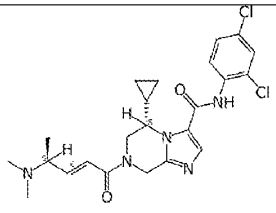
[01343] To a solution of (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (100 mg, 284.71 μmol, 1 eq) and (E)-4-(dimethylamino)but-2-enoic acid (56.58 mg, 341.66 μmol, 1.2 eq, HCl) in Pyridine (1 mL) was added EDCI (109.16 mg, 569.43 μmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 1hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The

residue was purified by prep-HPLC (column: Phenomenex luna C_{18} 100 * 40 mm * 5 um; mobile phase: [H_2O (0.04% HCl)-ACN]; gradient: 1%-45% B over 8.0 min). The residue was dried over lyophilization. Compound (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7- [(E)-4-(dimethylamino)but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (47.4 mg, 101.38 μmol, 35.61% yield, 98.89% purity) was obtained as a white solid. LCMS: m/z 462.2 $[M+H]^+$.

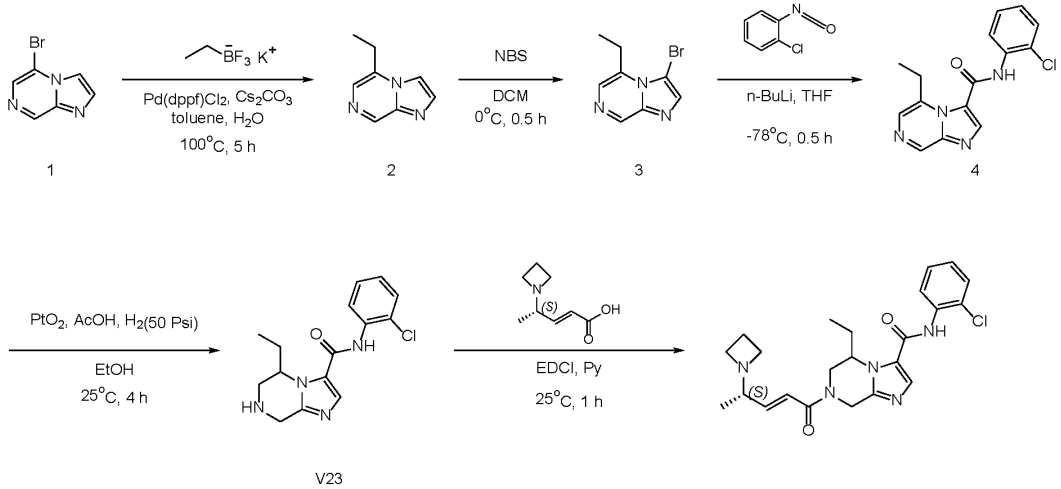
[01344] ^{1}H NMR (400 MHz, DMSO-d_6) 10.49-10.34 (m, 1H), 8.15 (m, 1H), 7.76 (s, 1H), 7.53-7.48 (m, 2H), 7.05-6.99 (m, 1H), 6.81-6.72 (m, 1H), 5.48-5.36 (m, 1H), 4.87-4.68 (m, 2H), 4.52-4.45 (m, 1.5H), 3.84-3.81 (m, 2H), 3.34-3.31 (m, 0.5H), 2.76-2.74 (m, 6H), 1.09-1.03 (m, 1H), 0.61-0.37 (m, 4H).

[01345] Compounds in Table AEA were synthesized following the procedure for (5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino) but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

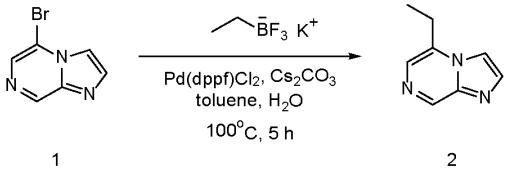
Table AEA

Name	Structure	NMR	LCMS
(5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but -2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.01 (s, 1H), 7.83-7.81 (m, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.54-7.52 (m, 1H), 7.48-7.46 (m, 1H), 6.76-6.68 (m, 2H), 5.30-5.22 (m, 1H), 4.82-4.60 (m, 2H), 4.45-4.31 (m, 1H), 3.72 (d, *J* = 11.6 Hz, 0.6H), 3.25-3.21 (m, 0.4H), 3.07-3.06 (m, 2H), 2.16 (s, 6H), 1.00-0.92 (m, 1H), 0.59-0.55 (m, 1H), 0.43-0.34 (m, 3H).	LCMS: m/z 462.1/464.1 $[M+H]^+$
(5R)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) δ 10.02 (s, 1H), 7.80-7.72 (m, 2H), 7.54-7.46 (m, 2H), 6.72-6.61 (m, 2H), 5.32-5.27 (m, 1H), 4.82-4.60 (m, 2H), 4.48-4.30 (m, 1H), 3.73-3.70 (m, 0.5H), 3.25-3.22 (m, 0.5H), 3.16-3.11 (m, 1H), 2.18-2.12 (m, 6H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.98-0.93 (m, 1H), 0.59 (s, 1H), 0.40-0.32 (m, 3H).	LCMS: m/z 476.1 $[M+H]^+$
(5S)-5-cyclopropyl-N-(2,4-dichlorophenyl)-7-[(E,4S)-4-(dimethylamino) pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.30-11.19 (m, 1H), 8.16-8.06 (m, 1H), 7.86-7.84 (m, 1H), 7.59-7.57 (m, 1H), 7.47-7.39 (m, 2H), 7.21-7.00 (m, 1H), 6.88-6.63 (m, 2H), 5.46-5.38 (m, 1H), 4.94-4.85 (m, 1H), 4.62-4.55 (m, 1H), 4.39 (d, *J* = 14.8 Hz, 0.6H), 3.95-3.89 (m, 3H), 3.47 (d, *J* = 10.8 Hz, 0.4H), 3.14-3.03 (m, 2H), 2.68 (s, 3H), 1.45-1.36 (m, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).	LCMS: m/z 476.1/478.1 $[M+H]^+$

Example 218: Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4- (azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



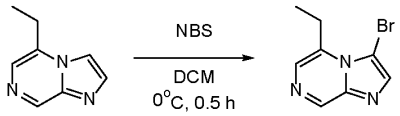
Step 1.1 Synthesis of 5-ethylimidazo[1,2-a]pyrazine



[01346] To the reaction mixture of 5-bromoimidazo[1,2-a]pyrazine (1 g, 5.05 mmol, 1 eq), potassium ethyltrifluoroborate (1.37 g, 10.10 mmol, 2 eq) in H_2O (2 mL) and toluene (10 mL) were added $Pd(dppf)Cl_2$ (369.51 mg, 505.00 µmol, 0.1 eq) and Cs_2CO_3 (3.29 g, 10.10 mmol, 2 eq) at 25°C. The reaction mixture was degassed and purged with N_2 for 3 times. The reaction mixture was heated to 100°C and stirred at 100°C for 5 hours. The reaction mixture was cooled to 25°C. To the reaction mixture was added water (35 mL) and then extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel

chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 80~90% Petroleum ether/ Ethyl acetate gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound 5-ethylimidazo[1,2-a]pyrazine (0.64 g, 4.35 mmol, 86.11% yield) as a yellow solid. LCMS: m/z 148.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.97 (s, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 3.00 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H).

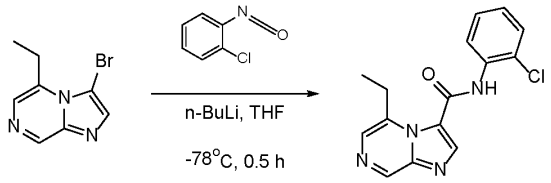
Step 1.2 Synthesis of 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine



2 3

[01347] To a solution of 5-ethylimidazo[1,2-a]pyrazine (0.6 g, 4.08 mmol, 1 eq) in DCM (5 mL) was added NBS (689.30 mg, 3.87 mmol, 0.95 eq) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hour. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (35 mL) and then extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 80~90% Petroleum ether/ Ethyl acetate gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine (0.78 g, 3.45 mmol, 84.63% yield) as a yellow solid. LCMS: m/z 226.0/228.0 $[M+H]^+$.^1H NMR (DMSO-d_6, 400 MHz) δ 8.95 (s, 1H), 7.90 (s, 1H), 7.75 (s, 1H), 3.37 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).

Step 1.3 Synthesis of N-(2-chlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide

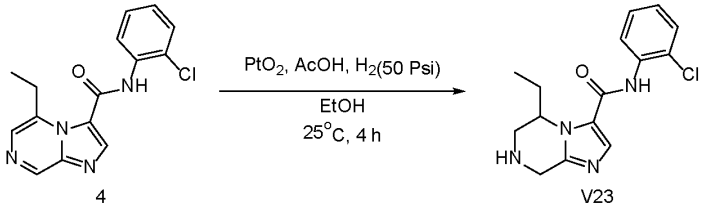


3 4

[01348] To a solution of 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine (0.63 g, 2.79 mmol, 1 eq) in THF (12 mL) was added n-BuLi (2.5 M, 1.67 mL, 1.5 eq) at -78°C, the mixture was stirred at -78°C for 15 mins, then 1-chloro-2-isocyanato-benzene (641.91 mg, 4.18 mmol, 504.25 µL, 1.5 eq) was added to the mixture at -78°C. The mixture was stirred at -78°C for 0.5 hour. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL) at -78°C. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (40 mL) and then extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15

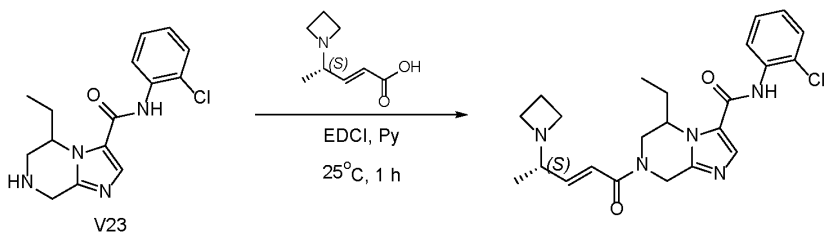
mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 12 g SepaFlash® Silica Flash Column, Eluent of 30~45% Petroleum ether/ Ethyl acetate gradient @ 40 mL/min). The eluent was removed under reduced pressure to give compound N-(2-chlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide (0.5 g, 1.66 mmol, 59.66% yield) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.65 (s, 1H), 9.14 (s, 1H), 8.34 (s, 1H), 7.97 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.37 (td, J = 8.0 Hz, 1H), 3.21 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).

Step 1.4 Synthesis of N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide



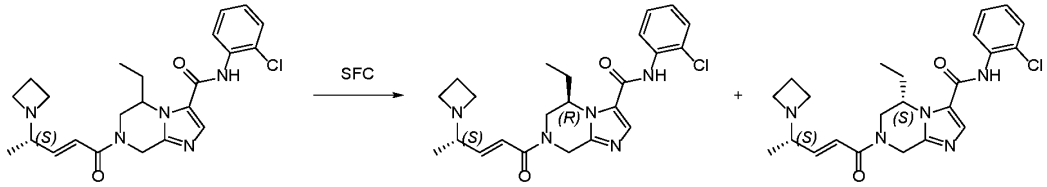
[01349] To a solution of PtO_2 (50 mg, 220.19 μmol) in EtOH (10 mL) were added N-(2-chlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide (0.5 g, 1.66 mmol, 1 eq) and AcOH (49.92 mg, 831.28 μmol, 47.59 μL, 0.5 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 4 hours under H_2 (50 Psi). LCMS showed the reaction was complete. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give compound N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.51 g, crude) as a brown solid. LCMS: m/z 305.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.74 (s, 1H), 7.79 (s, 1H), 7.53 (t, J = 6.4 Hz, 2H), 7.37 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.28 (td, J = 8.0 Hz, 1.6 Hz, 1H), 4.51-4.48 (m, 1H), 3.94 (d, J = 16.8 Hz, 1H), 3.82 (d, J = 16.8 Hz, 1H), 3.46-3.42 (m, 2H), 3.09 (d, J = 13.2 Hz, 1H), 2.95-2.91 (m, 1H), 0.87 (t, J = 7.6 Hz, 3H).

Step 1.5 Synthesis of 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01350] To a solution of N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine- 3-carboxamide (0.2 g, 656.22 μmol, 1 eq) in Pyridine (1.5 mL) was added (E,4S)-4-(azetidin-1-yl)pent-2-enoic acid (101.84 mg, 656.22 μmol, 1 eq) at 25°C. And then EDCI (251.60 mg, 1.31 mmol, 2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: WePure Biotech XP tC$_{18}$ 150 * 40 * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 17%-52% B over 8.0 min). The residue was dried over lyophilization to give compound 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (100.5 mg, 226.76 μmol, 34.56% yield, 99.72% purity) as an off-white solid. 5.5 mg for delivery, 95 mg for SFC separation. LCMS: m/z 442.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.53 (t, J = 8.8 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 6.65-6.61 (m, 1H), 6.60-6.51 (m, 1H), 5.26-5.15 (m, 1H), 4.84-4.70 (m, 2H), 4.37-4.26 (m, 1H), 3.66-3.63 (m, 0.5H), 3.17-3.14 (m, 0.5H), 3.10-3.07 (m, 4H), 2.95-2.91 (m, 1H), 1.93-1.89 (m, 2H), 1.70-1.69 (m, 1H), 1.52-1.36 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

Step 1.6 Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4- (azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

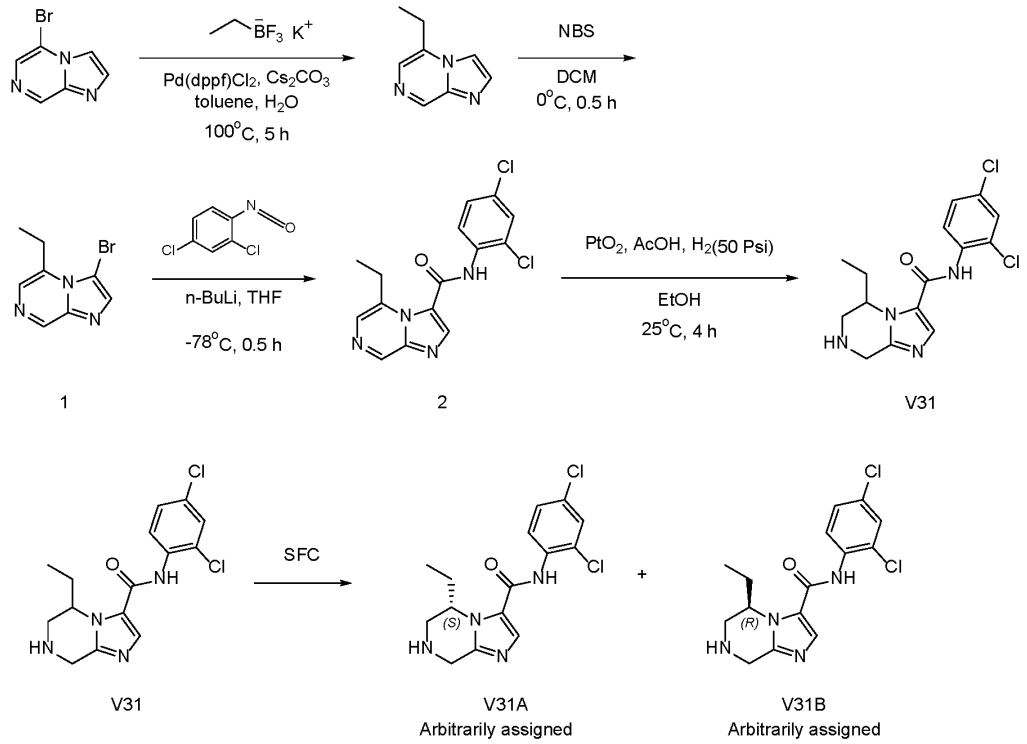


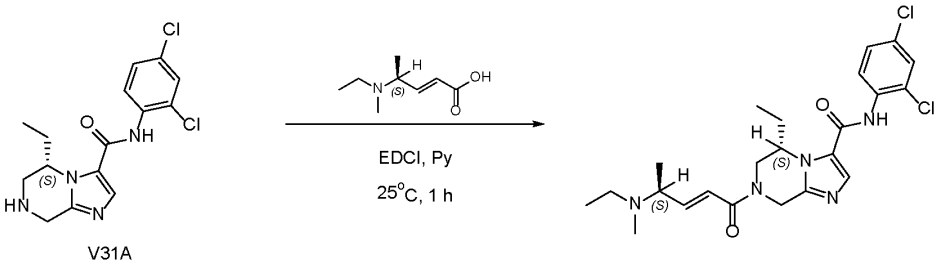
[01351] 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (95 mg, 214.96 μmol, 1 eq) was further separated by SFC (condition: column: Daicel ChiralPak IM (250*25 mm i.d. 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode). The residue was dried over lyophilization to give compound (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N- (2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (33 mg, 74.48 μmol, 34.65% yield, 99.75% purity) as a white solid and compound (5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (32.8 mg, 74.14 μmol, 34.49% yield, 99.90% purity) as a white solid.

[01352] LCMS: m/z 442.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88-9.87 (m, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.60-6.51 (m, 2H), 5.19 (t, J = 18.0 Hz, 1H), 4.83-4.66 (m, 2H), 4.41-4.26 (m, 1H), 3.66-3.62 (m, 0.5H), 3.17-3.14 (m, 0.5H), 3.08 (t, J = 7.2 Hz, 4H), 2.95-2.92 (m, 1H), 1.94-1.89 (m, 2H), 1.75-1.69 (m, 1H), 1.52-1.36 (m, 1H), 0.96 (t, J = 5.6 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H).

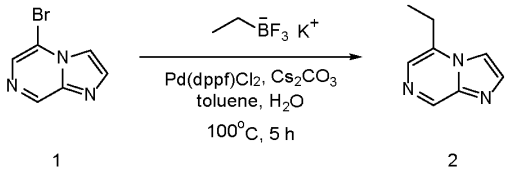
[01353] LCMS: m/z 442.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.88 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.68-6.63 (m, 1H), 6.51-6.49 (m, 1H), 5.21 (t, J = 18 Hz, 1H), 4.83-4.78 (m, 2H), 4.41-4.30 (m, 1H), 3.67-3.66 (m, 0.5H), 3.17-3.16 (m, 0.5H), 3.15-3.08 (m, 4H), 2.96-2.94 (m, 1H), 1.92-1.91 (m, 2H), 1.71-1.68 (m, 1H), 1.52-1.45 (m, 1H), 0.96 (d, J = 5.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

Example 219: Synthesis of (5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.





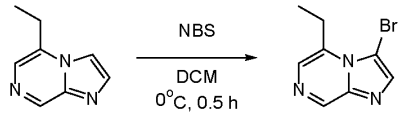
Step 1.1.1 Synthesis of 5-ethylimidazo[1,2-a]pyrazine



[01354] To the reaction mixture of 5-bromoimidazo[1,2-a]pyrazine (1 g, 5.05 mmol, 1 eq), potassium ethyltrifluoroborate (1.37 g, 10.10 mmol, 2 eq) in H_2O (2 mL) and toluene (10 mL) were added $Pd(dppf)Cl_2$ (369.51 mg, 505.00 µmol, 0.1 eq) and Cs_2CO_3 (3.29 g, 10.10 mmol, 2 eq) at 25°C. The reaction mixture was degassed and purged with N_2 for 3 times. The reaction mixture was heated to 100°C and stirred at 100°C for 5 hours. The reaction mixture was cooled

to 25°C. To the reaction mixture was added water (35 mL) and then extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 80~90% Petroleum ether/ Ethyl acetate gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound 5-ethylimidazo[1,2-a]pyrazine (0.64 g, 4.35 mmol, 86.11% yield) as a yellow solid. LCMS: m/z 226.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.97 (s, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 3.00 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H).

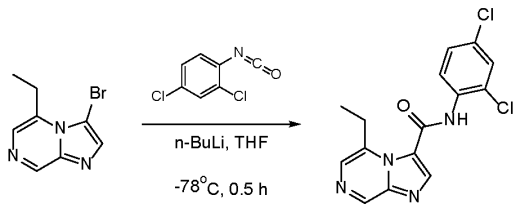
Step 1.1.2 Synthesis of 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine



2 3

[01355] To a solution of 5-ethylimidazo[1,2-a]pyrazine (0.6 g, 4.08 mmol, 1 eq) in DCM (5 mL) was added NBS (689.30 mg, 3.87 mmol, 0.95 eq) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hour. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (35 mL) and then extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 80~90% Petroleum ether/ Ethyl acetate gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine (0.78 g, 3.45 mmol, 84.63% yield) as a yellow solid. LCMS: m/z 324.9 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.95 (s, 1H), 7.90 (s, 1H), 7.75 (s, 1H), 3.37 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).

Step 1.2.1 Synthesis of N-(2,4-dichlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide

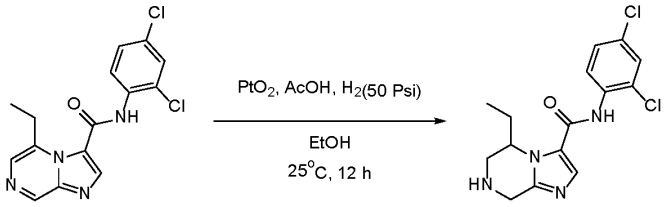


1 2

[01356] To a solution of 3-bromo-5-ethyl-imidazo[1,2-a]pyrazine (2 g, 8.85 mmol, 1 eq) in THF (35 mL) was added n-BuLi (2.5 M, 5.31 mL, 1.5 eq) dropwise at -78°C under N_2. Then a solution of 2,4-dichloro-1-isocyanato-benzene (2.49 g, 13.27 mmol, 1.5 eq) in THF (5 mL) was

added to the mixture at -78°C. The mixture was stirred at -78°C for 0.5 h under N_2. The reaction mixture was quenched by addition of sat.aq. NH_4Cl (10 mL) at -78 °C. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (50 mL) and then extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 40~70% Petroleum ether/ Ethyl acetate gradient @ 60 mL/min). The eluent was removed under reduced pressure to give compound N-(2,4-dichlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide (1.1 g, 3.28 mmol, 37.10% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.70 (s, 1H), 9.14 (s, 1H), 8.35 (s, 1H), 7.99 (s, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.54-7.51 (m, 1H), 3.20 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H).

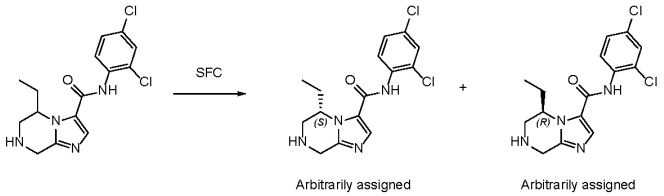
Step 1.2.2 Synthesis of N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide



2 V31

[01357] To a solution of PtO_2 (0.15 g, 660.56 μmol, 1.48e-1 eq) in EtOH (30 mL) were added N-(2,4-dichlorophenyl)-5-ethyl-imidazo[1,2-a]pyrazine-3-carboxamide (1.5 g, 4.48 mmol, 1 eq) and AcOH (134.37 mg, 2.24 mmol, 128.09 μL, 0.5 eq) under Ar_2 at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The reaction mixture was stirred at 25°C for 12 hrs under H_2 (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give compound N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (1.6 g, crude) as a brown oil. LCMS: m/z 338.9 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.79 (s, 1H), 7.80 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.57-7.54 (m, 1H), 7.46 (dd, J = 8.4Hz, 2.4 Hz, 1H), 4.49-4.47 (m, 1H), 3.98 (d, J = 16.4 Hz, 1H), 3.86 (d, J = 16.8 Hz, 1H), 3.45-3.42 (m, 2H), 3.12 (d, J = 13.2 Hz, 1H), 2.95-2.92 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H).

Step 1.2.3 Synthesis of (5S)-N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide and (5R)-N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

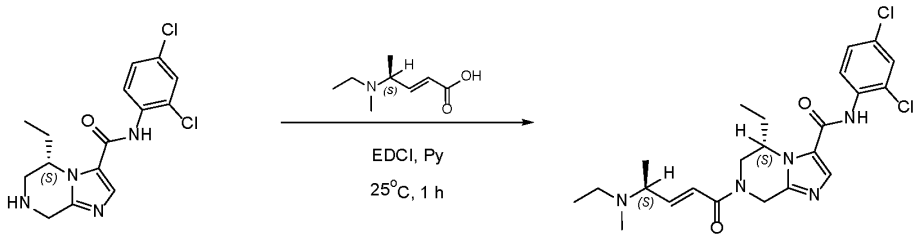


[01358] N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (1.8 g, 5.31 mmol, 1 eq) was further separated by SFC (column: DAICEL CHIRALCEL OD(250 mm * 30 mm, 10 um); mobile phase: [CO_2- MeOH(0.1% $NH_3 \cdot H_2O$)]; B%: 29%, isocratic elution mode). Compound (5S)-N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.65 g, 1.36 mmol, 25.64% yield, 70.99% purity) was obtained as yellow oil and compound (5R)-N-(2,4-dichlorophenyl)-5- ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.59 g, 1.51 mmol, 28.42% yield, 86.69% purity) was obtained as a yellow solid.

[01359] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.80 (s, 1H), 7.80 (s, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 4.50-4.48 (m, 1H), 4.00 (d, J = 16.8 Hz, 1H), 3.88 (d, J = 16.8 Hz, 1H), 3.45-3.42 (m, 2H), 3.14 (d, J = 13.6 Hz, 1H), 2.96 (dd, J = 13.6 Hz, 3.6 Hz, 1H), 0.87 (t, J = 7.6 Hz, 3H).

[01360] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.80 (s, 1H), 7.81 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 4.50-4.47 (m, 1H), 3.98 (d, J = 16.4 Hz, 1H), 3.86 (d, J = 8.8 Hz, 1H), 3.45-3.42 (m, 2H), 3.12 (d, J = 13.2 Hz, 1H), 2.94 (d, J = 13.2 Hz, 1H), 0.87 (t, J = 5.2 Hz, 3H).

Step 1.3 Synthesis of (5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



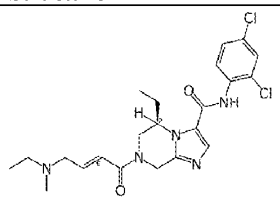
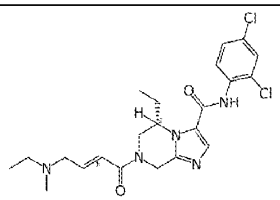
V31A

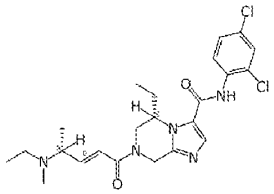
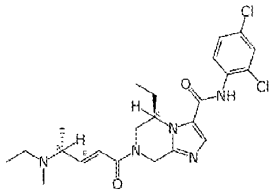
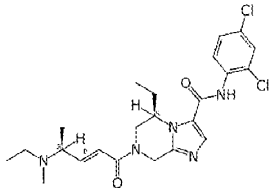
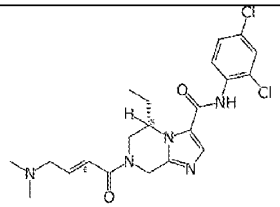
[01361] To a solution of (5S)-N-(2,4-dichlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (0.15 g, 442.19 µmol, 1 eq) in Pyridine (1 mL) was added (E,4S)-4-[ethyl(methyl)amino]pent-2-enoic acid (83.42 mg, 530.63 µmol, 1.2 eq) at 25°C. And then EDCI (169.54 mg, 884.38 µmol, 2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced

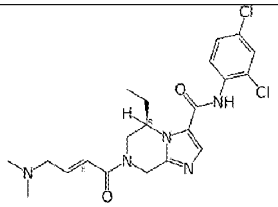
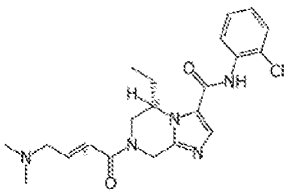
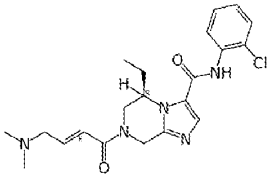
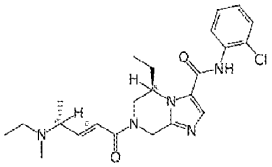
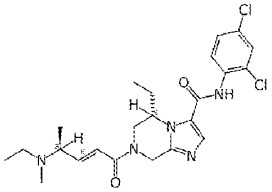
pressure. The crude product was purified by prep-HPLC (column: Waters X bridge BEH C_{18} 100 * 30 mm * 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 50%- 85% B over 8.0 min). The residue was dried over lyophilization. The crude product was further purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 25%-50% B over 8.0 min). The residue was dried over lyophilization to give compound (5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl (methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (24.3 mg, 50.12 μmol, 11.33% yield, 98.68% purity) as a white solid. LCMS: m/z 478.1/480.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.63 (d, J = 14.8 Hz, 1H), 5.27-5.20 (m, 1H), 4.82-4.70 (m, 2H), 4.44-4.26 (m, 1H), 3.67-3.64 (m, 0.5H), 3.17-3.14 (m, 0.5H), 2.45-2.37 (m, 2H), 2.13 (s, 3H), 1.73-1.67 (m, 1H), 1.51-1.40 (m, 1H), 1.28-1.21 (m, 1H), 1.11 (t, J = 5.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

[01362] Compounds in table were synthesized following the procedure for (5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table AF

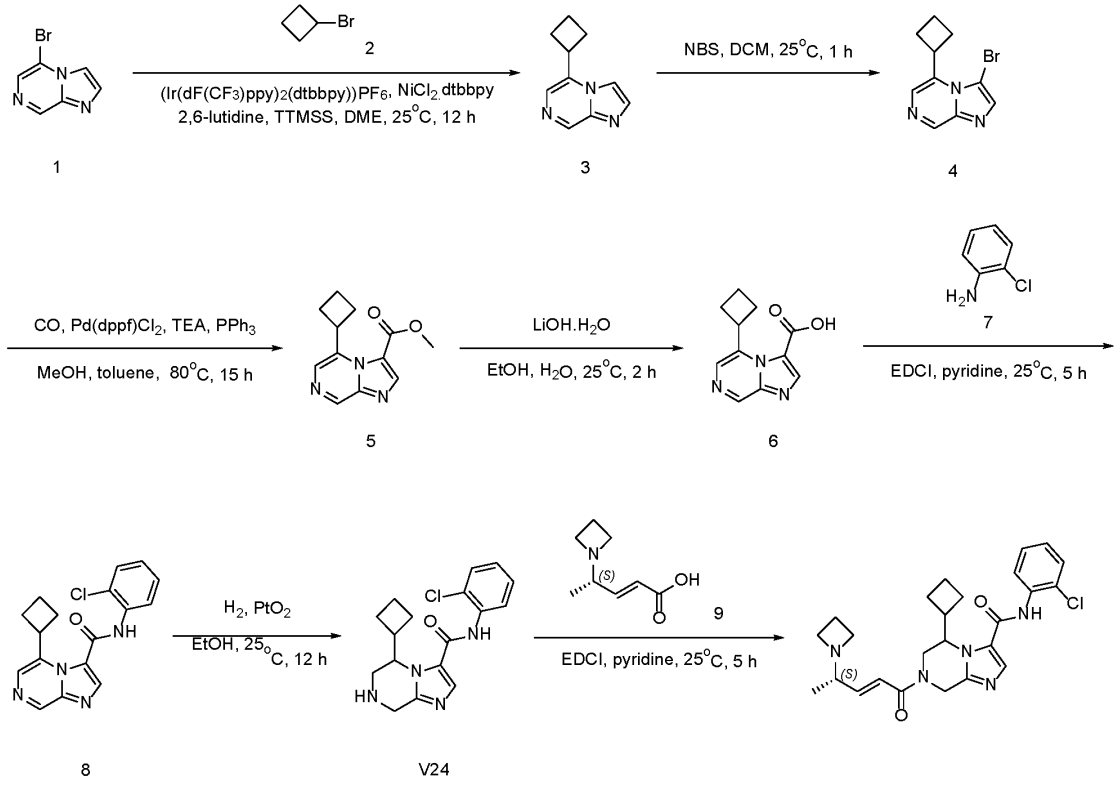
Name	Structure	NMR	LCMS
(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino] but-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.77-6.67 (m, 2H), 5.26-5.17 (m, 1H), 4.82-4.66 (m, 2H), 4.41-4.27 (m, 1H), 3.67-3.64 (m, 0.5H), 3.17-3.14 (m, 0.5H), 3.02-3.00 (m, 2H), 2.39-2.34 (m, 2H), 2.14 (s, 3H), 1.72-1.68 (m, 1H), 1.51-1.40 (m, 1H), 0.99 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).	LCMS: m/z 464.1/466.1 [M+H]+
(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E)-4-[ethyl(methyl)amino]but-2- enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^1H NMR (DMSO-d6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.56-7.54 (m, 1H), 7.48-7.45 (m, 1H), 6.78-6.69 (m, 2H), 5.22 (t, J = 18.8 Hz, 1H), 4.83-4.67 (m, 2H), 4.41-4.27 (m, 1H), 3.66-3.63 (m, 0.5H), 3.18 (s, 0.5H), 3.14-3.10 (m, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.75-1.66 (m, 1H), 1.51-1.42 (m, 1H), 0.99 (t, J =	LCMS: m/z 464.1/466.1 [M+H]+

Name	Structure	NMR	LCMS
		7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).	
(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.93 (s, 1H), 7.91 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.57-7.55 (m, 1H), 7.49-7.46 (m, 1H), 6.78-6.61 (m, 2H), 5.29-5.21 (m, 1H), 4.83-4.67 (m, 2H), 4.46-4.27 (m, 1H), 3.68 (d, J = 13.6 Hz, 0.5H), 3.38-3.36 (m, 1H), 3.16 (d, J = 12.0 Hz, 0.5H), 2.43-2.34 (m, 2H), 2.14 (s, 3H), 1.76-1.68 (m, 1H), 1.52-1.38 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 0.91 (t, J = 7.2 Hz, 3H).	LCMS: m/z 478.1 [M+H]+
(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-((R,E)-4-(ethyl(methyl)amino)pent-2-enoyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.91 (s, 1H), 7.90 (s, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.63-6.60 (m, 1H), 5.27-5.20 (m, 1H), 4.82-4.66 (m, 2H), 4.44-4.27 (m, 1H), 3.65 (d, J = 13.2 Hz, 0.5H), 3.38-3.34 (m, 1H), 3.20-3.13 (m, 0.5H), 2.45-2.32 (m, 2H), 2.13 (s, 3H), 1.75-1.67 (m, 1H), 1.48-1.38 (m, 1H), 1.08-1.13 (m, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.90 (d, J = 7.2 Hz, 3H).	LCMS: m/z 478.1/480.1 [M+H]+
(5R)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d6) 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.77-6.71 (m, 1H), 6.63-6.60 (m, 1H), 5.27-5.19 (m, 1H), 4.82-4.66 (m, 2H), 4.47-4.26 (m, 1H), 3.65-3.61 (m, 0.5H), 3.17-3.14 (m, 0.5H), 2.44-2.42 (m, 1H), 2.40-2.32 (m, 2H), 2.13 (s, 3H), 1.75-1.64 (m, 1H), 1.49-1.40 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 0.97 (s, 3H), 0.90 (t, J = 7.6 Hz, 3H).	LCMS: m/z 478.1 [M+H]+
(5S)-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5 -ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d6, 400 MHz) δ 9.92 (s, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 6.71-6.70 (m, 2H), 5.26-5.17 (m, 1H), 4.82-4.66 (m, 2H), 4.34 (dd, J = 39.2 Hz, 14.8 Hz, 1H), 3.65 (d, J = 12.8 Hz, 0.5H), 3.15 (d, J = 11.6 Hz, 0.5H), 3.10-3.02 (m, 2H), 2.15 (s, 6H), 1.69 (s, 1H), 1.45-1.40 (m, 1H), 0.89 (s, 3H).	LCMS: m/z 450.1/452.1 [M+H]+

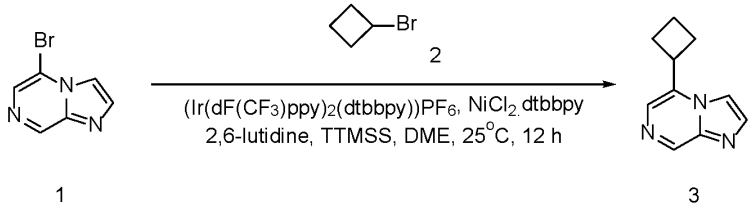
Name	Structure	NMR	LCMS
(5R)-N-(2,4-dichlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl] -5-ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (400 MHz, DMSO-d6) 9.91 (s, 1H), 7.89 (s, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.47 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.72-6.71 (m, 2H), 5.26-5.17 (m, 1H), 4.82-4.66 (m, 2H), 4.41-4.27 (m, 1H), 3.65 (d, J = 12.4 Hz, 0.4H), 3.18-3.02 (m, 2.6H), 2.15 (s, 6H), 1.72-1.67 (m, 1H), 1.51-1.39 (m, 1H), 0.90 (t, J = 6.8 Hz, 3H).	LCMS: m/z 450.1 [M+H]+
(5S)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.87 (s, 1H), 7.89 (s, 1H), 7.55-7.50 (m, 2H), 7.38 (t, J = 6.8 Hz, 1H), 7.29 (t, J = 6.8 Hz, 1H), 6.71-6.68 (m, 2H), 5.26-5.17 (m, 1H), 4.84-4.66 (m, 2H), 4.42-4.27 (m, 1H), 3.68-3.63 (m, 0.5H), 3.18-3.15 (m, 0.5H), 3.10-3.06 (m, 2H), 2.15 (s, 6H), 1.70-1.68 (m, 1H), 1.48-1.43 (m, 1H), 0.90 (t, J = 6.0 Hz, 3H).	LCMS: m/z 416.2 [M+H]$^+$
(5R)-N-(2-chlorophenyl)-7-[(E)-4-(dimethylamino)but-2-enoyl]-5- ethyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6,400 MHz) δ 10.47-10.32 (m, 1H), 8.35-8.26 (m, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.09-6.96 (m, 1H), 6.84-6.71 (m, 1H), 5.46-5.36 (m, 1H), 5.02-4.93 (m, 1H), 4.88-4.77 (m, 1H), 4.54-4.43 (m, 1H), 3.92 (s, 2H), 3.77 (d, J = 12.4 Hz, 0.5H), 3.28 (d, J = 13.2 Hz, 0.5H), 2.75 (d, J = 4.8 Hz, 6H), 1.77-1.74 (m, 1H), 1.64-1.45 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H).	LCMS: m/z 416.1 [M+H]$^+$
(5R)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H) 6.78-6.72 (m, 1H), 6.64-6.59 (m, 1H), 5.27-5.20 (m, 1H), 4.83-4.66 (m, 2H), 4.35 (dd, J = 50.4 Hz, 14.4 Hz, 1H), 3.65 (d, J = 16.8 Hz, 0.5H), 3.38-3.31 (m, 1H), 3.15(d, J = 11.6 Hz, 0.5H), 2.45-2.34 (m, 2H), 2.13 (s, 3H), 1.75-1.66 (m, 1H), 1.48-1.42 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).	LCMS: m/z 444.2 [M+H]$^+$
(5S)-N-(2,4-dichlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.90 (s, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4 Hz, 2.4 Hz, 1H), 6.76-6.71 (m, 1H), 6.63 (d, J = 14.8 Hz, 1H), 5.27-5.20 (m, 1H), 4.82-4.70 (m, 2H),	LCMS: m/z 478.1/480.1 [M+H]$^+$

Name	Structure	NMR	LCMS
		4.44-4.26 (m, 1H), 3.67-3.64 (m, 0.5H), 3.17-3.14 (m, 0.5H), 2.45-2.37 (m, 2H), 2.13 (s, 3H), 1.73-1.67 (m, 1H), 1.51-1.40 (m, 1H), 1.28-1.21 (m, 1H), 1.11 (t, J = 5.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H)	

Example 220: Synthesis of 7-((S,E)-4-(azetidin-1-yl)pent-2-enoyl)-N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide , (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

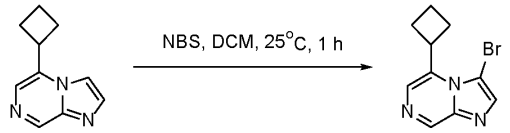


Step 1.1 Synthesis of 5-cyclobutylimidazo[1,2-a]pyrazine



[01363] To a solution of 5-bromoimidazo[1,2-a]pyrazine (400 mg, 2.02 mmol, 1 eq) and bromocyclobutane (1.36 g, 10.10 mmol, 950.85 μL, 5 eq) in DME (20 mL) were added TTMSS (502.29 mg, 2.02 mmol, 623.19 μL, 1 eq), bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridyl]phenyl]iridium(1+);4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine hexafluorophosphate (22.66 mg, 20.20 μmol, 0.01 eq), 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine;dichloronickel (4.02 mg, 10.10 μmol, 0.005 eq) and 2,6-lutidine (432.90 mg, 4.04 mmol, 470.54 μL, 2 eq) in one portion at 25°C under N_2. The mixture was stirred at 25°C for 12 h under 34 W blue LED. 16 batches reaction were work up together. The reaction mixture was quenched by addition of H_2O (40 mL) at 20°C, and extracted with ethyl acetate (40 mL x 3). The combined organic layers were washed with brine (40 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 20 g Sepa Flash® Silica Flash Column, Eluent of 0~90% Ethyl acetate/Petroleum ether gradient @ 75 mL/min) to give 5-cyclobutylimidazo[1,2-a]pyrazine (640 mg, crude) as a yellow solid. LCMS: m/z 174.0 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.03 (s, 1H), 7.84 (d, J = 0.4 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.52 (s, 1H), 3.86-3.77 (m, 1H), 2.63-2.57 (m, 2H), 2.40-2.33 (m, 2H), 2.29-2.20 (m, 1H), 2.07-2.01 (m, 1H).

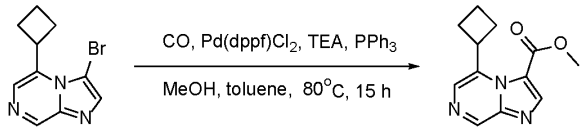
Step 1.2 Synthesis of 3-bromo-5-cyclobutyl-imidazo[1,2-a]pyrazine



3 4

[01364] To a solution of 5-cyclobutylimidazo[1,2-a]pyrazine (640 mg, 3.69 mmol, 1 eq) in DCM (20 mL) was added NBS (670.78 mg, 3.77 mmol, 1.02 eq) in one portion at 25°C. The mixture was stirred at 25°C for 1 h. The reaction mixture was quenched by addition of water (30 mL) at 25°C, and then extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 18 mL/min) to give 3-bromo-5-cyclobutyl-imidazo[1,2-a]pyrazine (800 mg, 3.17 mmol, 85.88% yield) as a yellow solid. LCMS: m/z 252.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 8.95 (s, 1H), 7.94 (s, 1H), 7.87 (s, 1H), 4.58-4.50 (m, 1H), 2.48-2.43 (m, 2H), 2.40-2.33 (m, 2H), 2.07-2.00 (m, 1H), 1.95-1.90 (m, 1H).

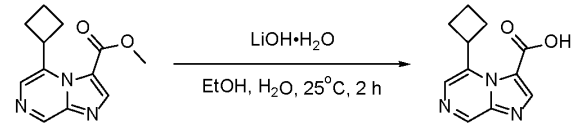
Step 1.3 Synthesis of methyl 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylate



4 5

[01365] A mixture of 3-bromo-5-cyclobutyl-imidazo[1,2-a]pyrazine (940 mg, 3.73 mmol, 1 eq), TEA (830.03 mg, 8.20 mmol, 1.14 mL, 2.2 eq), PPh_3 (293.38 mg, 1.12 mmol, 0.3 eq) and $Pd(dppf)Cl_2$ (818.45 mg, 1.12 mmol, 0.3 eq) in MeOH (30 mL) and toluene (30 mL) was degassed and purged with CO for 3 times at 25°C, and then the mixture was heated to 80°C and stirred at 80°C for 15 h under CO atmosphere. The reaction mixture was cooled to 20°C and concentrated under reduced pressure to give a residue. To the residue was added water (20 mL), and then the filtrate extracted with EtOAc (20 mL x 3), the combined organic phase was washed with brine (20 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 75 mL/min) to give methyl 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylate (700 mg, 3.03 mmol, 81.19% yield) as a yellow solid. LCMS: m/z 232.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.15 (s, 1H), 8.39 (s, 1H), 8.06 (d, J = 1.2 Hz, 1H), 4.44-4.37 (m, 1H), 3.92 (s, 3H), 2.32-2.26 (m, 2H), 2.17-2.10 (m, 2H), 2.07-2.00 (m, 1H), 1.82-1.76 (m, 1H).

Step 1.4 Synthesis of 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylic acid

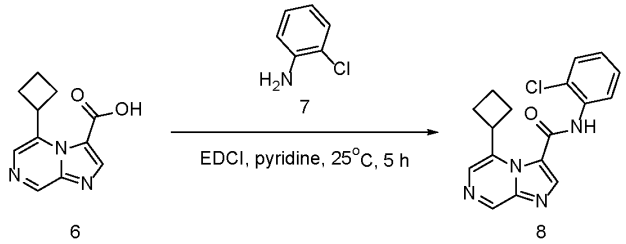


5 6

[01366] A solution of methyl 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylate (700 mg, 3.03 mmol, 1 eq) in EtOH (7 mL) and H_2O (3 mL) was added $LiOH•H_2O$ (317.56 mg, 7.57 mmol, 2.5 eq) in one portion. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was poured into water (15 mL) and cooled to 0°C, then adjusted pH to 4-5 with HCl (2 M) at 0°C. The aqueous phase was extracted with ethyl acetate (30 mL x 5). The combined organic phase was concentrated in vacuum to give 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylic acid (650 mg, 2.99 mmol, 98.85% yield) as a yellow solid. LCMS: m/z 218.1 $[M+H]^+$. ^1H NMR (DMSO-

d_6, 400 MHz) δ 9.12 (s, 1H), 8.34 (s, 1H), 8.01 (d, J = 1.2 Hz, 1H), 4.55-4.47 (m, 1H), 2.38-2.30 (m, 2H), 2.18-2.09 (m, 2H), 2.06-1.98 (m, 1H), 1.82-1.75 (m, 1H).

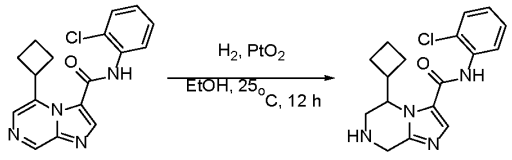
Step 1.5 Synthesis of N-(2-chlorophenyl)-5-cyclobutyl-imidazo[1,2-a]pyrazine-3-carboxamide



6 8

[01367] To a solution of 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylic acid (600 mg, 2.76 mmol, 1 eq) and 2-chloroaniline (422.84 mg, 3.31 mmol, 349.46 µL, 1.2 eq) in Pyridine (6 mL) was added EDCI (1.06 g, 5.52 mmol, 2 eq) in one portion at 25°C. The reaction mixture was stirred at 25°C for 5 h. LCMS showed 5-cyclobutylimidazo[1,2-a]pyrazine-3-carboxylic acid was consumed completely and desired mass was detected. The reaction mixture was quenched with water (12 mL) and stirred for 2 min. The aqueous phase was extracted with EtOAc (12 mL x 3). The combined organic phase was washed with brine (12 mL x 1), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (Biotage®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~45% Ethyl acetate/Petroleum ether gradient @ 45 mL/min) to give N-(2-chlorophenyl)-5-cyclobutyl-imidazo[1,2-a]pyrazine-3-carboxamide (1 g, crude) as a yellow solid. LCMS: m/z 327.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.62 (s, 1H), 9.14 (s, 1H), 8.32 (s, 1H), 8.00 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.59 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 7.44 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.33 (td, J = 8.0 Hz, 1.6 Hz, 1H), 4.37-4.28 (m, 1H), 2.38-2.32 (m, 2H), 2.25-2.13 (m, 2H), 2.07-1.99 (m, 1H), 1.84-1.77 (m, 1H).

Step 1.6 Synthesis of N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a] pyrazine-3-carboxamide (V24)

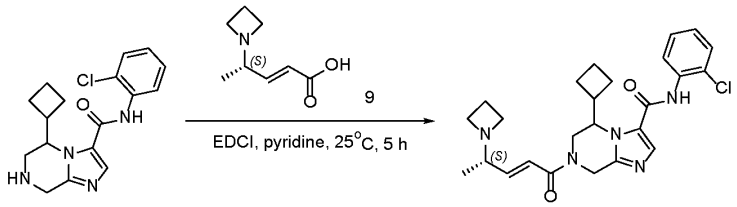


8 V24

[01368] A solution of N-(2-chlorophenyl)-5-cyclobutyl-imidazo[1,2-a]pyrazine-3-carboxamide (900 mg, 2.75 mmol, 1 eq) in EtOH (10 mL) was added into PtO_2 (90.00 mg, 396.34 µmol, 1.44e-1 eq) under Ar at 25°C. The reaction mixture was purged with H_2 for 3

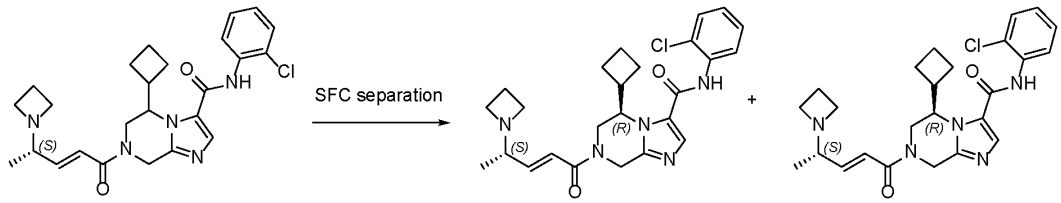
times at 25°C. The reaction mixture was stirred at 25°C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide (V24) (550 mg, 1.66 mmol, 60.37% yield) as yellow oil. LCMS: m/z 331.0 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.66 (s, 1H), 7.55-7.50 (m, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.30-7.28 (m, 1H), 4.05-4.02 (m, 1H), 3.93-3.89 (m, 1H), 3.04-3.01 (m, 2H), 2.76-2.74 (m, 1H), 2.05-1.97 (m, 1H), 1.91-1.87 (m, 1H), 1.78-1.63 (m, 6H).

Step 1.7 Synthesis of 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl -6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



[01369] To a solution of N-(2-chlorophenyl)-5-cyclobutyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine -3-carboxamide (200 mg, 604.57 µmol, 1 eq) and (E,4S)-4-(azetidin-1-yl)pent-2-enoic acid (103.21 mg, 665.03 µmol, 1.1 eq) in Pyridine (3 mL) was added EDCI (231.79 mg, 1.21 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was quenched with water (0.2 mL) and concentrated in vacuum. The residue was purified by prep-HPLC (column: We Pure Biotech X Pt C_{18} 150 * 40 * 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 30%-50% B over 8.0 min) to give 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (85.1 mg, 166.89 µmol, 27.60% yield, 97.63% purity). LCMS: m/z 468.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.80 (s, 1H), 7.56-7.49 (m, 2H), 7.40-7.35 (m, 1H), 7.31-7.27 (m, 1H), 6.63-6.46 (m, 2H), 5.20-5.11 (m, 2H), 4.69-4.64 (m, 1H), 4.32-4.28 (m, 1H), 3.62-3.59 (m, 1H), 3.10-3.07 (m, 4H), 2.96-2.90 (m, 1H), 2.47-2.44 (m, 1H), 1.91 (d, J = 6.8 Hz, 2H), 1.88-1.60 (m, 6H), 0.96-0.95 (m, 3H).

Step 1.7.1 Synthesis of (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide and (5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide



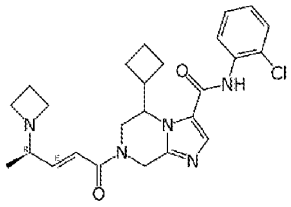
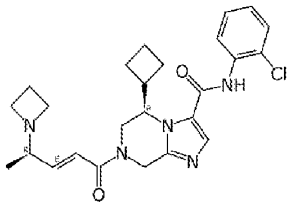
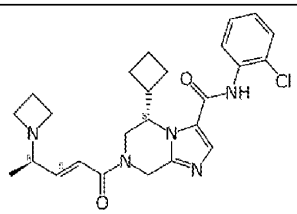
[01370] 7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (80 mg, 170.94 μmol, 1 eq) was separated by SFC (column: Daicel ChiralPak IM (250 * 25mm i.d. 10um); mobile phase: [CO_2-EtOH (0.1%NH_3H_2O)]; B%: 50%, isocratic elution mode) to give (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (35.1 mg, 72.47 μmol, 42.39% yield, 96.62% purity) as an off-white solid and (5S)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (32.0 mg, 68.24 μmol, 39.92% yield, 99.80% purity).

[01371] LCMS: m/z 468.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.80 (s, 1H), 7.55 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.61-6.46 (m, 2H), 5.16-5.11 (m, 2H), 4.68 (t, J = 15.2 Hz, 1H), 4.30 (d, J = 18.0 Hz, 1H), 3.60 (d, J = 12.0 Hz, 1H), 3.08 (t, J = 6.8 Hz, 4H), 2.95-2.90 (m, 1H), 2.46-2.40 (m, 1H), 1.95-1.88 (m, 2H), 1.84-1.61 (m, 6H), 0.96 (t, J = 6.4 Hz, 3H).

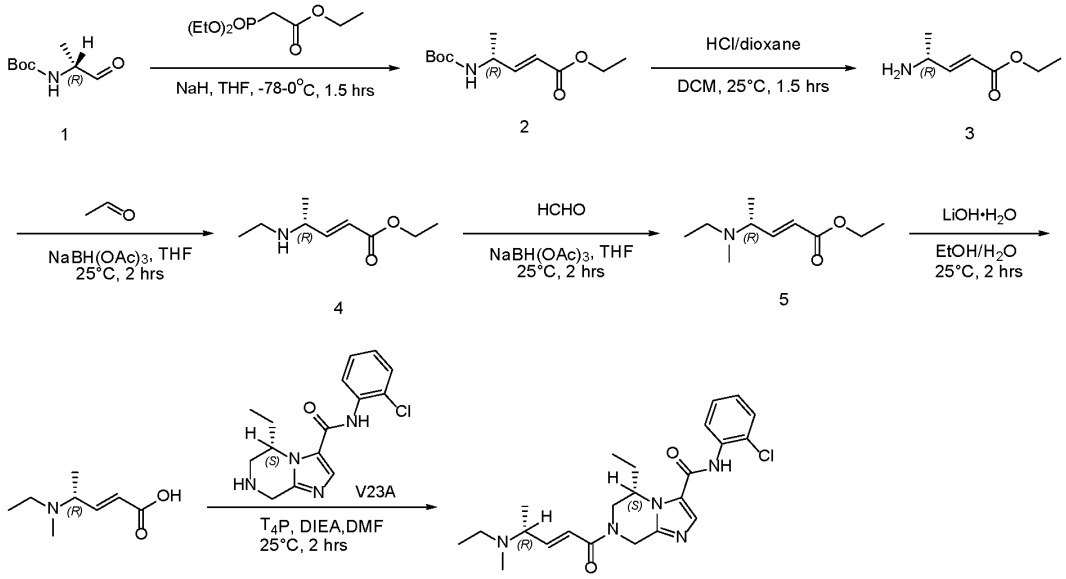
[01372] LCMS: m/z 468.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.95 (s, 1H), 7.80 (s, 1H), 7.55 (dd, J = 8.0 Hz, 1.2 Hz 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 8.0 Hz, 1.6 Hz, 1H), 6.63-6.45 (m, 2H), 5.18-5.13 (m, 2H), 4.71-4.67 (m, 1H), 4.32-4.27 (m, 1H), 3.60 (d, J = 12.0 Hz, 1H), 3.10-3.05 (m, 4H), 2.95-2.89 (m, 1H), 2.46-2.39 (m, 1H), 1.95-1.89 (m, 2H), 1.87-1.58 (m, 6H), 0.96-0.95 (m, 3H).

[01373] Compounds in Table AG were synthesized following the procedure for (5R)-7-[(E,4S)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl) -5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

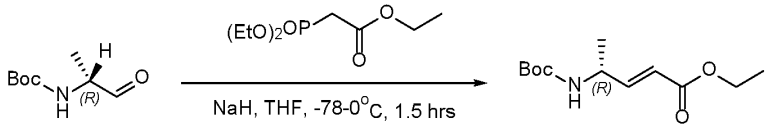
Table AG

Name	Structure	NMR	LCMS	SFC conditions
7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.93 (s, 1H), 7.80 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 6.63-6.45 (m, 2H), 5.17-5.11 (m, 2H), 4.71-4.64 (m, 1H), 4.32-4.28 (m, 1H), 3.60 (d, J = 12.4 Hz, 0.5H), 3.16-3.14 (m, 0.5H), 3.10-3.07 (m, 4H), 2.93-2.90 (m, 1H), 2.46-2.42 (m, 1H), 1.95-1.90 (m, 2H), 1.86-1.58 (m, 6H), 0.96-0.95 (m, 3H).	LCMS: m/z 468.2 $[M+H]^+$	
(5R)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5- cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.80 (s, 1H), 7.56-7.49 (m, 2H), 7.38 (td, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.63-6.45 (m, 2H), 5.17-5.13 (m, 2H), 4.71-4.64 (m, 1H), 4.32-4.28 (m, 1H), 3.60 (d, J = 12.0 Hz, 0.5H), 3.15-3.13 (m, 0.5H), 3.10-3.05 (m, 4H), 2.95-2.89 (m, 1H), 2.46-2.39 (m, 1H), 1.93-1.89 (m, 2H), 1.88-1.61 (m, 6H), 0.96-0.95 (m, 3H).	LCMS: m/z 468.2 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 40%, isocratic elution mode)
(5S)-7-[(E,4R)-4-(azetidin-1-yl)pent-2-enoyl]-N-(2-chlorophenyl)-5-cyclobutyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.94 (s, 1H), 7.80 (s, 1H), 7.56-7.49 (m, 2H), 7.38 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 6.62-6.46 (m, 2H), 5.16-5.11 (m, 2H), 4.72-4.64 (m, 1H), 4.30 (d, J = 18.0 Hz, 1H), 3.60 (d, J = 12.0 Hz, 0.6H), 3.14 (s, 0.4H), 3.08 (t, J = 6.8 Hz, 4H), 2.95-2.89 (m, 1H), 2.46-2.42 (m, 1H), 1.95-1.89 (m, 2H), 1.88-1.61 (m, 6H), 0.96 (t, J = 6.8 Hz, 3H).	LCMS: m/z 468.2 $[M+H]^+$	SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%: 40%, isocratic elution mode)

Example 221: Synthesis of (5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

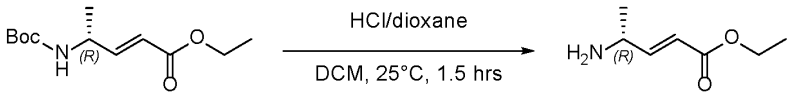


Step 1.1 Synthesis of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate



[01374] To a solution of NaH (4.58 g, 114.47 mmol, 60% purity, 1.2 eq) in THF (200 mL) was added ethyl 2-diethoxyphosphorylacetate (25.66 g, 114.47 mmol, 22.71 mL, 1.2 eq) in one portion at -78°C, nitrogen atmosphere protection was applied. The reaction mixture was stirred at -78°C for 10 min. Then a solution of tert-butyl N-[(1R)-1-methyl-2-oxo-ethyl]carbamate (20 g, 95.39 mmol, 1 eq, HCl) in THF (200 mL) was added to the reaction mixture at -78°C. The reaction mixture was warmed to 0°C and stirred at 0°C for 1.5 hrs. The reaction mixture was quenched with sat. aq. NH_4Cl (200 mL) at 0°C, and then diluted with EtOAc (200 mL x 3). The combined organic phase was washed with brine (200 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®;220 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 100 mL/min). Compound ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (16 g, 65.76 mmol, 68.94% yield) was obtained as pale yellow oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.12 (d, J = 7.6 Hz, 1H), 6.79 (dd, J = 16.0 Hz, 5.2 Hz, 1H), 5.81 (d, J = 15.6 Hz, 1H), 4.21-4.09 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 1.38 (s, 9H), 1.20 (t, J = 6.8 Hz, 3H), 1.14 (d, J = 7.2 Hz, 3H).

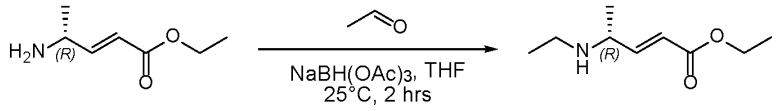
Step 1.2 Synthesis of ethyl (E,4R)-4-aminopent-2-enoate



2 3

[01375] To a solution of ethyl (E,4R)-4-(tert-butoxycarbonylamino)pent-2-enoate (16 g, 65.76 mmol, 1 eq) in DCM (100 mL) was added HCl/dioxane (4 M) at 25°C. The reaction mixture was stirred at 25°C for 1.5 hrs. The reaction mixture was concentrated under reduced pressure to give a residue. Compound ethyl (E,4R)-4-aminopent-2-enoate (15.8 g, crude, HCl) was obtained as yellow oil. LCMS: m/z 144.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.89 (dd, J = 16.0 Hz, 6.0 Hz, 1H), 6.12 (dd, J = 17.2 Hz, 1.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.01 (s, 1H), 1.34 (d, J = 6.8 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H).

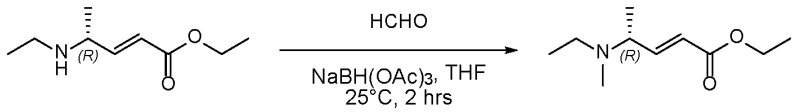
Step 1.3 Synthesis of ethyl (E,4R)-4-(ethylamino)pent-2-enoate



3 4

[01376] To a solution of ethyl (E,4R)-4-aminopent-2-enoate (9.00 g, 50.10 mmol, 1 eq, HCl) in THF (50 mL) was added acetaldehyde (5 M, 12.02 mL, 1.2 eq) at 25°C. The reaction mixture was stirred at 25°C for 20 min. Then $NaBH(OAc)_3$ (15.93 g, 75.15 mmol, 1.5 eq) was added to the reaction mixture. The reaction mixture was stirred at 25°C for 2 hrs. Saturated $NaHCO_3$ solution was added to the mixture to adjust pH=9 at 25°C, and extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (30 mL x 2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Welch Xtimate C_{18} 180 * 70 mm # 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:5%-35% B over 17.0 min). Compound ethyl (E,4R)-4-(ethylamino)pent-2-enoate (4.9 g, 28.62 mmol, 57.12% yield) was obtained as yellow oil. LCMS: m/z 172.4 $[M+H]^+$ ^1H NMR (DMSO-d_6, 400 MHz) δ 6.68 (dd, J = 15.6 Hz, 7.2 Hz, 1H), 5.87 (d, J = 16.0 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.30-3.23 (m, 1H) 2.41 (t, J = 7.2 Hz, 2H), 1.22-1. 93 (m, 3H), 1.07 (d, J = 6.8 Hz, 3H) 0.97 (t, J = 7.2 Hz, 3H).

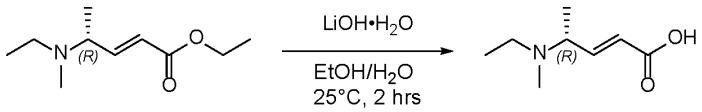
Step 1.4 Synthesis of ethyl (E,4R)-4-[ethyl(methyl)amino]pent-2-enoate



4 5

[01377] To a solution of ethyl (E,4R)-4-(ethylamino)pent-2-enoate (4.9 g, 28.62 mmol, 1 eq) in THF (50 mL) was added HCHO (3.02 g, 37.20 mmol, 2.77 mL, 1.3 eq) at 25°C. The reaction mixture was stirred at 25°C for 20 min. Then sodium;triacetoxyboranuide (9.10 g, 42.92 mmol, 1.5 eq) was added the reaction mixture. The reaction mixture was stirred at 25°C for 2 hrs. Saturated $NaHCO_3$ solution was added to the mixture solution to adjust pH = 9 at 25°C, and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. Compound ethyl (E,4R)-4-[ethyl(methyl)amino]pent-2-enoate (4.1 g, crude) was obtained as yellow oil. LCMS: m/z 186.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.81 (dd, J = 15.6 Hz, 6.8 Hz, 1H), 5.91 (d, J = 15.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.35-3.27 (m, 1H), 2.41-2.32 (m, 2H), 1.98 (s, 3H), 1.22-1.19 (m, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H).

Step 1.5 Synthesis of (E,4R)-4-[ethyl(methyl)amino]pent-2-enoic acid



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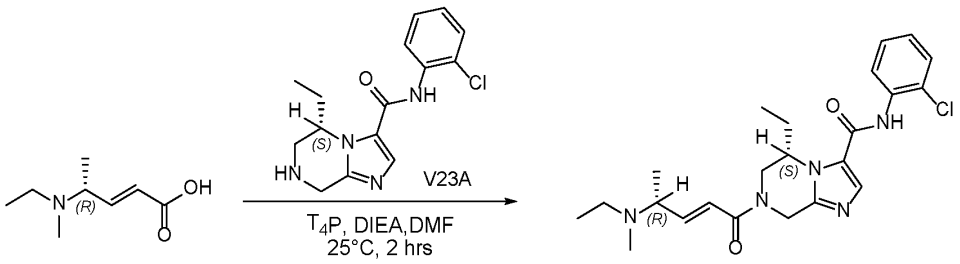
To a solution of ethyl (E,4R)-4-[ethyl(methyl)amino]pent-2-enoate (4.1 g, 22.13 mmol, 1 eq) in EtOH (30 mL) and H_2O (10 mL) was added LiOH•H_2O (2.32 g, 55.33 mmol, 2.5 eq) at 25°C . The reaction mixture was stirred at 25°C for 2 hrs. The mixture was adjusted pH = 3 by (1M) HCl at 25°C. The combined organic phase was filtered and the filtrate was concentrated under reduced pressure to give crude product. The residue was purified by prep-HPLC (column: FLM Titank C_{18} Bulk 250 * 70 mm 10 u; mobile phase: [H_2O (0.04% HCl)-ACN]; B%:0%, isocratic elution mode). Compound (E,4R)-4-[ethyl(methyl)amino]pent-2-enoic acid (1.5 g, 9.54 mmol, 43.11% yield) was obtained as colorless oil. LCMS: m/z 158.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.23 (dd, J = 15.6 Hz, 7.2 Hz, 1H), 6.45 (d, J = 16 Hz, 1H), 4.23 (t, J = 6.8 Hz, 1H), 3.23-3.15 (m, 2H), 2.83 (s, 3H), 1.69 (d, J = 6.4 Hz, 3H), 1.55 (t, J = 7.2 Hz, 3H).

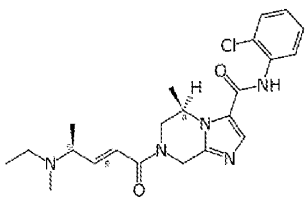
Step 1.6 Synthesis of (5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

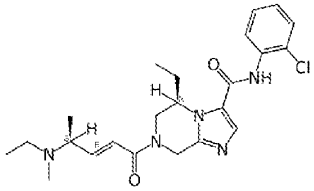


[01378] To a solution of (5S)-N-(2-chlorophenyl)-5-ethyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxamide (100 mg, 328.11 µmol, 1 eq) and (E,4R)-4-[ethyl(methyl)amino]pent-2-enoic acid (56.74 mg, 360.92 µmol, 1.1 eq) in DMF (1 mL) were added T_4P (354.62 mg, 492.17 µmol, 50% purity, 1.5 eq) and DIEA (127.22 mg, 984.34 µmol, 171.45 µL, 3 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hrs. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 150 * 40 * 7 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:15%-45% B over 8.0 min). Compound (5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (86.7 mg, 195.28 µmol, 59.52% yield) was obtained. LCMS: m/z 444.2 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.85 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H) 6.77-6.69 (m, 1H), 6.64-6.60 (m, 1H), 5.27-5.20 (m, 1H), 4.83-4.66 (m, 2H), 4.35 (dd, J = 57.6 Hz, 14.0 Hz, 1H), 3.65 (d, J = 14.8 Hz, 0.5H), 3.37-3.34 (m, 1H), 3.15(d, J = 2.0 Hz, 0.5H), 2.44-2.32 (m, 2H), 2.13 (s, 3H), 1.75-1.66 (m, 1H), 1.53-1.34 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 0.98-0.96 (m, 3H), 0.90 (t, J = 7.2 Hz, 3H).

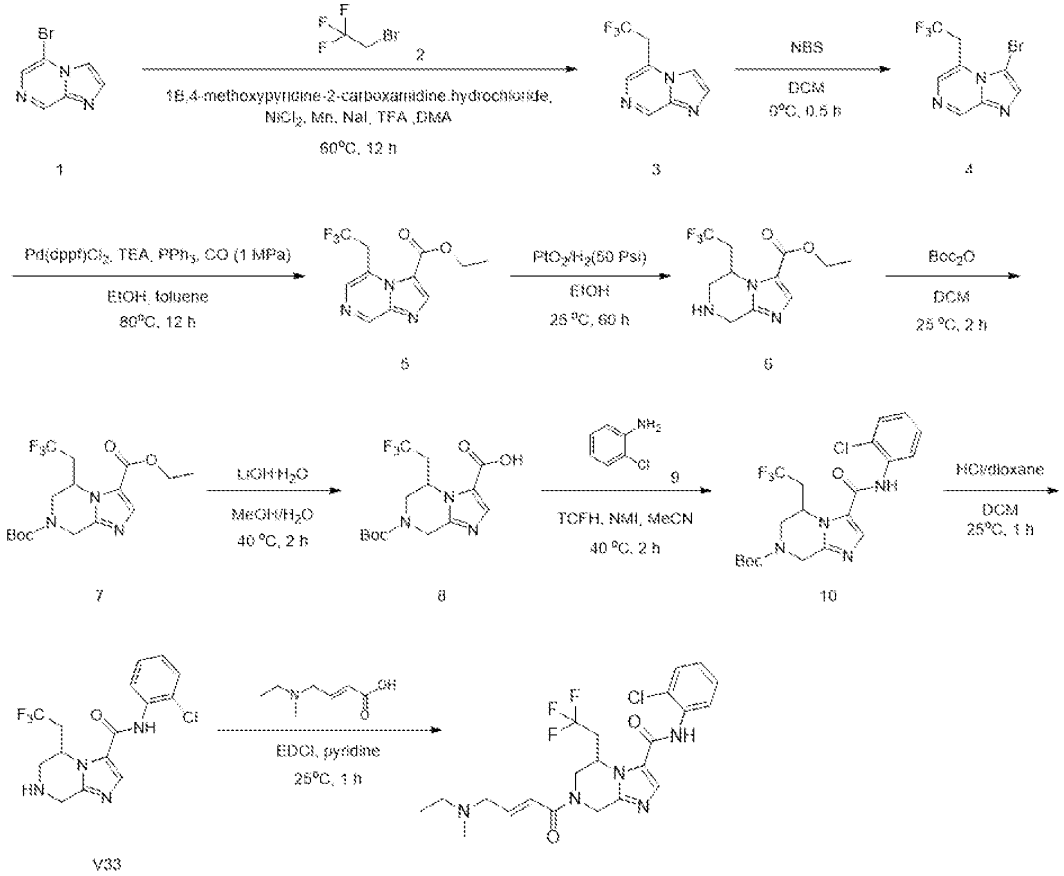
[01379] Compounds in Table AH were synthesized following the procedure for (5S)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4R)-4-[ethyl(methyl)amino]pent- 2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.

Table AH

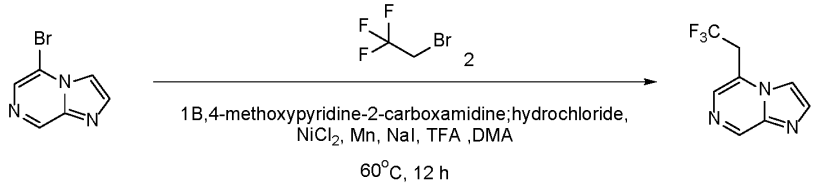
Name	Structure	NMR	LCMS
(5R)-N-(2-chlorophenyl)-7-[(E,4S)-4-[ethyl(methyl)amino]pent-2-enoyl] -5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d6*, 400 MHz) δ 9.86 (br.s, 1H), 7.89 (s, 1H), 7.56-7.51 (m, 2H), 7.37 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.29 (td, J = 7.6 Hz, 1.6 Hz, 1H), 6.77-6.71 (m, 1H), 6.63 (t, J = 10.8 Hz, 1H), 5.27-5.21 (m, 1H), 5.05 (s, 1H), 4.62 (dd, J = 17.2 Hz, 8.0 Hz, 1H), 4.30 (t, J = 14.8 Hz, 0.5H), 3.72-3.68 (m, 1H), 3.27-3.21 (m, 0.5H), 2.45-2.32 (m, 2H), 2.13 (s, 3H),	LCMS: m/z 430.2 $[M+H]^+$

Name	Structure	NMR	LCMS
		1.29-1.24 (m, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).	
(5R)-N-(2-chlorophenyl)-5-ethyl-7-[(E,4S)-4-[ethyl(methyl)amino] pent-2-enoyl]-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide		^{1}H NMR (DMSO-*d*6, 400 MHz) 9.86 (s, 1H), 7.89 (s, 1H), 7.56-7.50 (m, 2H), 7.38 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.30 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 6.77-6.60 (m, 2H), 5.27-5.20 (m, 1H), 4.83-4.65 (m, 2H), 4.45-4.26 (m, 1H), 3.69-3.63 (m, 0.4H), 3.37-3.34 (m, 2H), 3.17-3.14 (m, 0.6H), 2.41-2.34 (m, 1H), 2.13 (s, 3H), 1.73-1.67 (m, 1H), 1.50-1.38 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.97-0.88 (m, 6H).	LCMS: m/z 444.2 $[M+H]^+$

Example 222: Synthesis of N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5- (2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide.



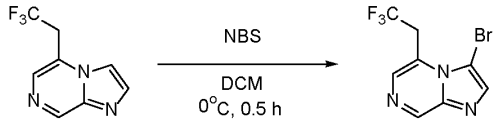
Step 1.1 Synthesis of 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine



1 3

[01380] To the reaction mixture of 5-bromoimidazo[1,2-a]pyrazine (0.2 g, 1.01 mmol, 1 eq) and 2-bromo-1,1,1-trifluoro-ethane (987.39 mg, 6.06 mmol, 6 eq) in DMA (7 mL) were added TFA (11.52 mg, 101.00 μmol, 7.50 μL, 0.1 eq), NaI (37.85 mg, 252.50 μmol, 0.25 eq), Manganese (221.96 mg, 4.04 mmol, 219.98 μL, 4 eq), dichloronickel;1,2-dimethoxyethane (22.19 mg, 101.00 μmol, 0.1 eq), 4-methoxypyridine-2-carboxamidine;hydrochloride (18.95 mg, 101.00 μmol, 0.1 eq) at 25°C in glovebox. The reaction mixture was heated to 60°C and stirred at 60°C for 12 hours. 12 parallel reactions were combined to workup. The reaction mixture was cooled to 25°C and poured into ice water (200 mL). The reaction mixture was warmed to 25°C, filtered through a pad of Celite. The filtrate was extracted with EtOAc (70 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 20 g SepaFlash® Silica Flash Column, Eluent of 45~55% Petroleum ether/ Ethyl acetate gradient @ 50 mL/min). The eluent was removed under reduced pressure to give compound 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine (0.7 g, 3.48 mmol, 28.71% yield) as yellow oil. LCMS: m/z 202.0 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.10 (s, 1H), 8.40 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 4.37 (q, J = 10.8 Hz, 2H).

Step 1.2 Synthesis of 3-bromo-5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine

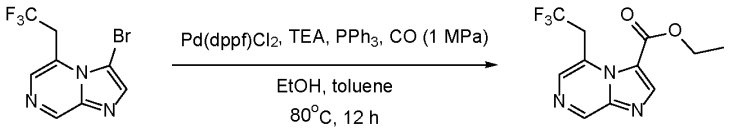


3 4

[01381] To a solution of 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine (0.5 g, 2.49 mmol, 1 eq) in DCM (5 mL) was added NBS (398.17 mg, 2.24 mmol, 0.9 eq) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hours. The reaction mixture was warmed to 25°C. To the reaction mixture was added water (40 mL) and then the organic phase was separated. The aqueous phase was extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (15 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography

(BIOTAGE®; 12 g SepaFlash® Silica Flash Column, Eluent of 30~45% Petroleum ether/ Ethyl acetate gradient @ 60 mL/min). The eluent was removed under reduced pressure to give compound 3-bromo-5-(2,2,2-trifluoroethyl)imidazo [1,2-a]pyrazine (0.5 g, 1.79 mmol, 71.83% yield) as a yellow solid. LCMS: m/z 279.9 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.11 (s, 1H), 8.00 (s, 1H), 7.97 (s, 1H), 4.68 (q, J = 10.4 Hz, 2H).

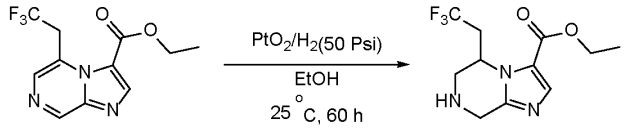
Step 1.3 Synthesis of ethyl 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine-3-carboxylate



4 5

[01382] To the reaction mixture of 3-bromo-5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine (0.5 g, 1.79 mmol, 1 eq) in EtOH (10 mL) and toluene (10 mL) were added $Pd(dppf)Cl_2$ (391.92 mg, 535.63 μmol, 0.3 eq),TEA (397.47 mg, 3.93 mmol, 546.73 μL, 2.2 eq) and PPh_3 (140.49 mg, 535.63 μmol, 0.3 eq) at 25°C. The reaction mixture was heated to 80°C and stirred at 80°C for 12 hours under CO (1 MPa). The reaction mixture was cooled to 25°C and to the filtrate was added water (30 mL). The filtrate extracted with EtOAc (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 12 g SepaFlash® Silica Flash Column, Eluent of 30~45% Petroleum ether/ Ethyl acetate gradient @ 60 mL/min). The eluent was removed under reduced pressure to give compound ethyl 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine-3-carboxylate (0.43 g, 1.57 mmol, 88.15% yield) as a yellow solid. LCMS: m/z 274.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.32 (s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 4.83 (q, J = 10.8 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.35 (q, J = 6.4 Hz, 3H).

Step 1.4 Synthesis of ethyl 5-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxylate

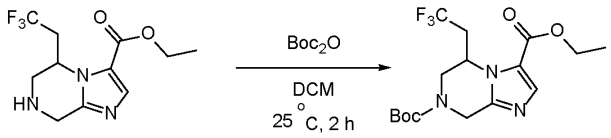


5 6

[01383] To a solution of ethyl 5-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyrazine-3-carboxylate (0.25 g, 915.04 μmol, 1 eq) in EtOH (15 mL) was added PtO_2 (25.00 mg, 110.09 μmol, 0.12 eq) under Ar_2 at 25°C. The reaction mixture was purged with H_2 for 3 times at 25°C. The

reaction mixture was stirred at 25°C for 60 hours under H_2 (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give compound ethyl 5-(2,2,2-trifluoroethyl)-5,6,7,8- tetrahydroimidazo[1,2-a]pyrazine-3-carboxylate (0.27 g, crude) as yellow oil. LCMS: m/z 278.2 $[M+H]^+$.

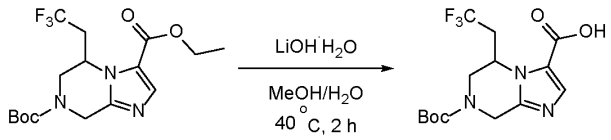
Step 1.5 Synthesis of O7-tert-butyl O3-ethyl 5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3,7-dicarboxylate



6 7

[01384] To a solution of ethyl 5-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3- carboxylate (0.27 g, 973.88 μmol, 1 eq) in DCM (4 mL) was added DIEA (188.80 mg, 1.46 mmol, 254.44 μL, 1.5 eq) at 25°C. And then Boc_2O (255.06 mg, 1.17 mmol, 268.48 μL, 1.2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was cooled to 0°C and adjusted pH = 6 with sat. aq. citric acid at 0°C, nitrogen atmosphere protection was applied. The reaction mixture was warmed up to 20°C and to the reaction mixture was added water (30 mL). The organic phase was separated, the aqueous phase was extracted with DCM (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound O7-tert-butyl O3-ethyl 5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7- dicarboxylate (0.5 g, crude) as a yellow solid. LCMS: m/z 378.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.68 (s, 1H), 5.16 (s, 1H), 4.92-4.87 (m, 1H), 4.33-4.26 (m, 4H), 3.49-3.46 (m, 1H), 2.74-2.66 (m, 2H), 1.44 (s, 9H), 1.28 (t, J = 6.8 Hz, 3H).

1.6 Synthesis of 7-tert-butoxycarbonyl-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid

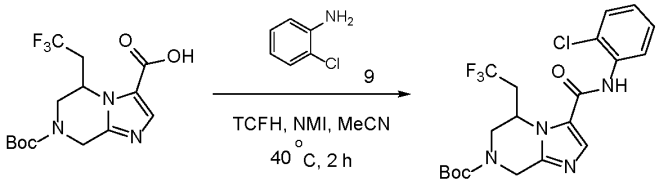


7 8

[01385] To the reaction mixture of O7-tert-butyl O3-ethyl 5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3,7-dicarboxylate (0.5 g, 1.33 mmol, 1 eq) in H_2O (2 mL) and MeOH (6 mL) was added $LiOH{\cdot}H_2O$ (166.79 mg, 3.98 mmol, 3 eq) at 25°C. The reaction mixture was heated to 40°C and stirred at 40°C for 2 hours. The reaction mixture was cooled

to 25°C and concentrated under reduced pressure. To the reaction mixture was added water (5 mL). Then the reaction mixture was cooled to 0°C and adjusted pH= 4 with 1M HCl at 0°C. There was precipitate formed. The precipitate was collected through filtrate and concentrated under reduced pressure to give compound 7-tert-butoxycarbonyl-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxylic acid (0.22 g, 629.82 μmol, 47.53% yield) as a white solid. LCMS: m/z 350.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.98-12.89 (m, 1H), 7.61 (s, 1H), 5.10 (s, 1H), 4.91-4.84 (m, 1H), 4.34-4.27 (m, 2H), 3.49-3.41 (m, 1H), 2.69-2.66 (m, 2H), 1.44 (s, 9H).

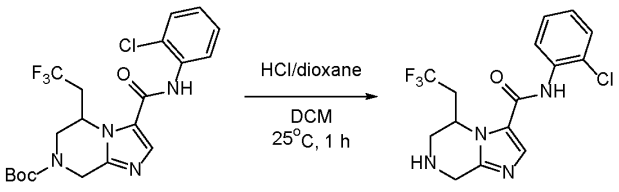
Step 1.7 Synthesis of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate



8 10

[01386] To a solution of 7-tert-butoxycarbonyl-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (0.22 g, 629.82 μmol, 1 eq) in MeCN (4 mL) were added 2-chloroaniline (104.45 mg, 818.77 μmol, 86.32 μL, 1.3 eq) at 25°C. The reaction mixture was cooled to 0°C. And then TCFH (883.58 mg, 3.15 mmol, 5 eq) was added to the reaction mixture at 0°C. The reaction mixture was warmed to 25°C and stirred at 25°C for 2 hours. The reaction mixture was added water (30 mL) at 25°C. The reaction mixture was extracted with EtOAc (10 mL x 3), the combined organic phase was washed with brine (10 mL x 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (BIOTAGE®; 12 g SepaFlash® Silica Flash Column, Eluent of 30~35% Petroleum ether/ Ethyl acetate gradient @ 45 mL/min). The eluent was removed under reduced pressure to give compound tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-7-carboxylate (0.7 g, crude) as yellow oil. LCMS: m/z 458.9 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.90 (s, 1H), 7.94 (s, 1H), 7.56-7.52 (m, 2H), 7.39 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.30 (td, J = 8.0 Hz, 2.0 Hz, 1H), 5.25 (s, 1H), 4.92-4.88 (m, 1H), 4.41-4.30 (m, 2H), 3.51-3.43 (m, 1H), 2.77-2.72 (m, 2H), 1.44 (s, 9H).

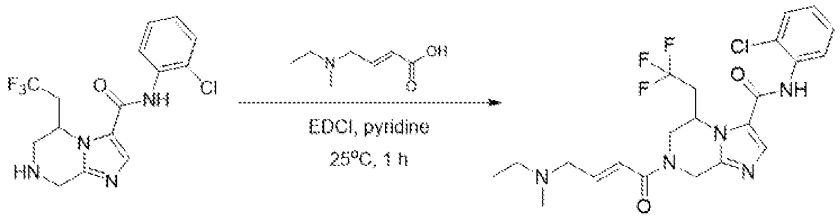
Step 1.8 Synthesis of N-(2-chlorophenyl)-5-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide



10 V33

[01387] To a solution of tert-butyl 3-[(2-chlorophenyl)carbamoyl]-5-(2,2,2-trifluoroethyl)-6,8- dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (0.7 g, 1.53 mmol, 1 eq) in DCM (4 mL) was added HCl/dioxane (4 M, 3.50 mL, 9.18 eq) at 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure to give compound N-(2-chlorophenyl)-5-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide (0.6 g, crude, HCl) as a yellow solid. LCMS: m/z 359.1 $[M+H]^+$.

Step 1.9 Synthesis of N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide

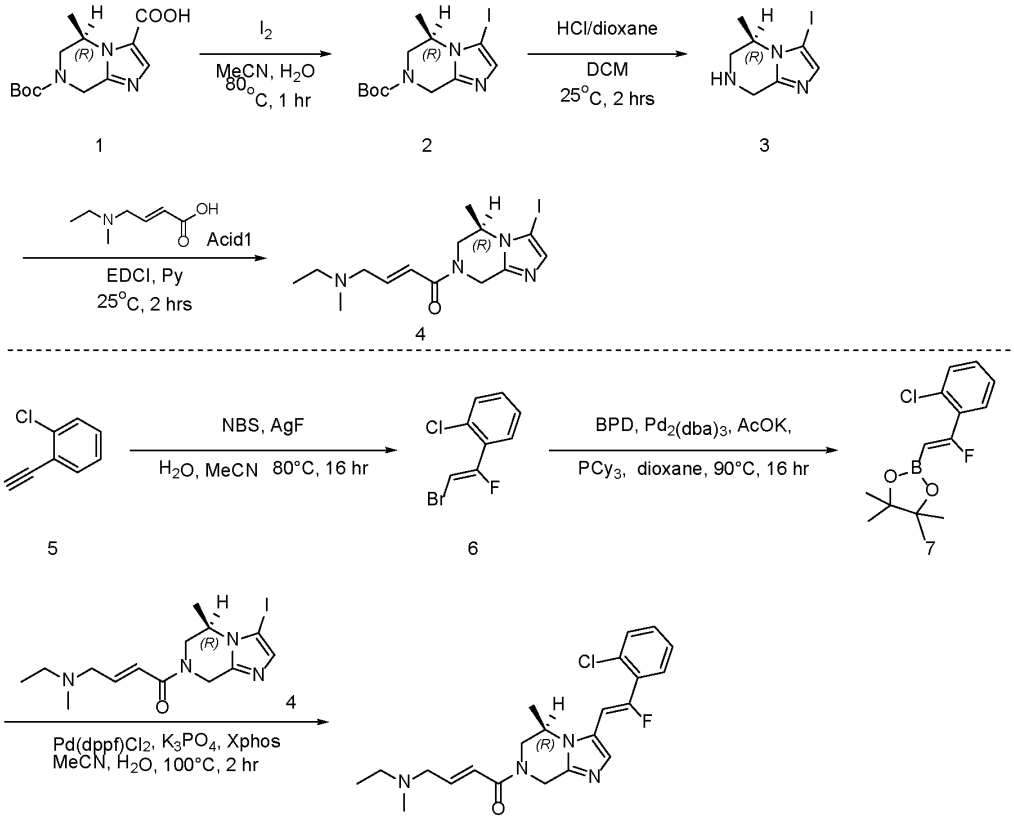


V33

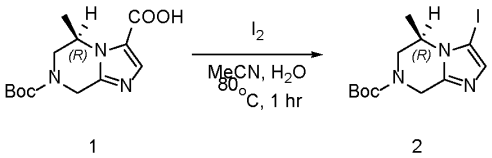
[01388] To a solution of N-(2-chlorophenyl)-5-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroimidazo [1,2-a]pyrazine-3-carboxamide (0.6 g, 759.10 μmol, 1 eq, HCl) in Pyridine (5 mL) was added (E)-4-[ethyl(methyl)amino]but-2-enoic acid (126.80 mg, 885.61 μmol, 1 eq) at 25°C. And then EDCI (339.54 mg, 1.77 mmol, 2 eq) was added to the reaction mixture at 25°C. The reaction mixture was stirred at 25°C for 1 hour. The reaction mixture was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75*40 mm*5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient: 30%-60% B over 8.0 min). The residue was dried over lyophilization to give compound N-(2-chlorophenyl)-7-[(E)-4-[ethyl(methyl)amino]but-2-enoyl]-5-(2,2,2-trifluoroethyl)-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-3-carboxamide (162.8 mg, 327.58 μmol, 43.15% yield, 97.37% purity) as a yellow solid. LCMS: m/z 484.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ 9.92 (s, 1H), 7.93 (s, 1H), 7.57-7.52 (m, 2H), 7.39 (t, J = 6.8 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 6.78-6.59 (m, 2H), 5.34 (s, 1H), 5.22-5.14 (m, 1H), 4.84-4.68 (m, 1H),

4.38-4.35 (m, 1H), 3.77-3.73 (m, 0.5H), 3.27-3.24 (m, 0.5H), 3.14-3.13 (m, 2H), 2.78-2.67 (m, 2H), 2.38-2.36 (m, 2H), 2.15 (s, 3H), 0.99 (t, J = 6.8 Hz, 3H).

Example 223: Synthesis of (E)-1-[(5R)-3-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-5-methyl-6,8- dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-[ethyl(methyl)amino]but-2-en-1-one.



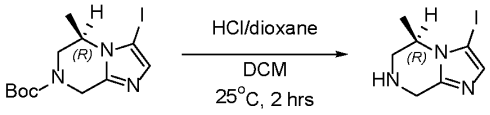
Step 1.1 Synthesis of tert-butyl (5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazine-7-carboxylate.



[01389] To the reaction mixture of (5R)-7-tert-butoxycarbonyl-5-methyl-6,8-dihydro-5H-imidazo [1,2-a]pyrazine-3-carboxylic acid (1 g, 3.55 mmol, 1 eq) in MeCN (10 mL) and H_2O (0.05 mL), was added I_2 (4.51 g, 17.77 mmol, 3.58 mL, 2 eq) at 25°C. The reaction mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 1 hour under N_2 atmosphere. The reaction mixture was cooled to 25°C and to the reaction mixture was added sat. aq. Na_2SO_3 (2 mL) at 25°C. 4 parallel reactions were combined to workup. The

reaction mixture was adjusted pH = 8 with aq. Na_2CO_3 at 0°C. To the reaction mixture was added water (80 mL) at 25°C. The reaction mixture was extracted with EtOAC (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound tert-butyl (5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine-7-carboxylate (3.3 g, 9.09 mmol, 63.90% yield) was obtained. LCMS: m/z 364.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.01 (s, 1H), 4.88-4.86 (m, 1H), 4.23-4.08 (m, 3H), 3.44-3.38 (m, 1H), 1.44 (s, 9H), 1.24 (d, J = 5.2 Hz, 3H).

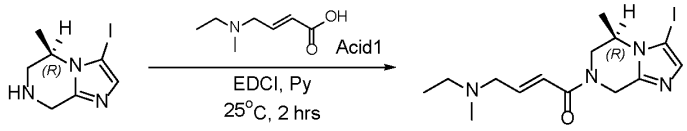
Step 1.2 Synthesis of (5R)-3-iodo-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine.



2 3

[01390] To a solution of tert-butyl (5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazine- 7-carboxylate (3.3 g, 9.09 mmol, 1 eq) in DCM (25 mL) was added HCl/dioxane (4 M, 2.27 mL, 1 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was concentrated under reduced pressure to give compound (5R)-3-iodo-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (3 g, crude, HCl) as a white solid. LCMS: m/z 264.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 4.64-4.60 (m, 2H), 4.51-4.47 (m, 1H), 3.67-3.62 (m, 2H), 1.64 (d, J = 6.8 Hz, 3H).

Step 1.3 Preparation of (E)-4-[ethyl(methyl)amino]-1-[(5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]but-2-en-1-one.

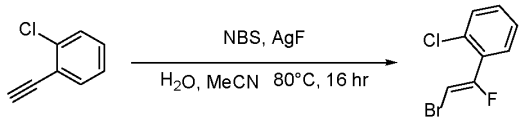


3 4

[01391] To a solution of (5R)-3-iodo-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (3 g, 10.02 mmol, 1 eq, HCl) and (E)-4-[ethyl(methyl)amino]but-2-enoic acid (2.16 g, 12.02 mmol, 1.2 eq, HCl) in Pyridine (30 mL) was added EDCI (3.84 g, 20.03 mmol, 2 eq) at 25°C. The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (column: We Pure Biotech XP tC_{18} 250* 70* 10um; mobile phase: [H_2O (10 mM NH_4HCO_3)- ACN]; gradient: 0%-45% B over 22.0 min). The residue was dried over lyophilization to give compound (E)-4-[ethyl(methyl)amino]-1-[(5R)-3-iodo-5- methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]but-2-en-1-one (2.3 g, 5.92 mmol, 59.15% yield) as brown oil. LCMS: m/z 388.9 $[M+H]^+$.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01 (s, 1H), 6.72-6.70 (m, 2H), 5.26-5.12 (m, 1H), 4.67-4.54 (m, 1H), 4.33-4.29 (m, 2H), 4.17-4.12 (m, 0.5H), 3.69-3.65 (m, 0.5H), 3.13 (s, 2H), 2.35 (q, J = 6.8 Hz, 2H), 2.14 (s, 3H), 1.25-1.19 (m, 3H), 0.99 (q, J = 7.2 Hz, 3H).

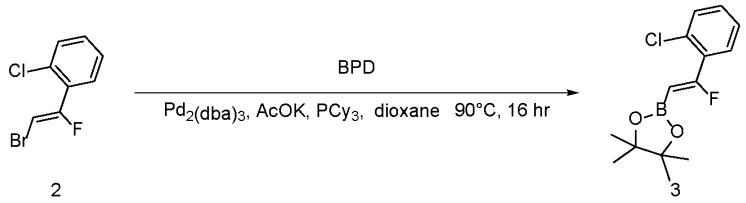
Step 1.4 Preparation of 1-[(Z)-2-bromo-1-fluoro-vinyl]-2-chloro-benzene



1 2

[01392] To a solution of 1-chloro-2-ethynyl-benzene (1.5 g, 10.98 mmol, 1 eq) in MeCN (21 mL) and H_2O (1.2 mL) were added NBS (2.15 g, 12.08 mmol, 1.1 eq) and AgF (3.48 g, 27.46 mmol, 595.24 µL, 2.5 eq) at 25°C. The reaction mixture was heated to 80°C and stirred at 80°C for 16 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~0% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). Compound 1-[(Z)-2-bromo-1-fluoro-vinyl]-2-chloro-benzene (1 g, 4.25 mmol, 38.67% yield) was obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 7.52-7.44 (m, 2H), 7.40-7.29 (m, 2H), 6.24 (d, J = 27.6 Hz, 1H).

Step 1.5 Synthesis of 2-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

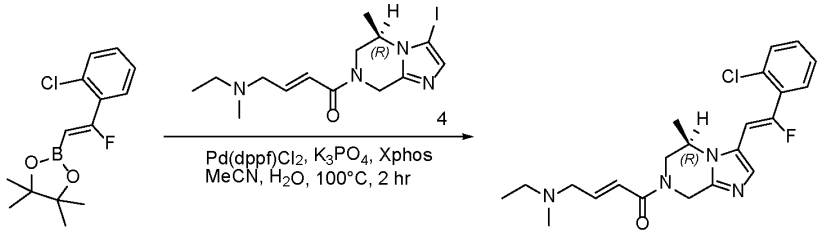


2 3

[01393] A mixture of 1-[(Z)-2-bromo-1-fluoro-vinyl]-2-chloro-benzene (400 mg, 1.70 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (862.70 mg, 3.40 mmol, 2 eq), $Pd_2(dba)_3$ (155.55 mg, 169.87 µmol, 0.1 eq), AcOK (500.13 mg, 5.10 mmol, 3 eq) and PCy_3 (190.54 mg, 679.46 µmol, 220.28 µL, 0.4 eq) in 1,4-dioxane (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was heated to 90°C and stirred at 90°C for 16 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage ®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~0% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). Compound 2-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (290 mg, 1.03 mmol, 60.42% yield) was

obtained as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 7.56-7.52 (m, 1H), 7.43-7.39 (m, 1H), 7.33-7.23 (m, 2H), 5.35 (d, *J* = 54.0 Hz, 1H), 1.34 (s, 12H).

Step 1.6 Synthesis of (E)-1-[(5R)-3-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-[ethyl(methyl)amino]but-2-en-1-one



[01394] A mixture of 2-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (355 mg, 1.26 mmol, 1 eq), (E)-4-[ethyl(methyl)amino]-1-[(5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]but-2-en-1-one (585.37 mg, 1.51 mmol, 1.2 eq), (E)-4-[ethyl(methyl)amino]-1-[(5R)-3-iodo-5-methyl-6,8-dihydro-5H-imidazo[1,2-a] pyrazin-7-yl]but-2-en-1-one (585.37 mg, 1.51 mmol, 1.2 eq) , K_3PO_4 (533.40 mg, 2.51 mmol, 2 eq), $Pd_2(dba)_3$ (115.05 mg, 125.64 μmol, 0.1 eq) and XPhos (119.79 mg, 251.29 μmol, 0.2 eq) in MeCN (3 mL) and H_2O (0.6 mL) was degassed and purged with N_2 for 3 times, and then the mixture was heated to 100°C and stirred at 100°C for 2 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 2_Phenomenex Gemini C_{18} 75 * 40 mm * 5 um; mobile phase: [H_2O (10 mM NH_4HCO_3)-ACN]; gradient:25%-55% B over 10.0 min). Compound (E)-1-[(5R)-3-[(Z)-2-(2-chlorophenyl)-2-fluoro-vinyl]-5-methyl-6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl]-4-[ethyl(methyl)amino]but-2-en-1-one (70.0 mg, 167.90 μmol, 13.36% yield) was obtained. LCMS: m/z 417.1 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.70-7.68 (m, 1H), 7.60-7.58 (m, 1H), 7.50-7.45 (m, 2H), 7.31 (s, 1H), 6.75-6.74 (m, 2H), 6.50 (d, *J* = 39.2 Hz, 1H), 5.28-5.13 (m, 1H), 4.64 (s, 2H), 4.30 (dd, *J* = 49.2 Hz, 15.2 Hz, 1H), 3.71 (d, *J* = 12.8 Hz, 0.5H), 3.25-3.24 (m, 0.5H), 3.16-3.14 (m, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 2.15 (s, 3H), 1.24 (s, 3H), 0.99 (t, *J* = 6.8 Hz, 3H).

Example 224. Biological Activity of the Compounds of the Present Disclosure

[01395] The biological activity of the compounds of the present disclosure was determined utilizing the assay described herein. The results of those assays are provided in Table 4A and Table 4B below.

In vitro kinase assay – EphB2

[01396] All compounds were initially prepared as 10 mM stocks in DMSO and subsequently diluted in DMSO to 100 × their final concentrations. 100 nL of each compound dilution was subsequently added to 384-well plate in duplicate. To each well, 5 µL of enzyme solution containing EphB2 (final concentration 0.0025 nM) in 1 × Kinase buffer (50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 0.01% BSA and 0.01% Tween-20) and the mix incubated at room temperature for 60 min. To initiate each reaction, 5 µL of substrate solution containing Fluorescein-Poly GT (final concentration 0.2 µM) and ATP (final concentration 1000 µM) in 1 × Kinase buffer was added to each well. Reaction was incubated at 25°C for 60 min and then terminated by the addition of 10 µL of detection solution containing Tb-PY20 Antibody (final concentration 2 nM) and EDTA (final concentration 20 mM) in 1 × Kinase buffer.

[01397] The plates were mixed briefly with Centrifuge and incubated at room temperature 60 minutes. All samples were then subjected to analysis using Envision2104 Multilable Reader (Excitation at 340 nm and Emission at 520 nm and 495 nm). Calculate the ratio of RFU 520 nm / RFU 495 nm, Convert ratio values to percent inhibition values. Percent inhibition = (max-sample ratio)/(max-min)*100. IC_{50} values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

In vitro kinase assay – EphB3

[01398] All compounds were initially prepared as 10 mM stocks in DMSO and subsequently diluted in DMSO to 100 × their final concentrations. 100 nL of each compound dilution was subsequently added to 384-well plate in duplicate. To each well, 5 µL of enzyme solution containing EphB3 (final concentration 0.001 nM) in 1 × Kinase buffer (50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 2 mM DTT, 0.01% BSA and 0.01% Tween-20) and the mix incubated at room temperature for 60 min. To initiate each reaction, 5 µL of substrate solution containing Fluorescein-Poly GT (final concentration 0.2 µM) and ATP (final concentration 1000 µM) in 1 × Kinase buffer was added to each well. Reaction was incubated at 25°C for 60 min and then terminated by the addition of 10 µL of detection solution containing Tb-PY20 Antibody (final concentration 2 nM) and EDTA (final concentration 20 mM) in 1 × Kinase buffer.

[01399] The plates were mixed briefly with Centrifuge and incubated at room temperature 60 minutes. All samples were then subjected to analysis using Envision2104 Multilable Reader(Excitation at 340 nm and Emission at 520 nm and 495 nm). Calculate the ratio of RFU 520 nm / RFU 495 nm, Convert ratio values to percent inhibition values. Percent inhibition = (max-sample ratio)/(max-min)*100. IC_{50} values were then calculated by plotting dose-response curves and then using the XLfit application in Excel software.

NanoBRET Target Engagement Assay for EphB2 and EphB3 Kinase

[01400] Compounds were tested in the NanoBRET™ Target Engagement (TE) Intracellular Kinase Assay which measures the apparent cellular affinity of test compounds by competitive displacement of a cell-permeable fluorescent NanoBRET™ tracer, reversibly bound to a NanoLuc® luciferase-kinase fusions in cells. The assay is based on an energy transfer technique designed to measure molecular proximity in living cells.

[01401] The HEK293 cells were grown in T75 flasks in DMEM medium containing 10% Fetal Bovine Serum and Penicillin/Streptomycin at 37°C in a humidified, 5% CO_2 incubator. For subculturing, the HEK293 cells were grown to about 80% confluency, culture medium was aspirated and the cell layer was rinsed with PBS. Two mL trypsin solution (0.25%) was added to the flask and observed under an inverted microscope until cell layer is dispersed. Eight mL media was added, cells were spun down at 200 X g for 5 minutes. Cell pellet was re-suspended in 10 mL media and an appropriate volume was inoculated into a new culture flask.

[01402] The HEK293 cells were treated with trypsin as described above, centrifuged at 200 X g and the cell pellet was resuspended in assay medium (RPMI medium, no phenol red with 1% FBS) at a density of 110,000 cells/mL.

[01403] 1 μg of EphB2 or EphB3 plasmid DNA was mixed with 9 μg of carrier DNA and 5 μL of FuGENE transfection reagent in 500 μL of assay medium. The lipid:DNA mix was incubated for 20 minutes at room temperature.

[01404] 500 μL of lipid:DNA complex was mixed with 10 mL of HEK293 cells. 100 μL/well, cells mixed with lipid:DNA complex were dispensed in black 96-well plates. The 96-well plates were incubated at 37°C in a humidified, 5% CO_2 incubator for 24 hours.

[01405] Compounds were dissolved in DMSO to make stock solutions of 10 mM concentration.

[01406] Compounds were serially diluted 3-fold as shown below:

Level	From	Volume (uL)	DMSO (uL)	Conc (mM)
C1	Stock Solution	10	0	10.000
C2	C1	10	20	3.333
C3	C2	10	20	1.111
C4	C3	10	20	0.370
C5	C4	10	20	0.123
C6	C5	10	20	0.041
C7	C6	10	20	0.014
C8		0	20	0.000

[01407] The serially diluted compounds were diluted 100-fold in the assay medium. 10 µL of assay medium containing the serially diluted compounds was added to the HEK293 cells in triplicates resulting in a final dilution of 1000-fold, with the concentrations of compounds ranging from 0 to 10 µM. The HEK293 cells were incubated with the compounds for varying times prior to the treatment with the NanoBRET Tracer reagent. The time of incubation with the compounds varied: 30 minutes, 2 hours or 4 hours.

[01408] For the EphB2 enzyme, 5 µL of the K4 tracer reagent was mixed with 495 µL of tracer dilution buffer for each time of compound incubation. 5 µL of the diluted tracer was added to each well in the 96-well plate and the plates were incubated for 2 hours at 37°C in a humidified, 5% CO_2 incubator. For the EphB3 enzyme, 12 µL of the K4 tracer reagent was mixed with 468 µL of tracer dilution buffer for each time of compound incubation. 5 µL of the diluted tracer was added to each well in the 96-well plate and the plates were incubated for 2 hours at 37°C in a humidified, 5% CO_2 incubator.

[01409] The plates were removed from incubator and equilibrated at room temperature for 15 minutes. 3X Substrate/Inhibitor solution was prepared by mixing 27 µL of Nanoglo substrate and 9 µL of Nanoluc inhibitor in 4.464 mL of assay medium. 50 µL of the mix added to each well of the 96-well plate and incubated at room temperature for 2 minutes.

[01410] The plates were read in GloMax reader to obtain the BRET ratio values by dividing the acceptor emission value (610 nm) by the donor emission value (450 nm). IC_{50} values were calculated by plotting the BRET ratio values against the concentrations of the compounds.

Table 4A.

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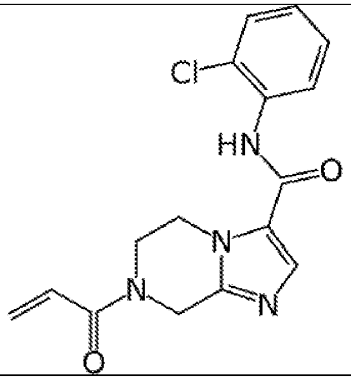
1		++++	
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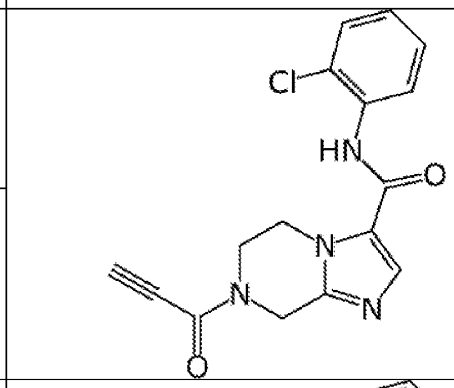
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (µM)	EphB2 1mM ATP[B]: Vendor IC_{50} (µM)
3		++++	
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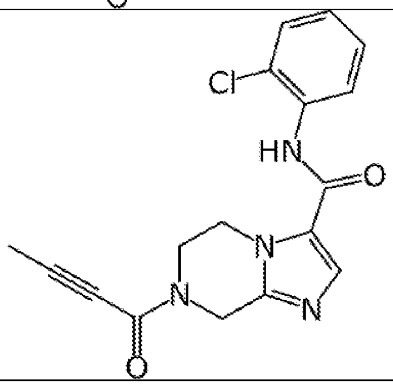
5		++	
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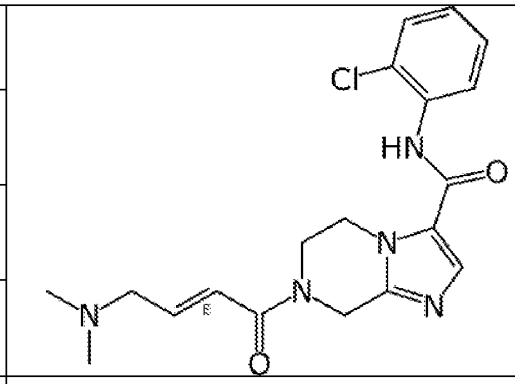
7		++++	
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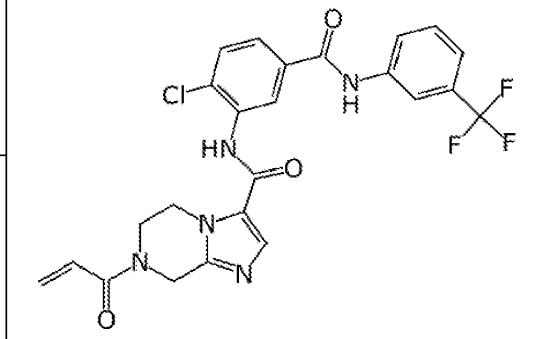
11		++++	+++
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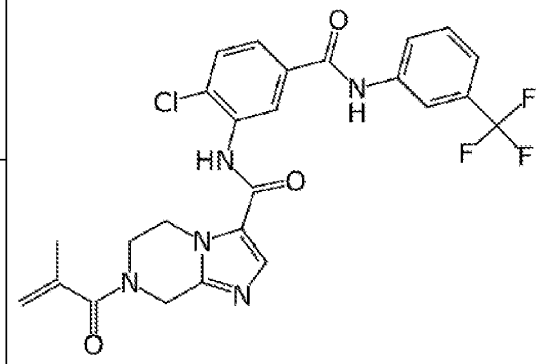
13		+++	+++
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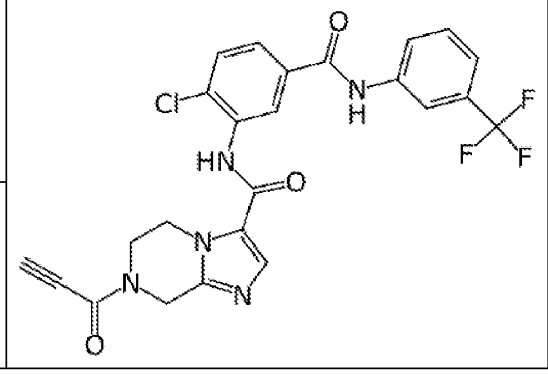
15		++++	+++
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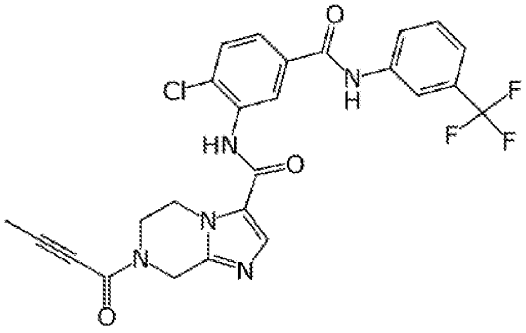
17		++++	+++
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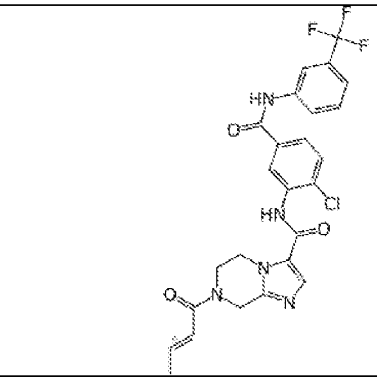
19		++++	+++
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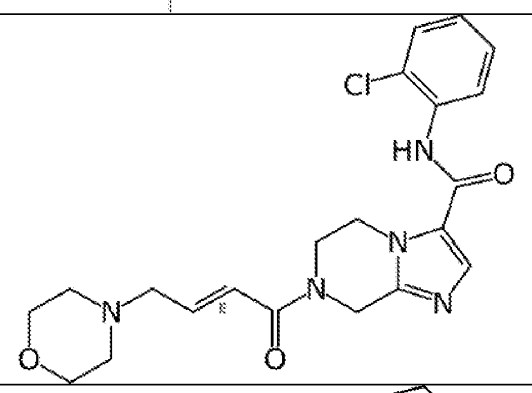
21		++	
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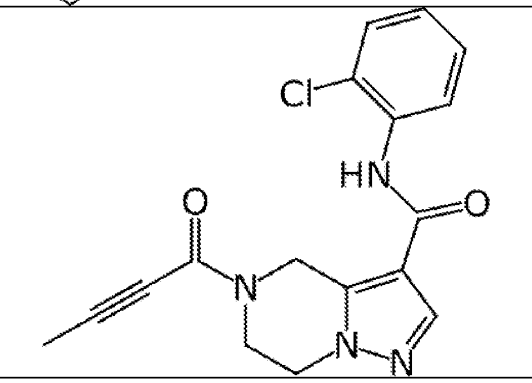
24		++	
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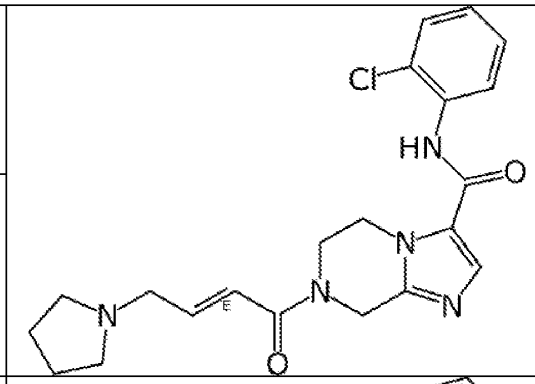
26		++++	
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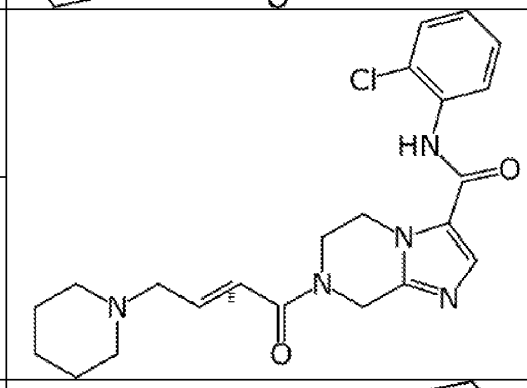
28		++++	
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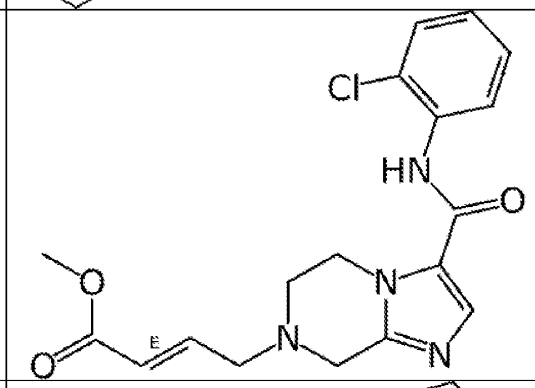
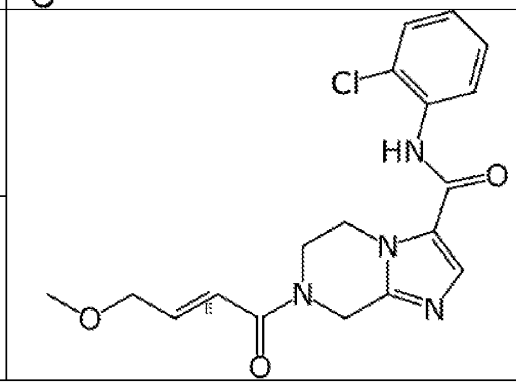
30		++	+
31		+	
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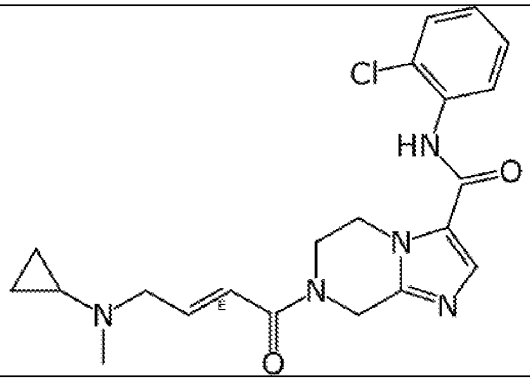
33		+++	
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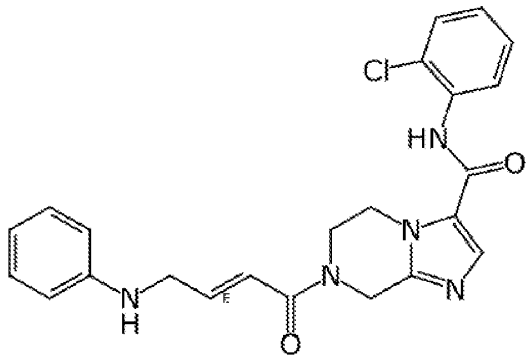
35		+++	
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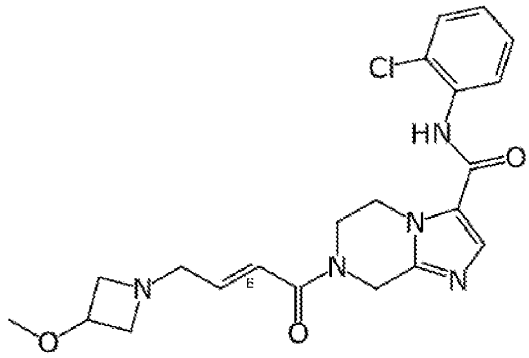
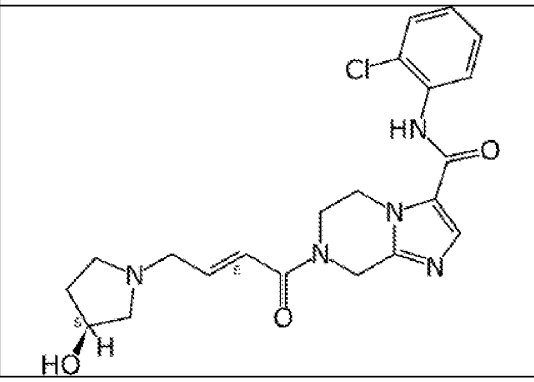
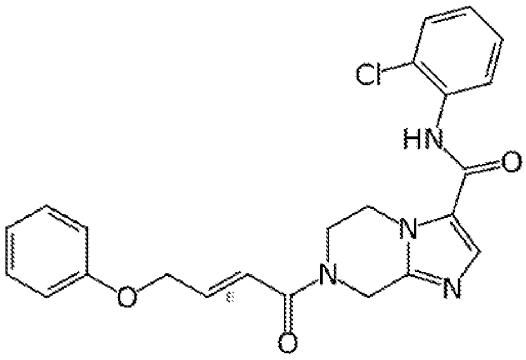
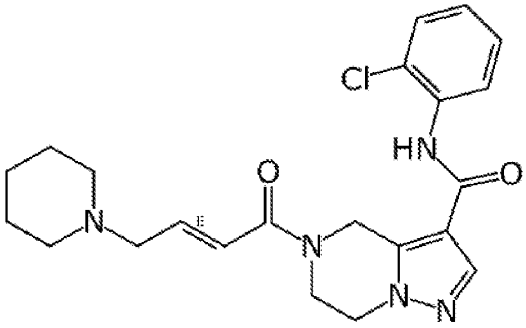
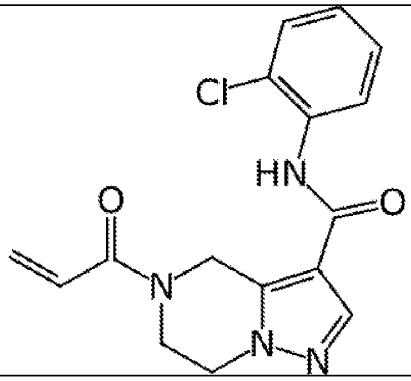
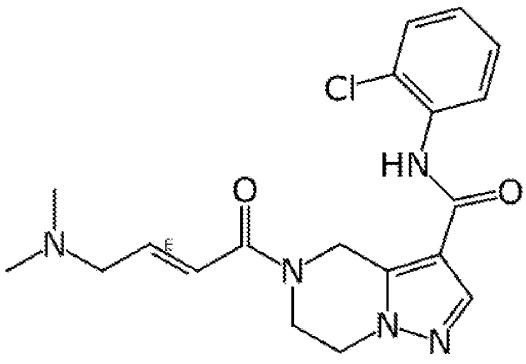
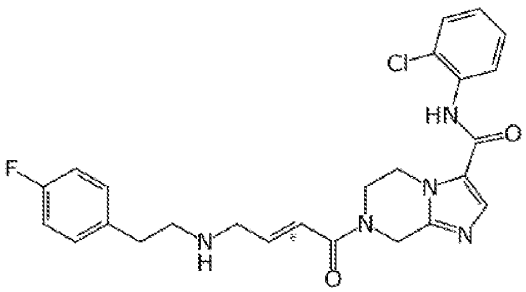
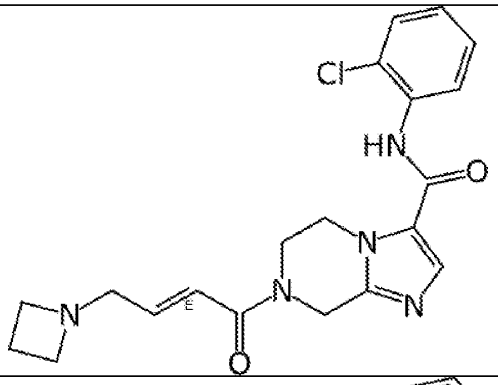
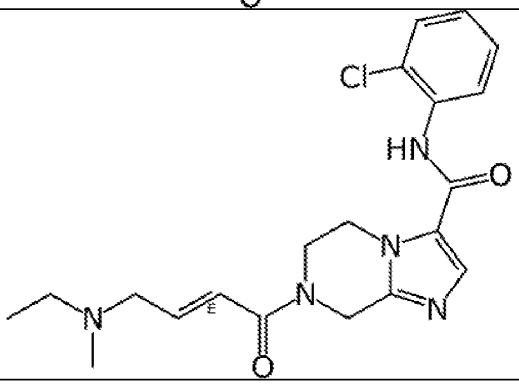
37		++++	+
38		++++	+

39		+	+
40		++	+
41		++	+
42		++	+

43		++++	+
44		++++	++
45		++++	+
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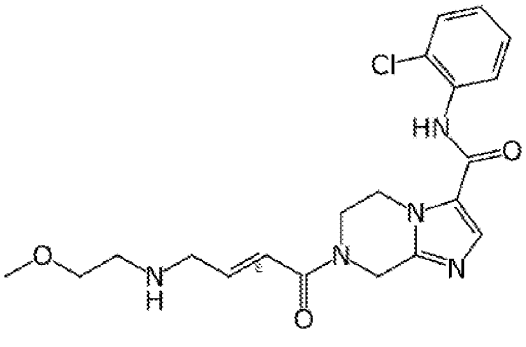
50		++++	+
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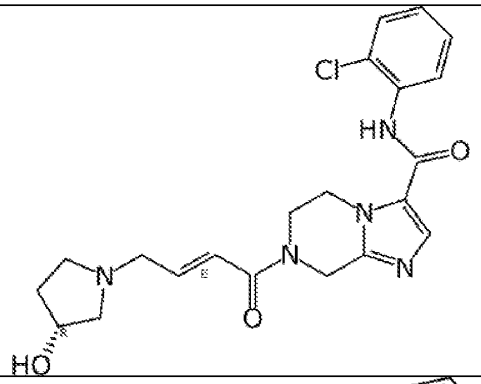
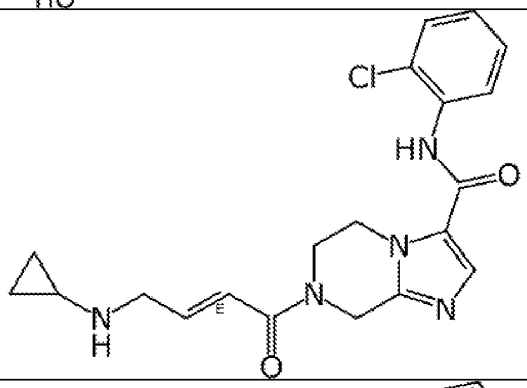
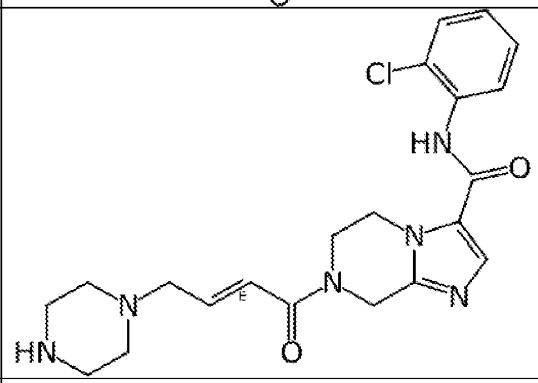
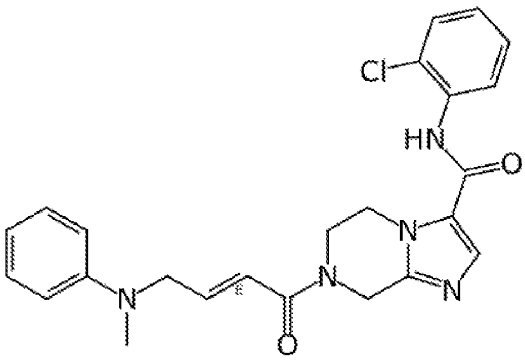
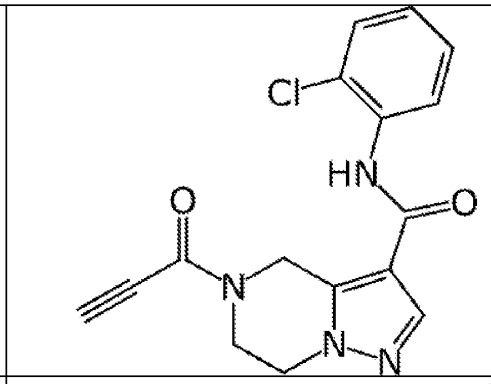
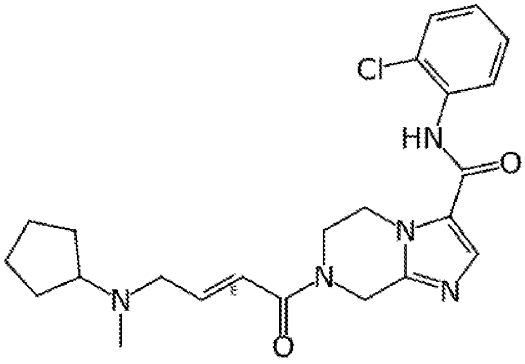
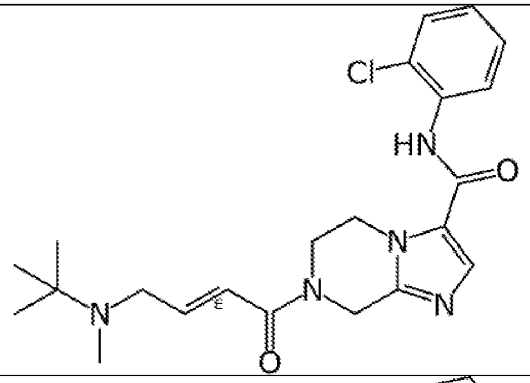
52		++++	+
53		++++	+
54		++	+
55		++	+

56		++++	+
57		++++	+
58		++++	+
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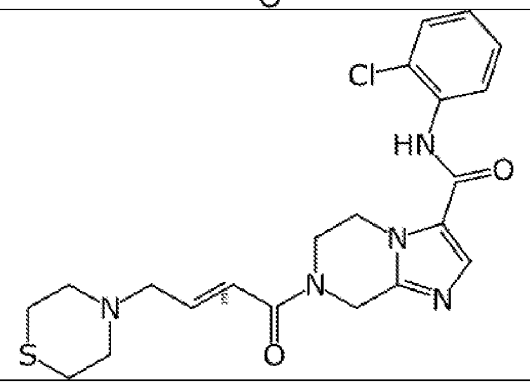
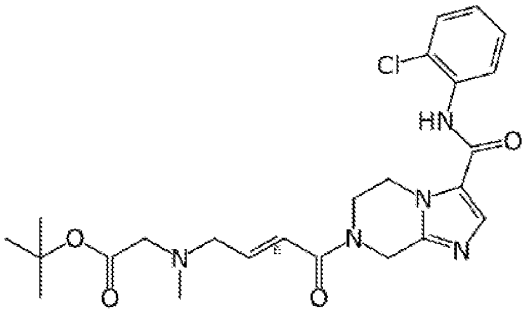
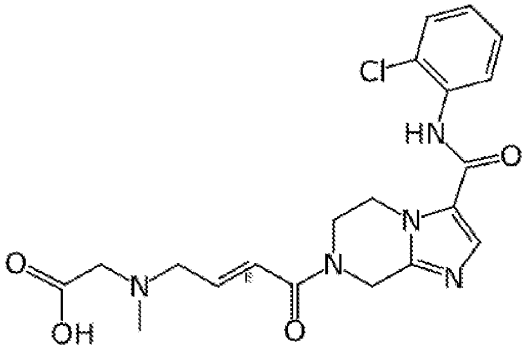
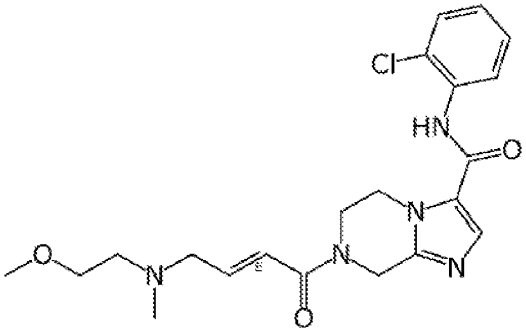
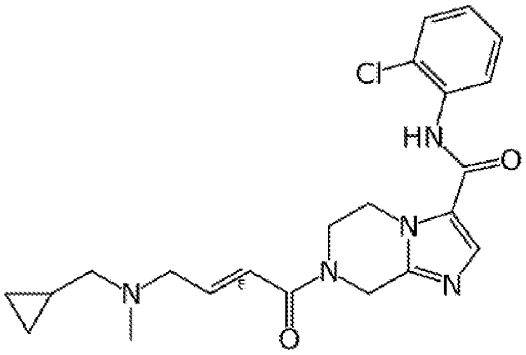
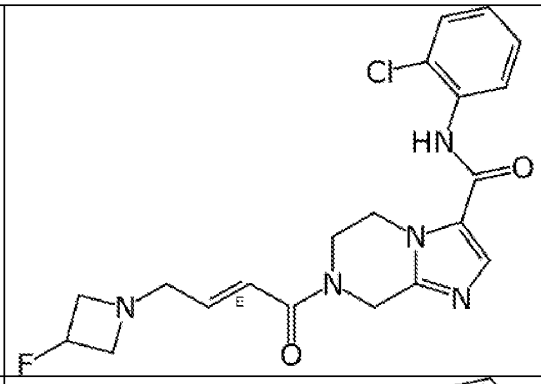
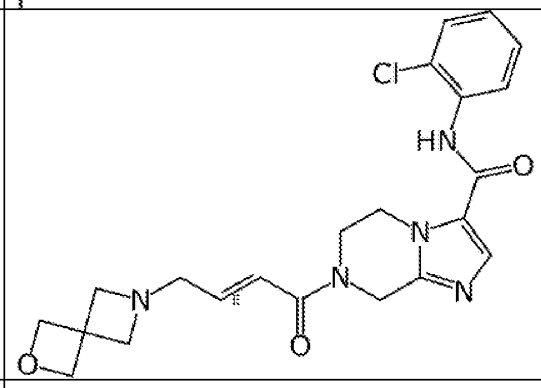
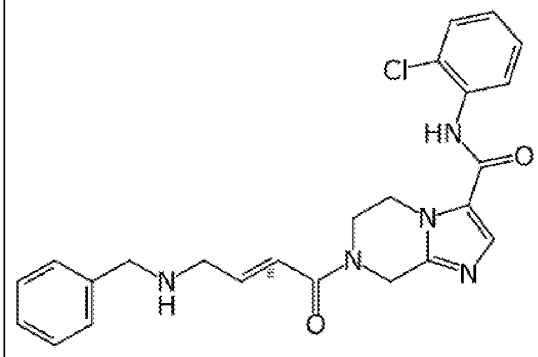
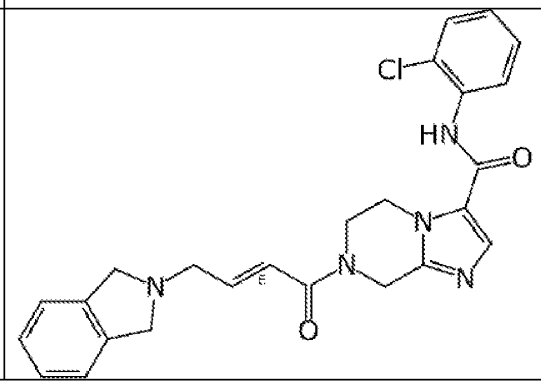
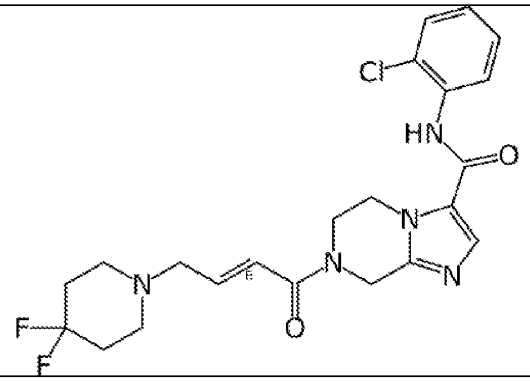
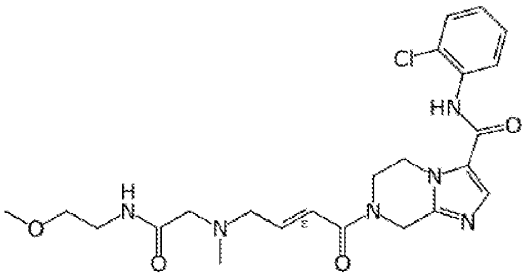
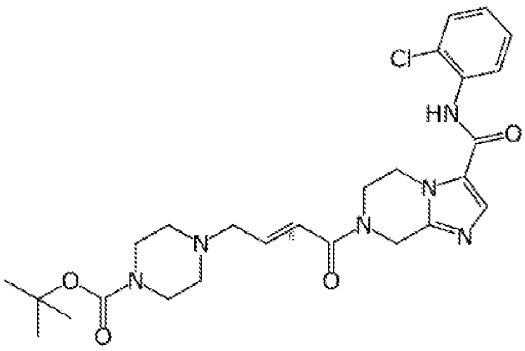
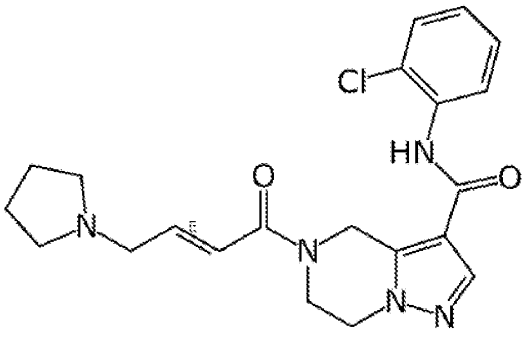
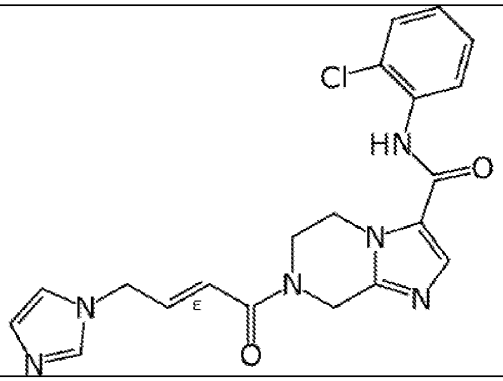
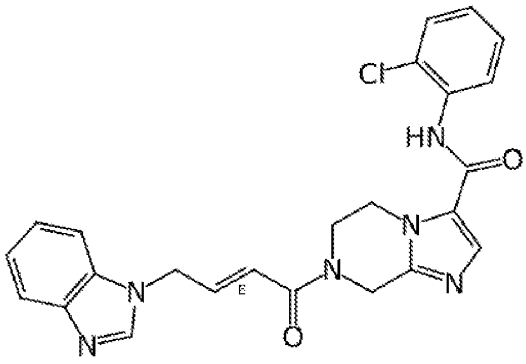
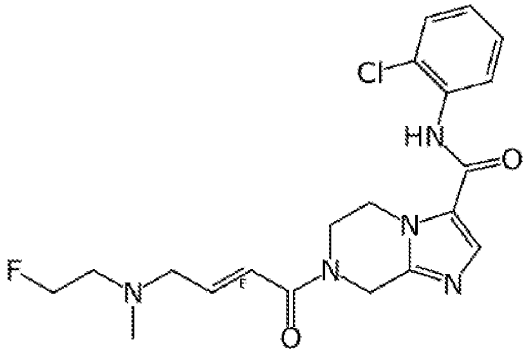
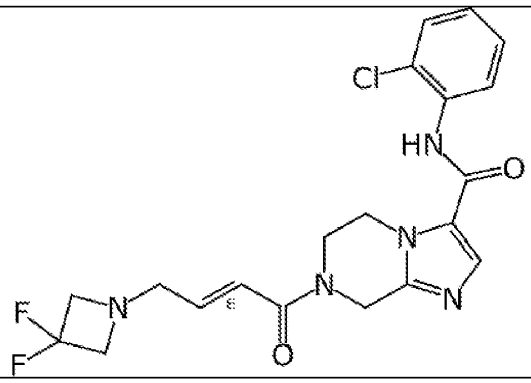
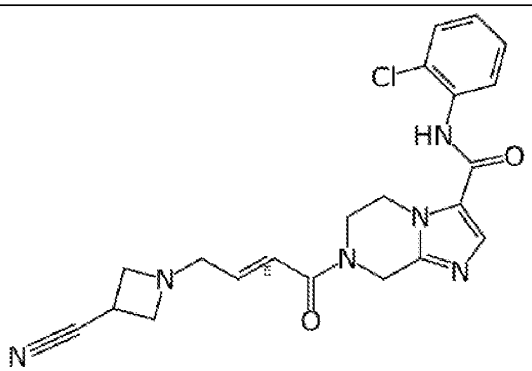
60		+++	+

61		++++	+
62		+++	+
63		++++	+
64		++++	+

65		++++	+
66		++++	+
67		++++	+
68		++++	+

69		++	+
70		++	+
71		++	+
72		++	+

73		+++	+
74		++	+
75		++++	+
76		++	+

77		+++	+
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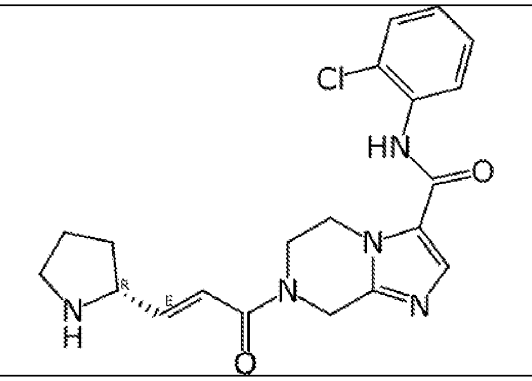
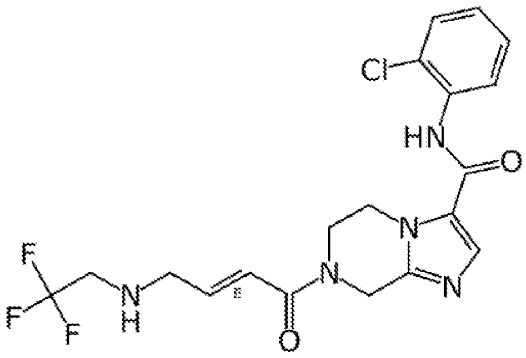
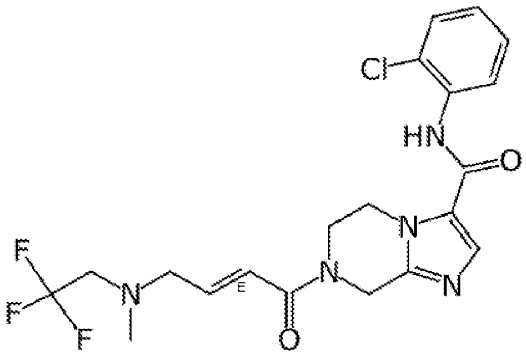
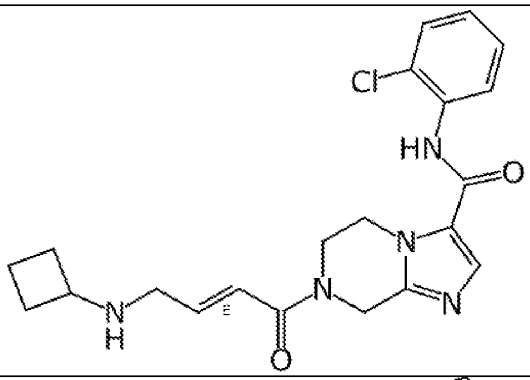
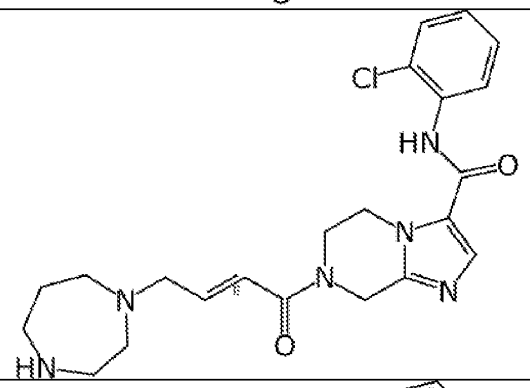
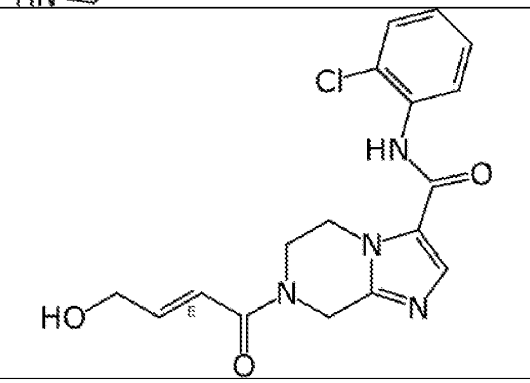
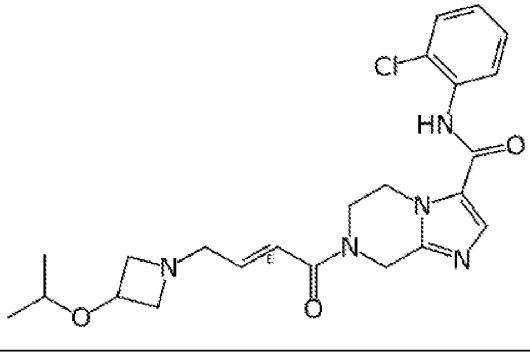
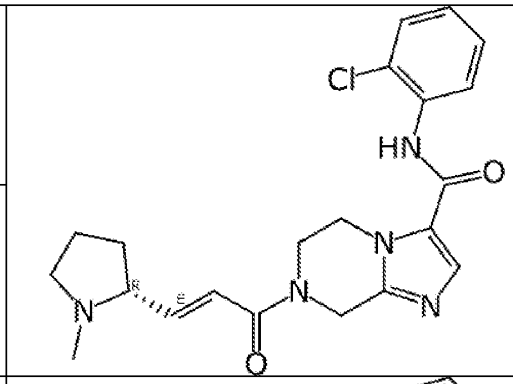
79		++++	+
80		+++	+
81		++	+

82		++++	+
83		++++	+
84		+++	+
85		++++	+

86		++++	
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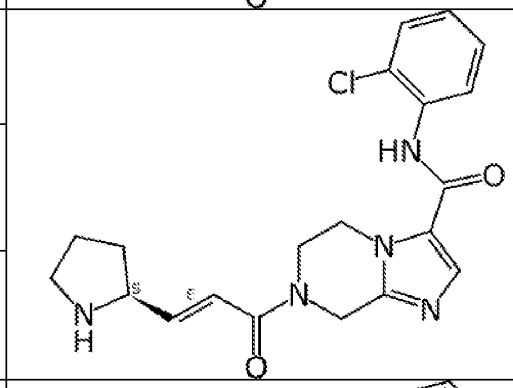
88		++++	
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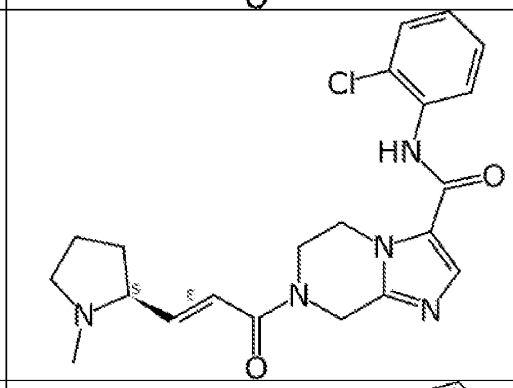
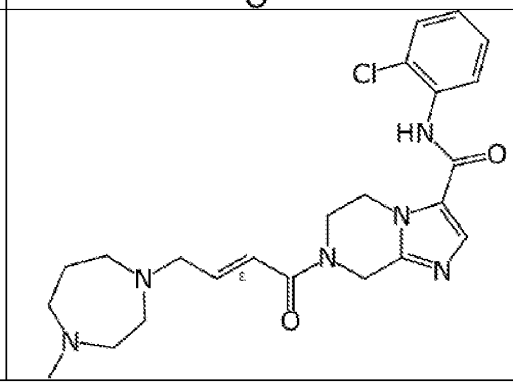
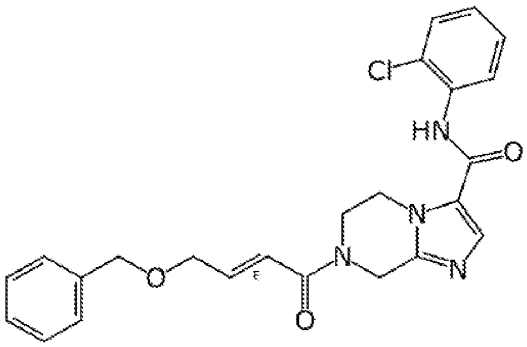
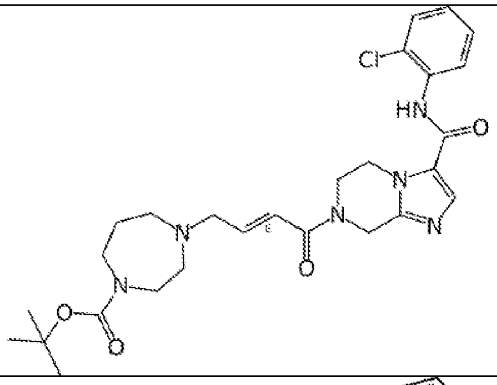
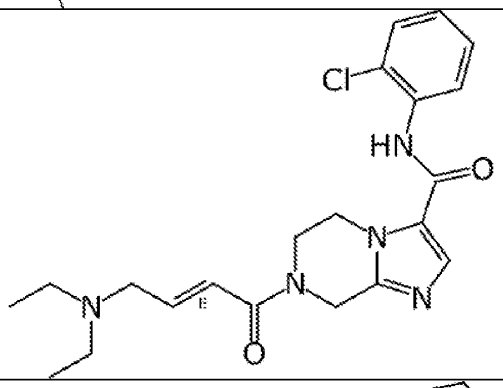
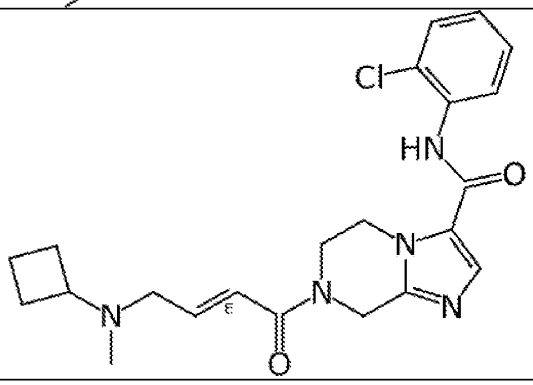
91		++++	+
92		++	+

93		++	+
94		++++	+
95		++++	+
96		++++	+
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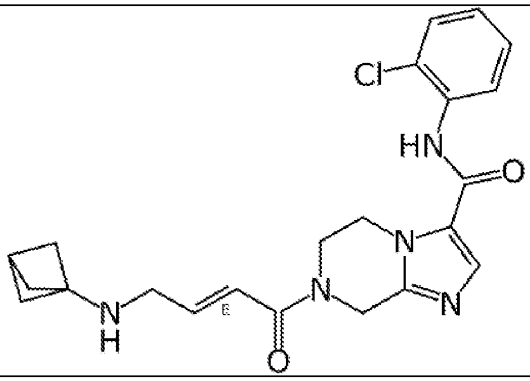
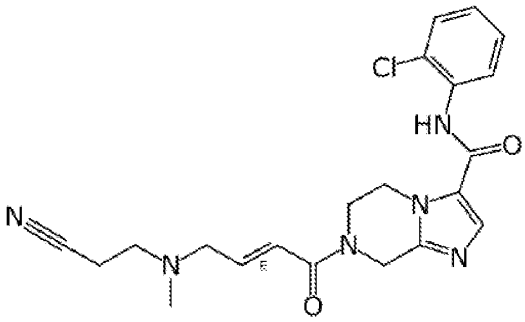
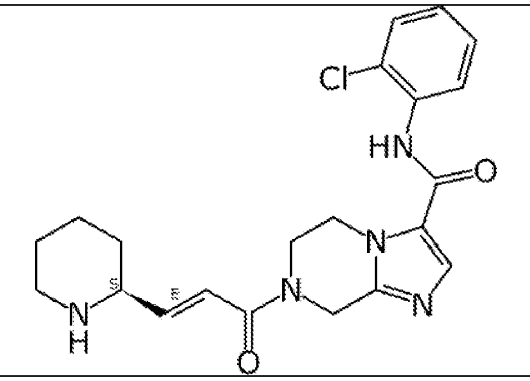
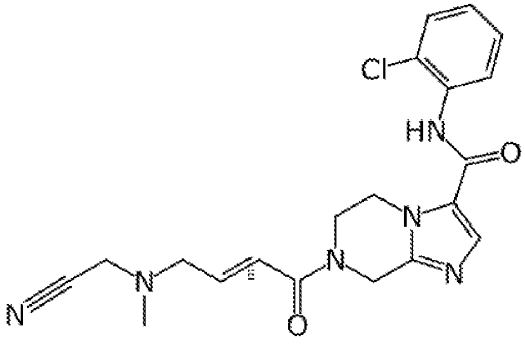
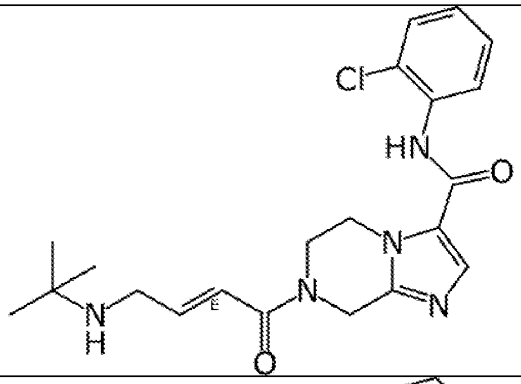
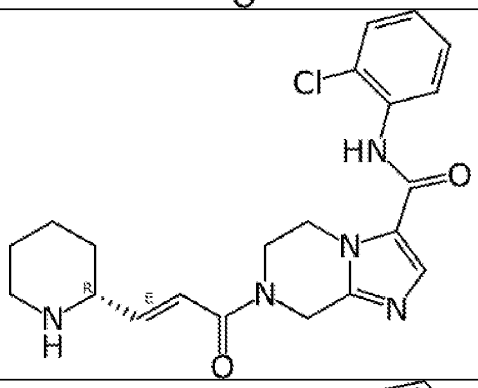
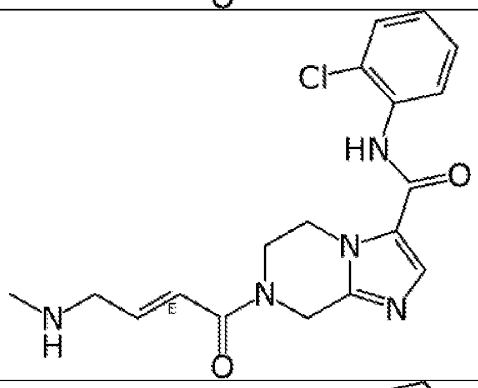
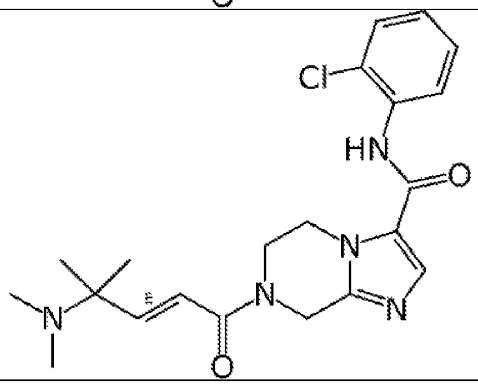
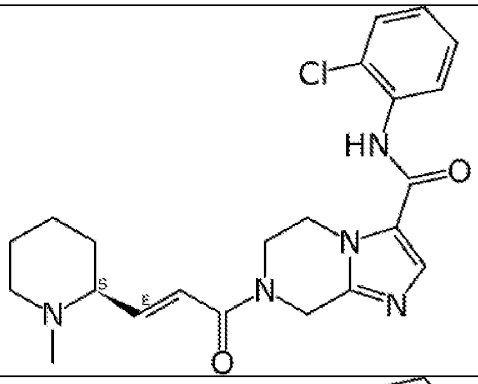
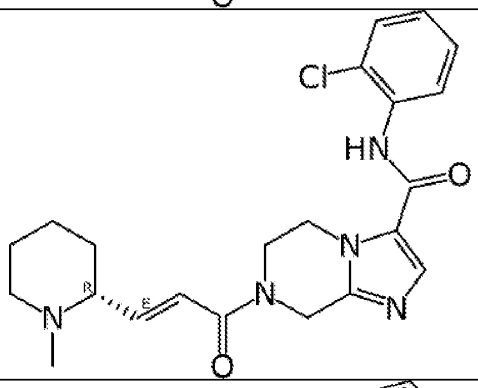
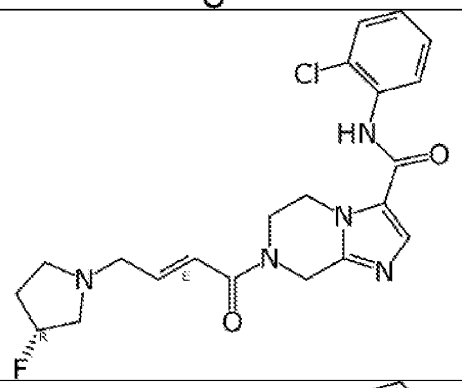
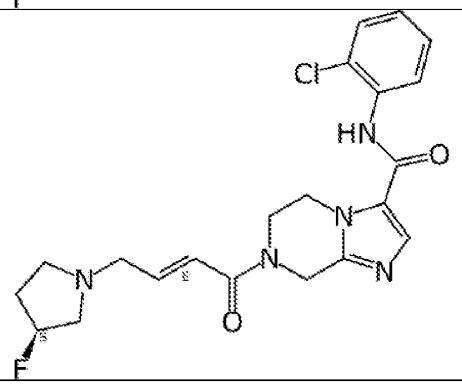
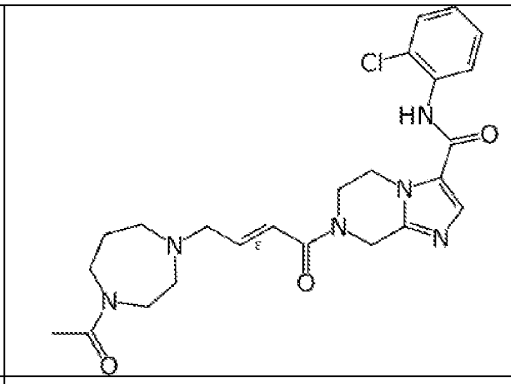
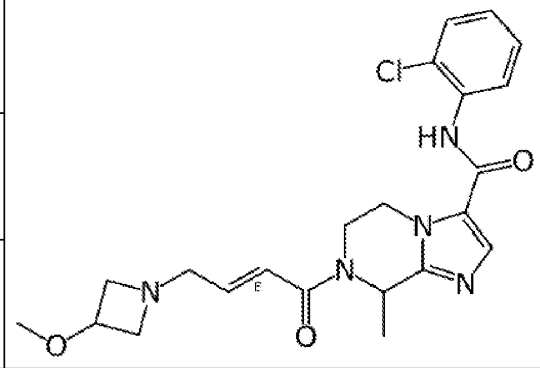
98		++++	+
99		++	+
100		++++	+
101		+++	+

102		++++	+
103		++++	+
104		++++	+
105		++	+

106		++	+
107		++	+
108		++++	+
109		++++	+

110		+++	+
111		+++	+
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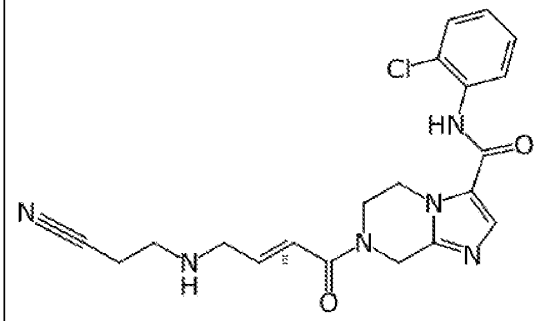
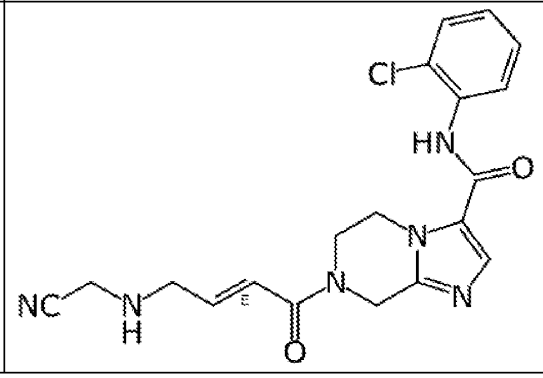
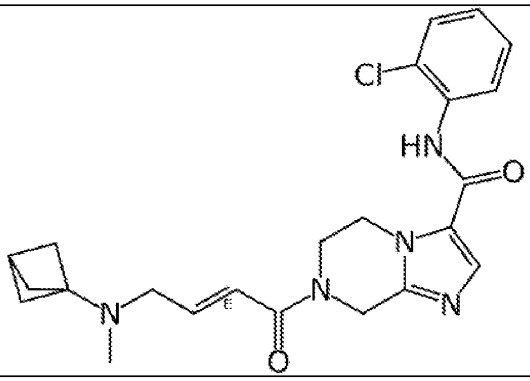
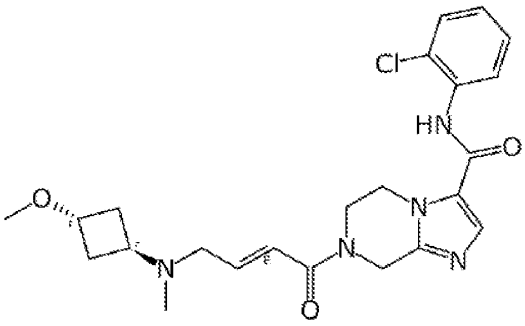
114		++++	+
115		++	+

116		+++	+
117		++++	+
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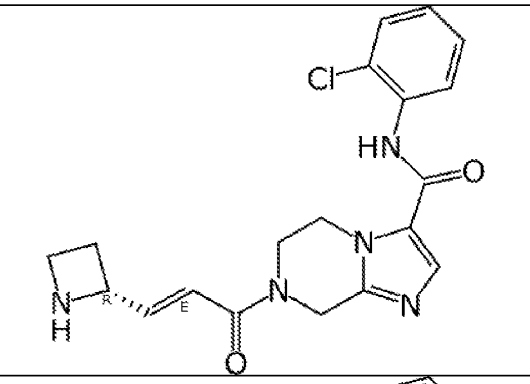
119		++++	
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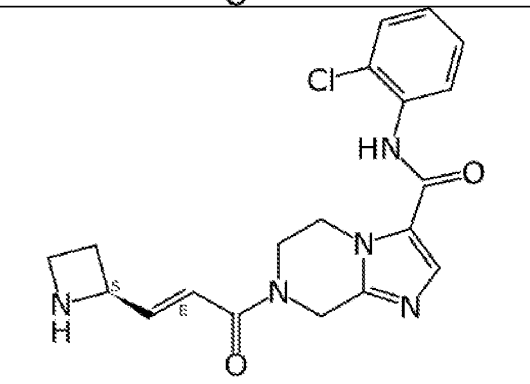
121		++++	
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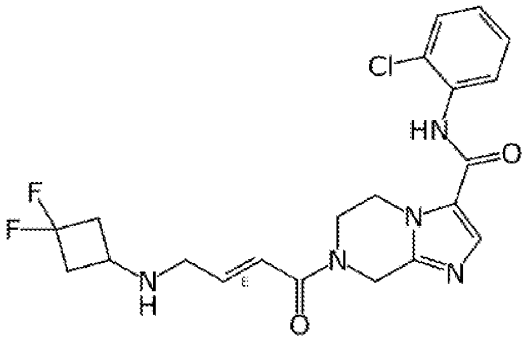
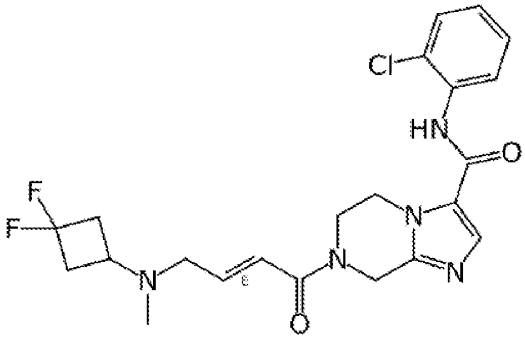
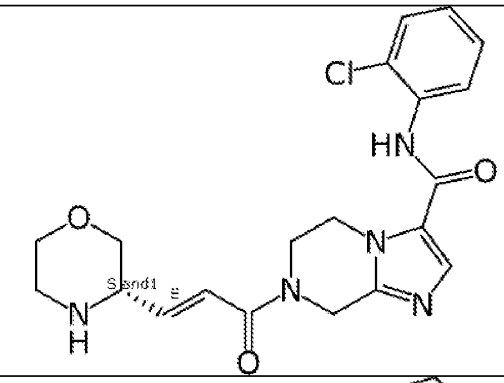
123		++++	+
124		+++	+
125		++++	+
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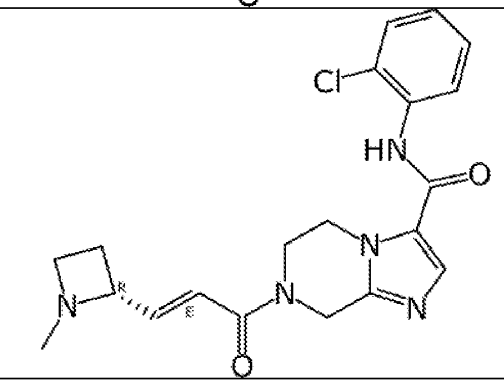
127		++++	
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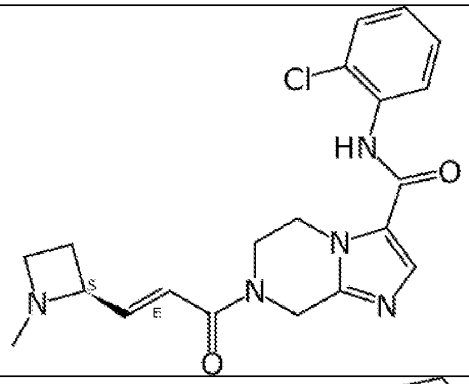
129		++++	
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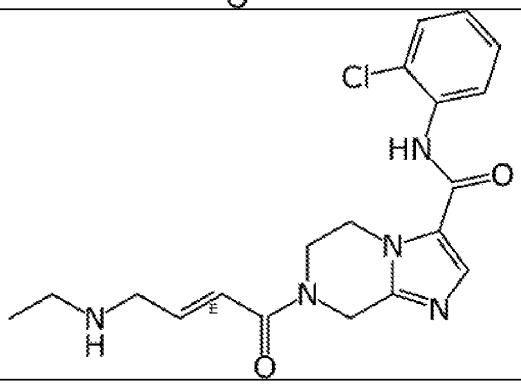
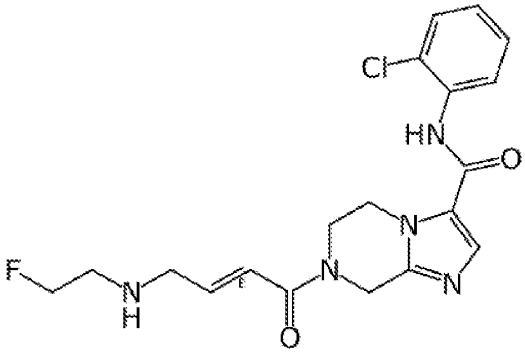
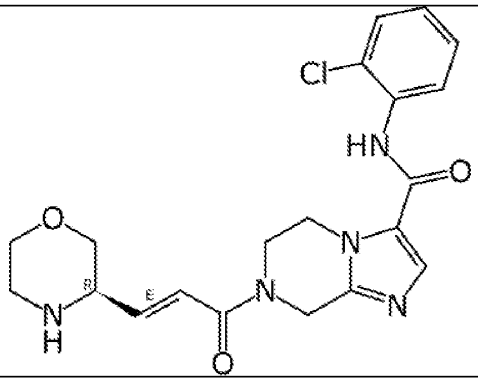
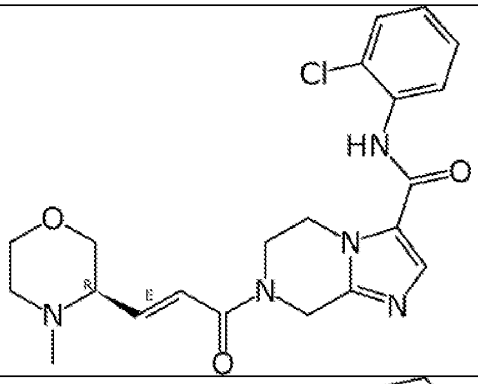
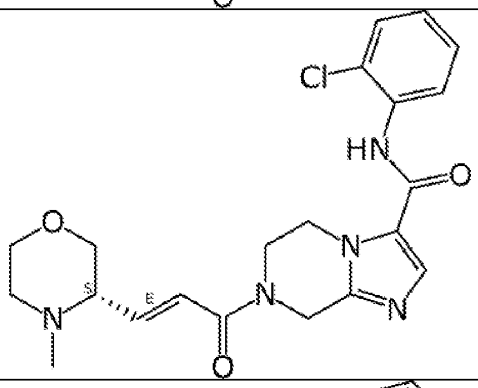
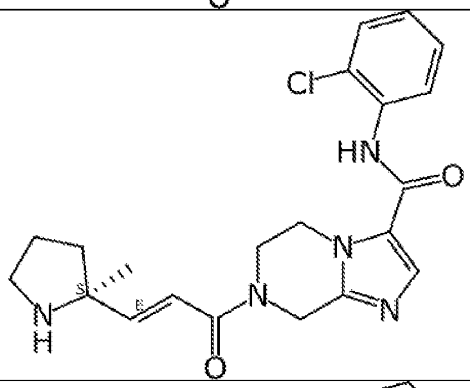
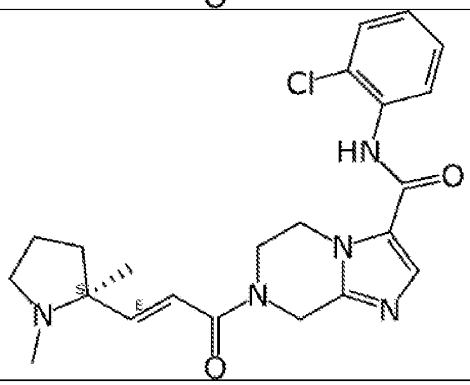
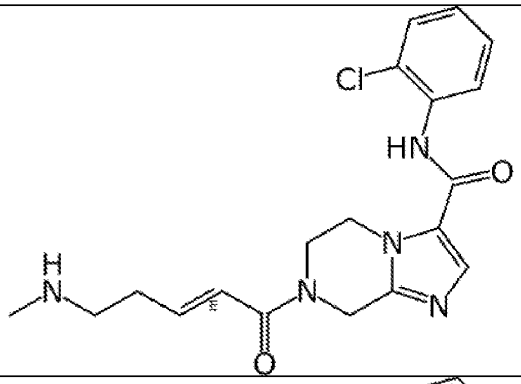
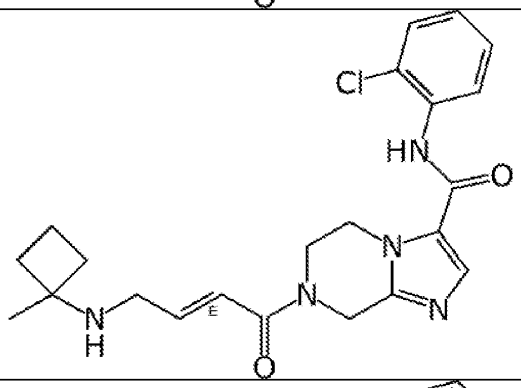
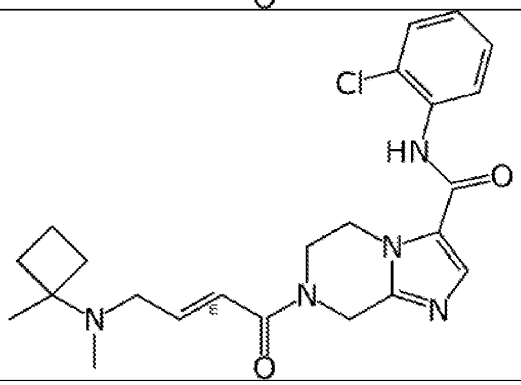
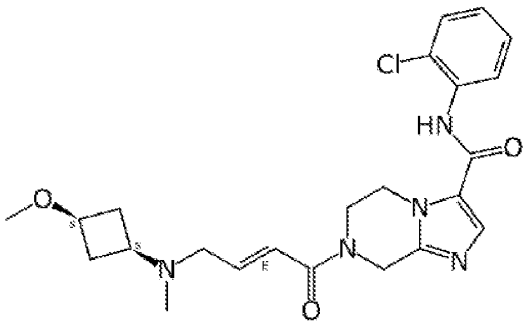
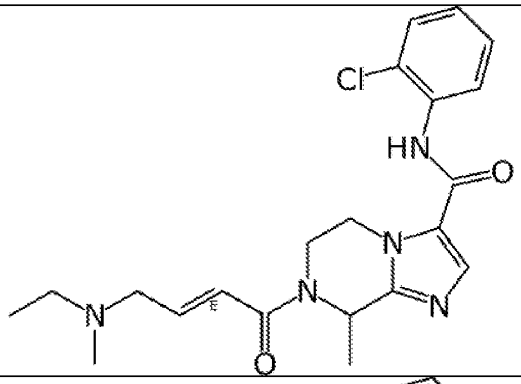
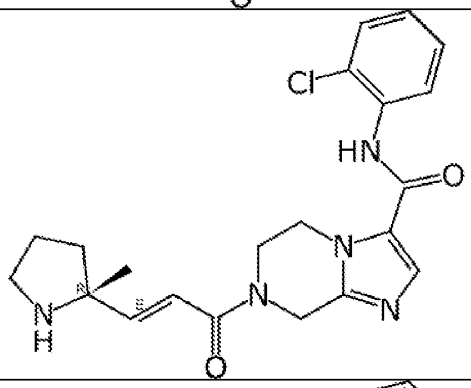
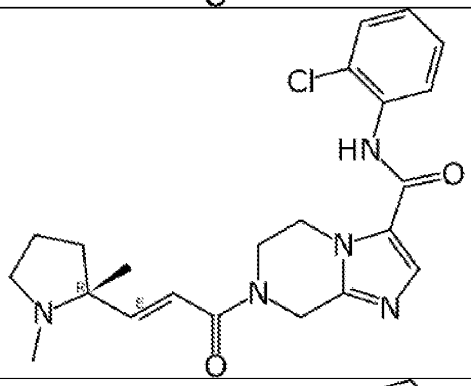
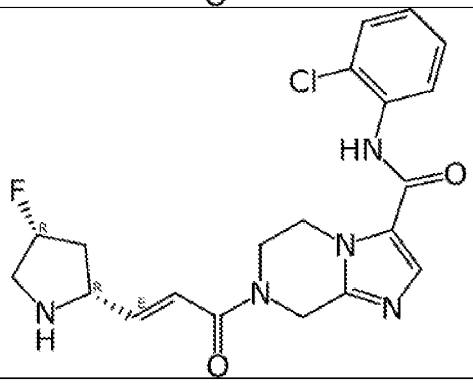
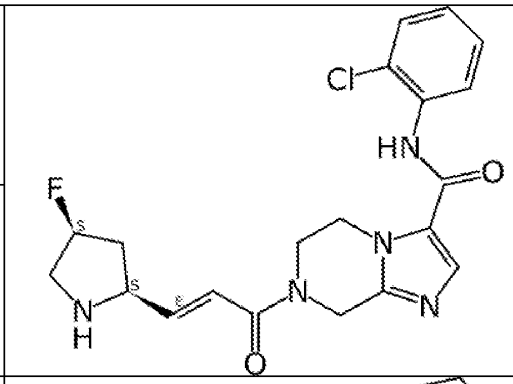
131		++++	+
132		++++	+
133		++++	+

134		+	+
135		+	+
136		++++	+
137		+++	+

138		+++	+
139		++++	+
140		++++	+
141		++++	+

142		+++	+
143		++++	+
144		++++	+
145		++++	+

146		++++	
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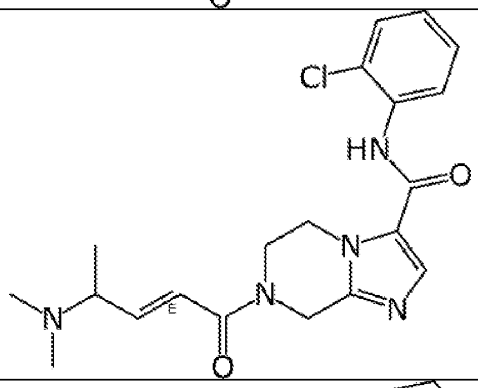
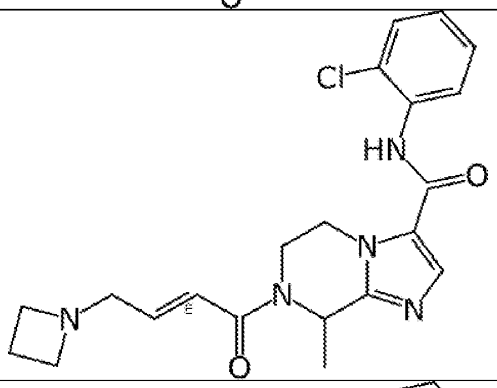
148		++++	+
149		++++	
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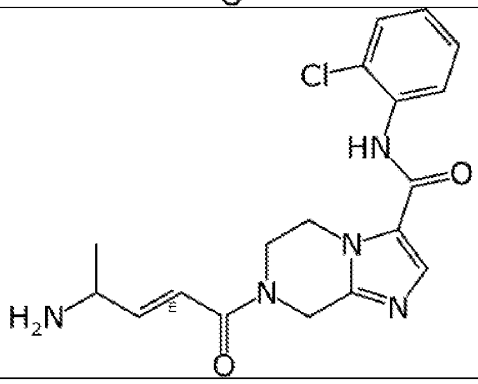
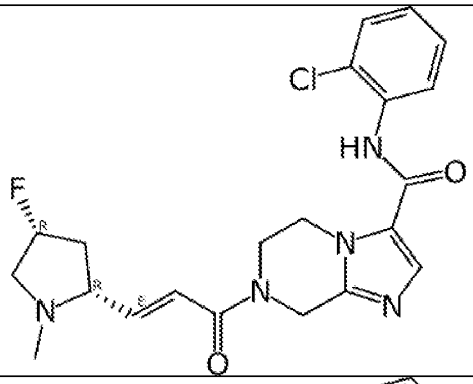
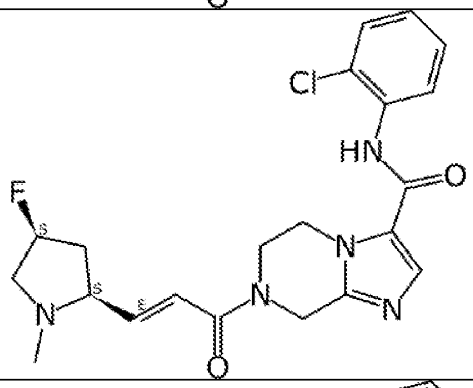
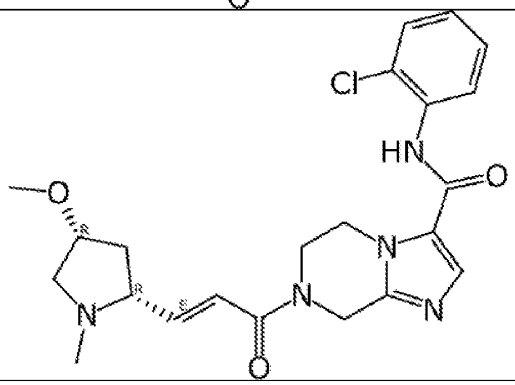
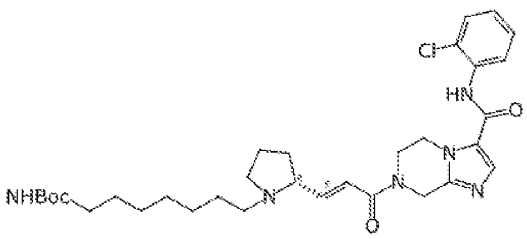
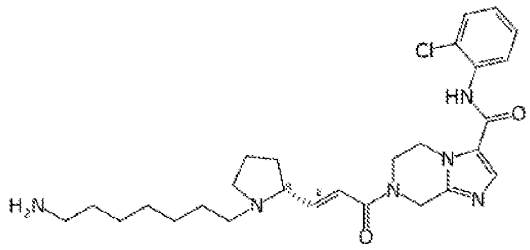
151		++++	+

152		++++	+
153		++++	+
154		++++	+
155		++++	+

156		++++	++
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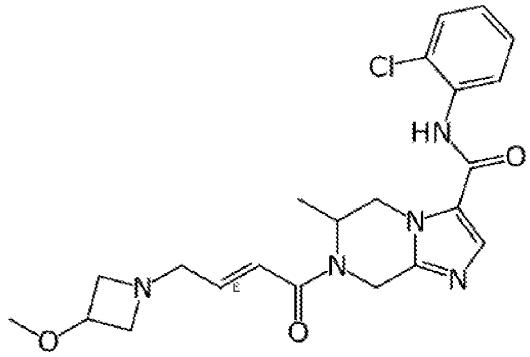
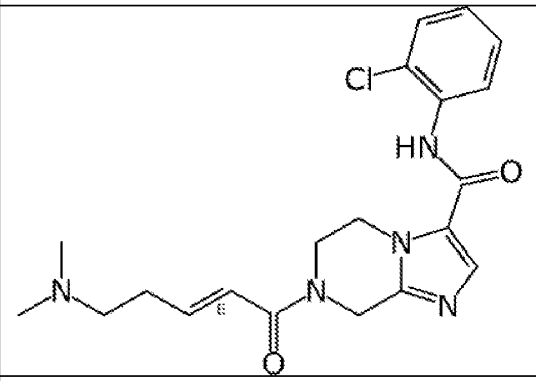
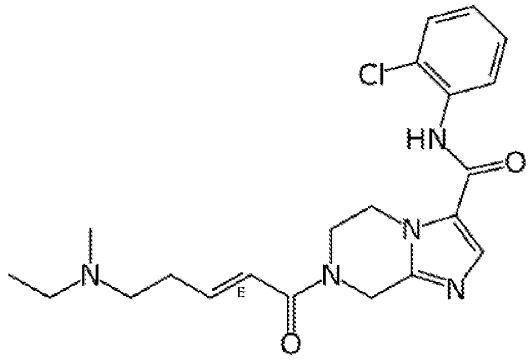
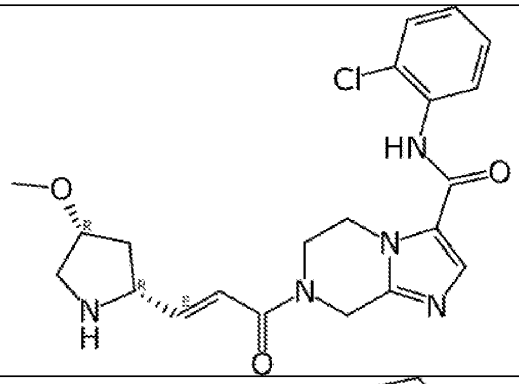
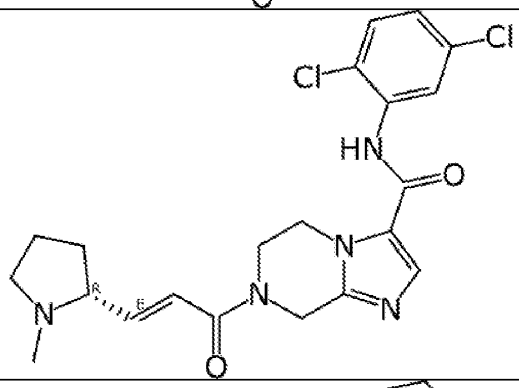
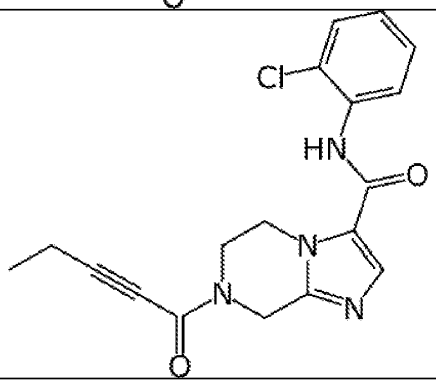
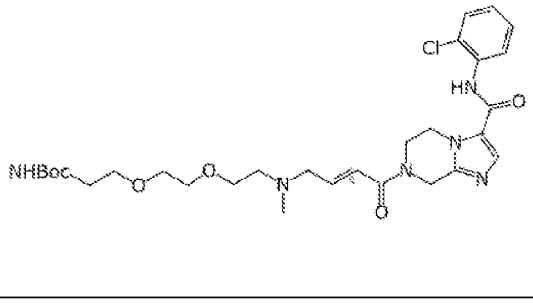
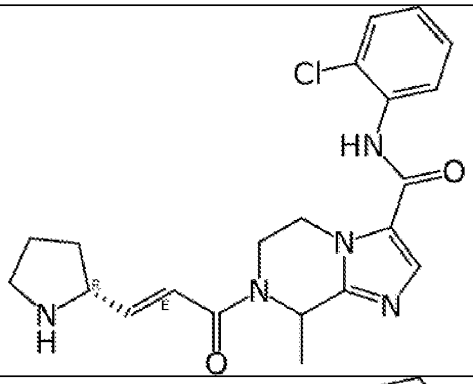
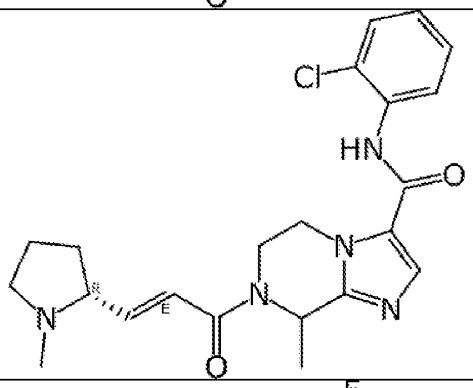
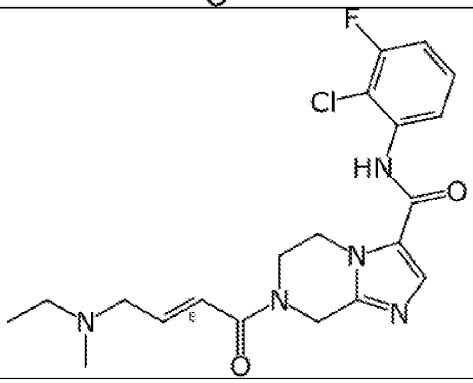
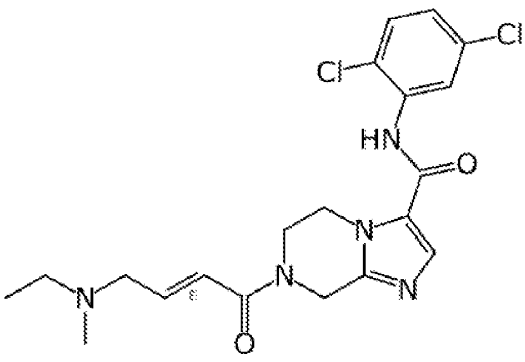
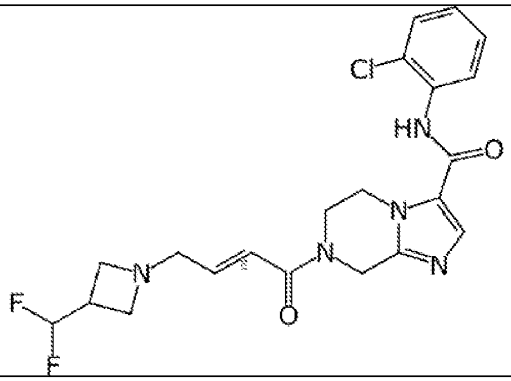
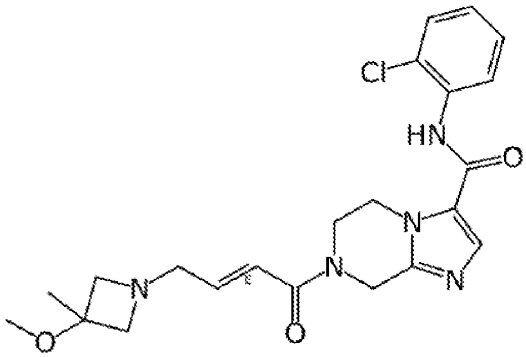
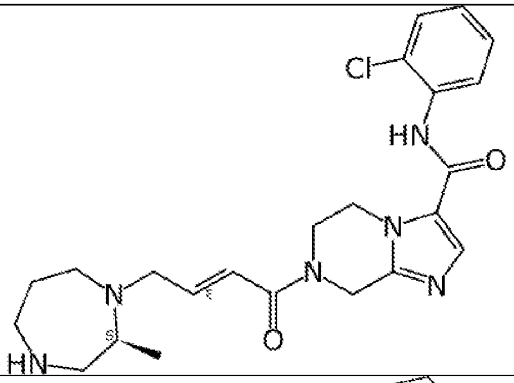
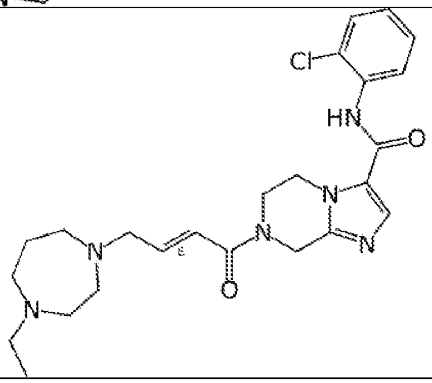
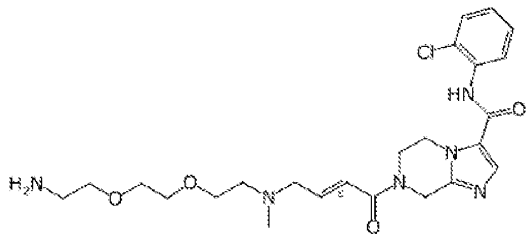
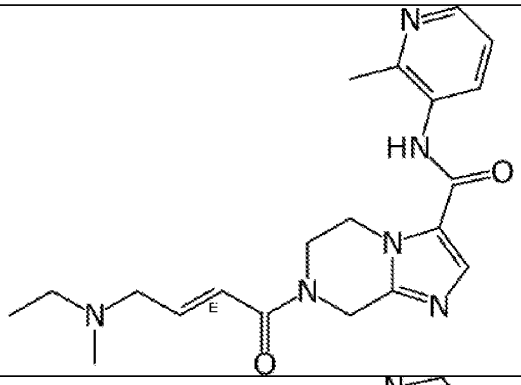
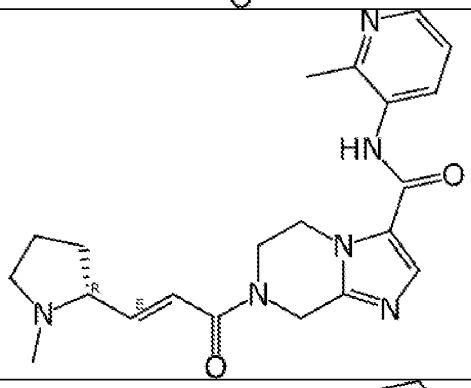
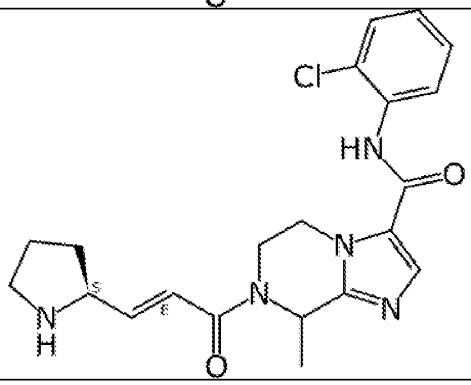
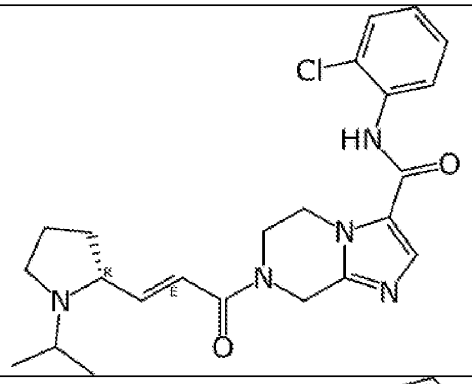
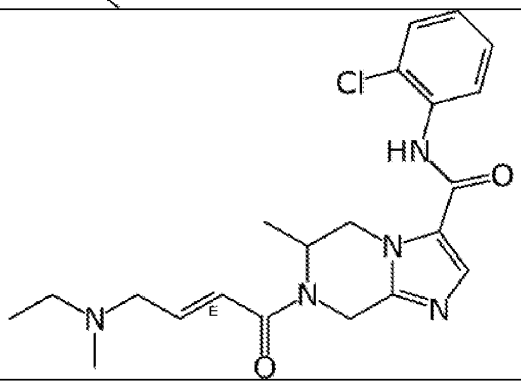
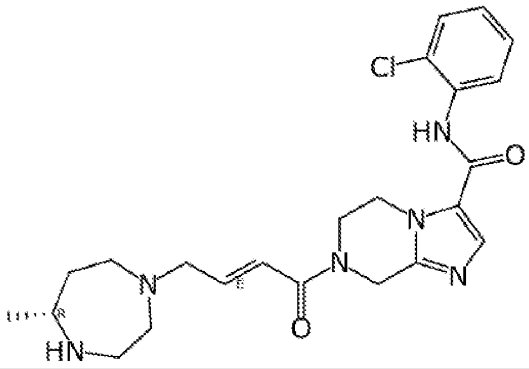
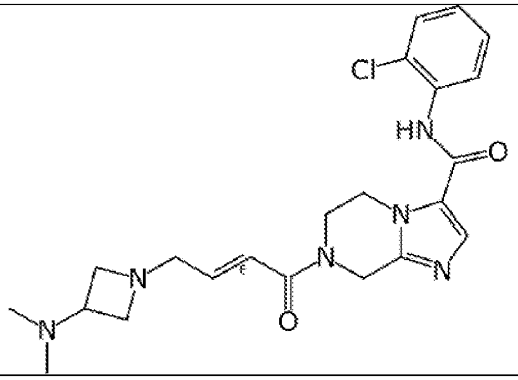
158		++++	+
159		+++	+
160		+++	+

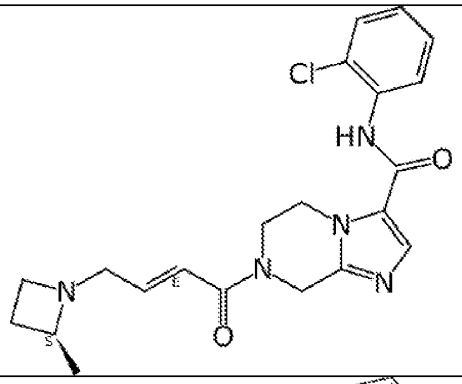
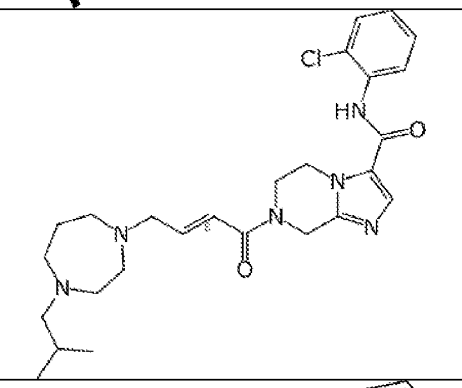
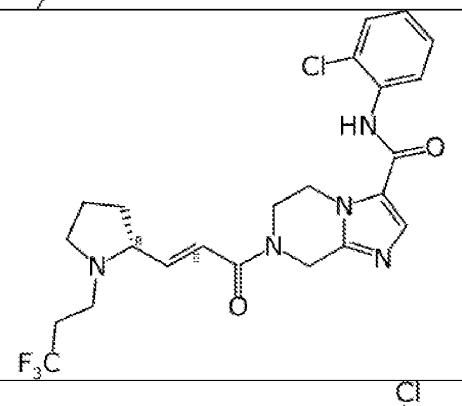
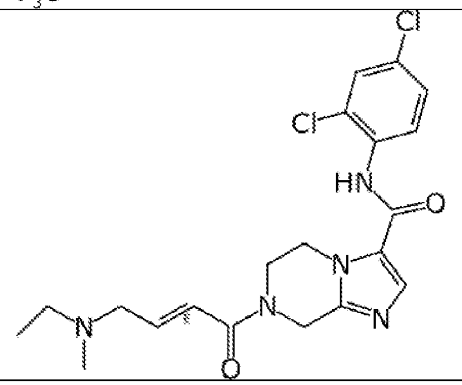
161		++++	+
162		++++	+
163		+++	+
164		++++	+

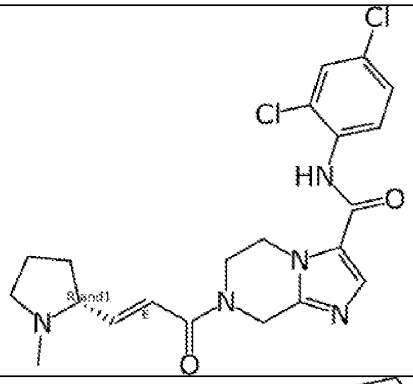
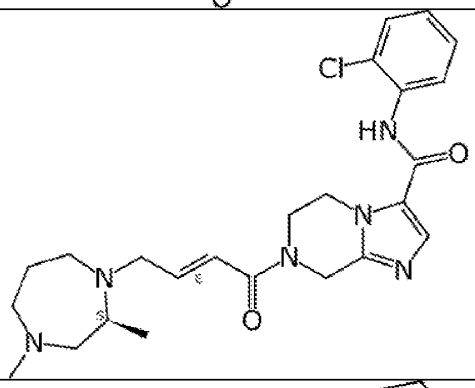
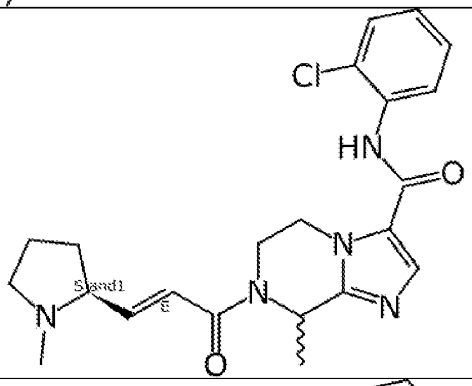
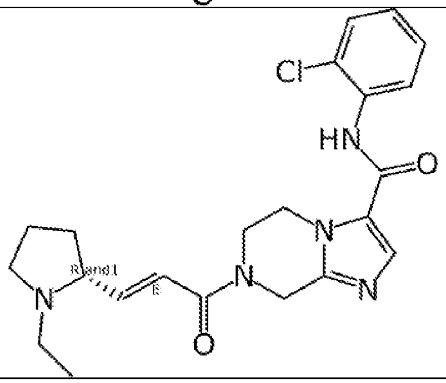
165		++++	+
166		++++	+
167		++++	
168		+++	+

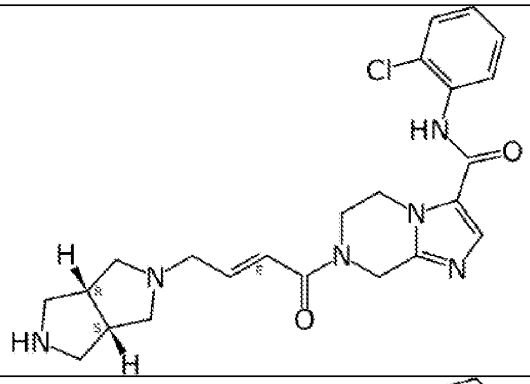
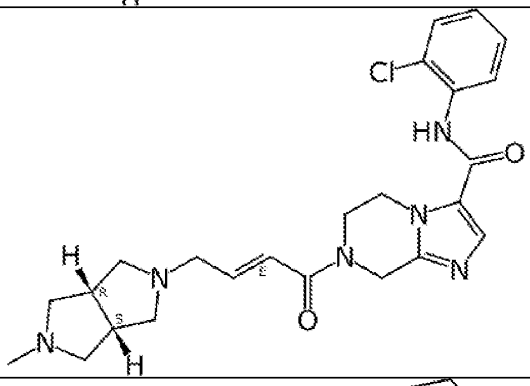
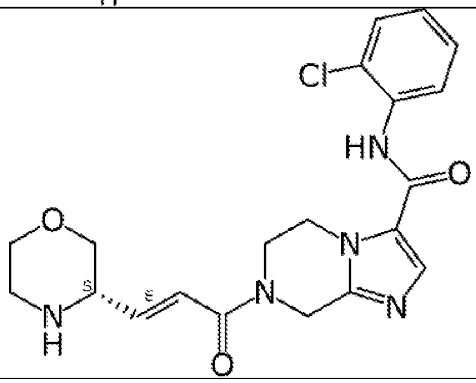
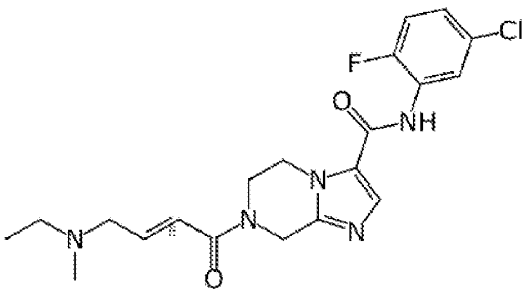
169		++++	+
170		++++	
171		++	
172		++	

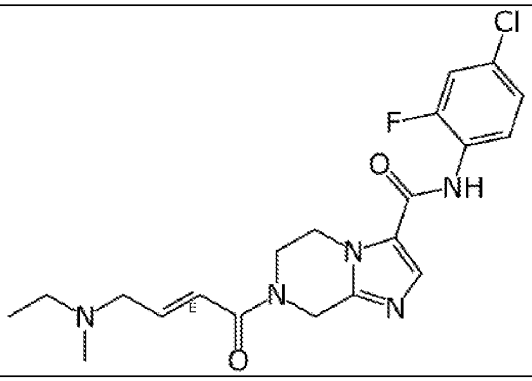
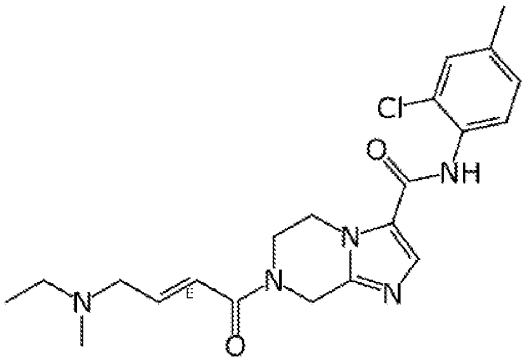
173		++++	
174		++	
175		++	
176		+++	

177		++++	
178		++++	
179		+	
180		++++	

181		++++	
182		++	
183		+++	
184		++++	+

185		++++	
186		++	
187		++	
188		++++	

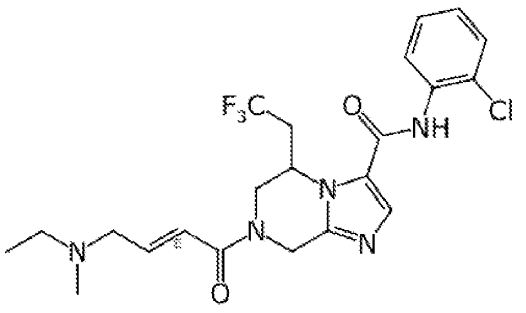
189		+	
190		+++	
191			
192		+	+

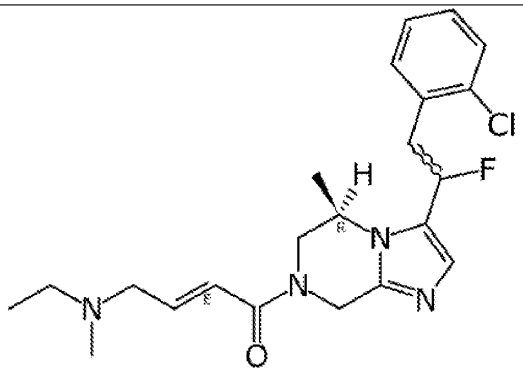
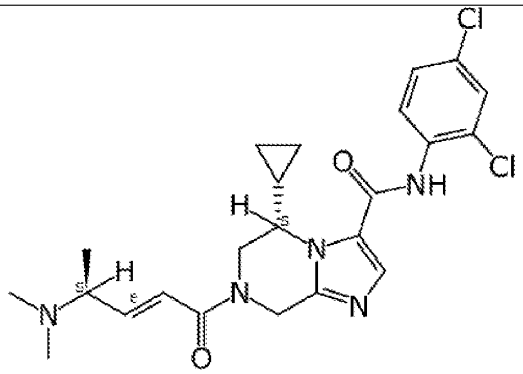
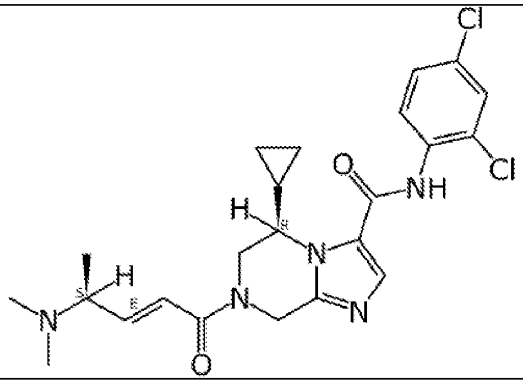
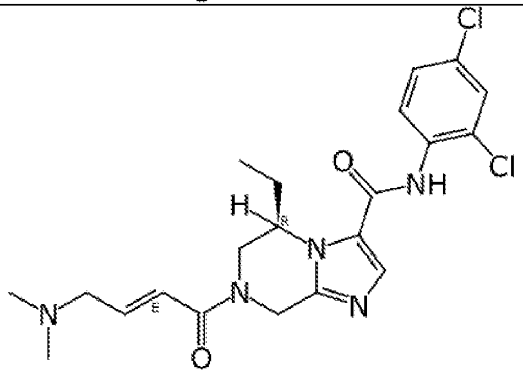
193		++	+
194		++++	+

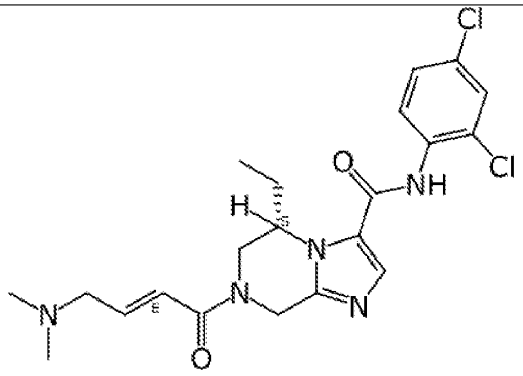
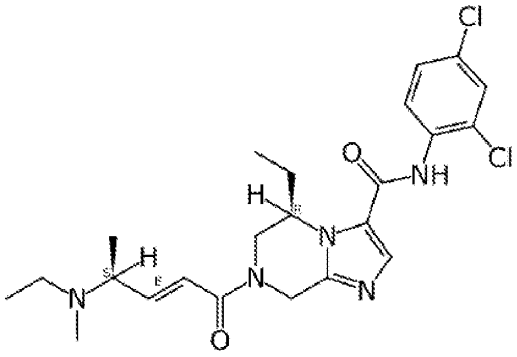
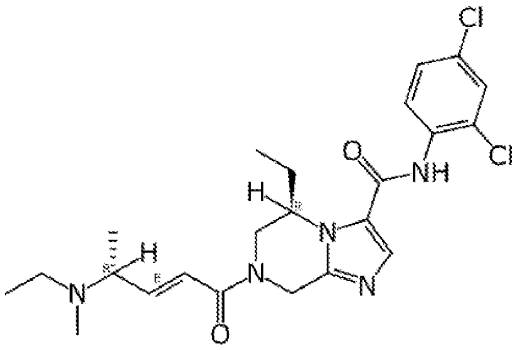
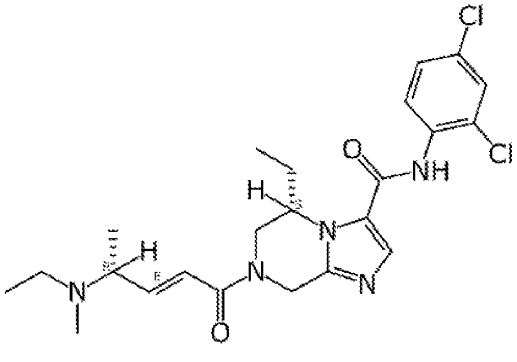
A: +: > 5 uM, ++: 0.5-5 uM, +++: 0.19-0.5 uM, ++++: < 0.19 uM

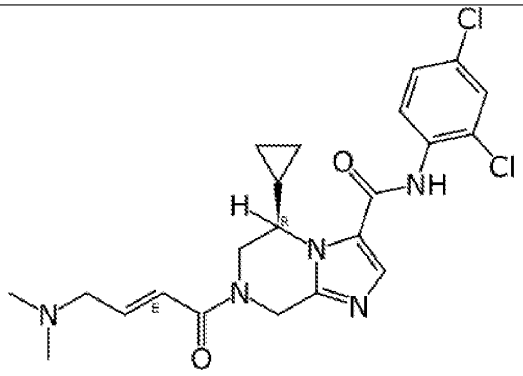
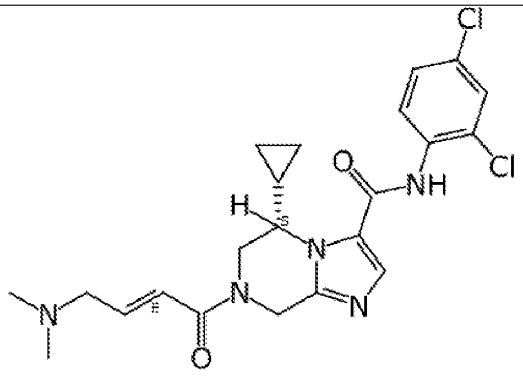
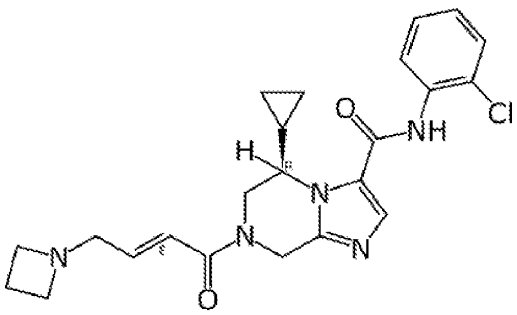
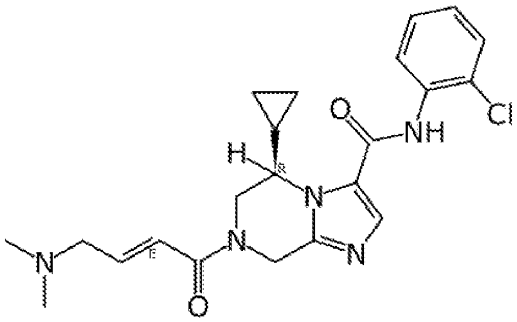
B: +: >1 uM, ++: 0.3-1 uM, +++: < 0.3 uM

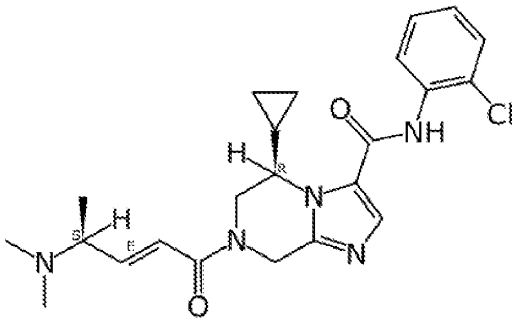
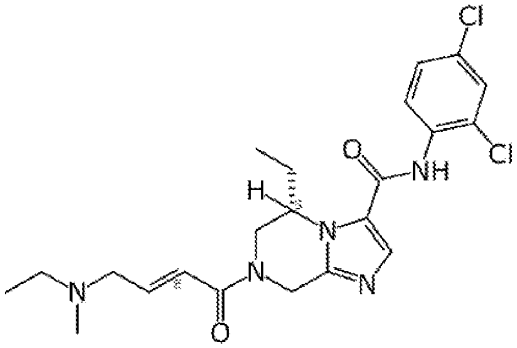
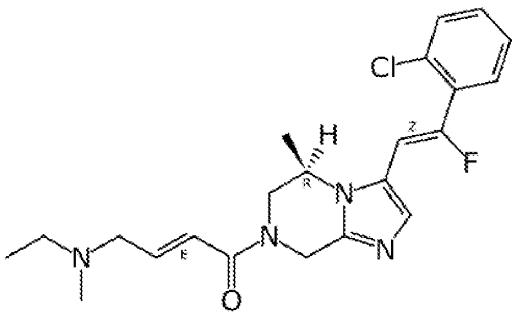
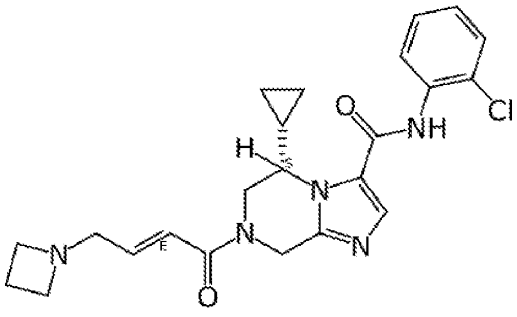
Table 4B.

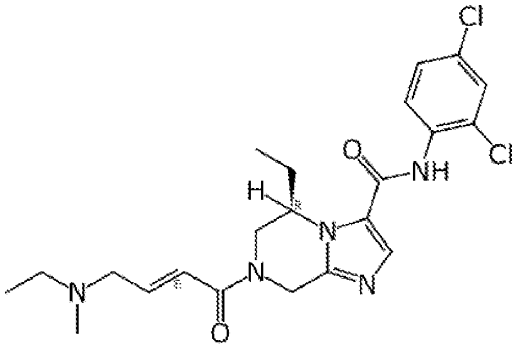
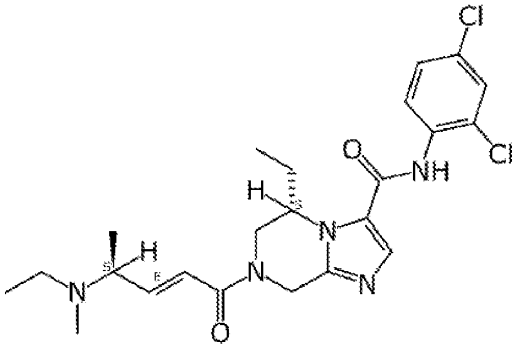
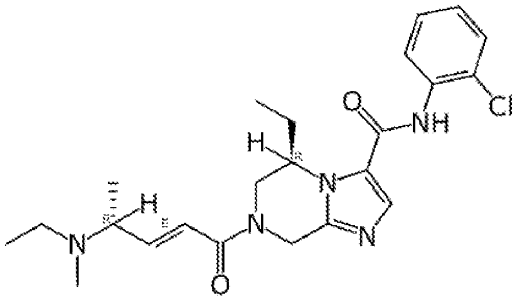
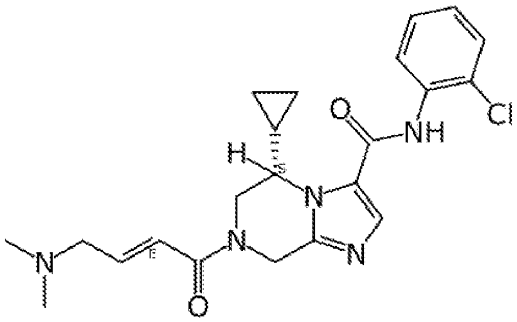
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
195		+++++	

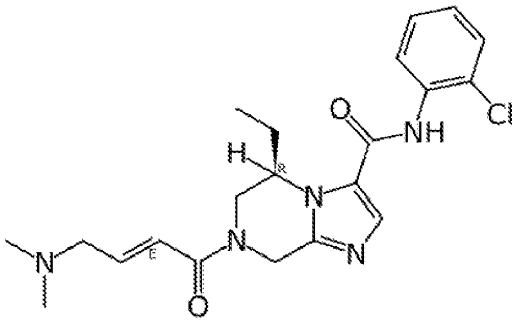
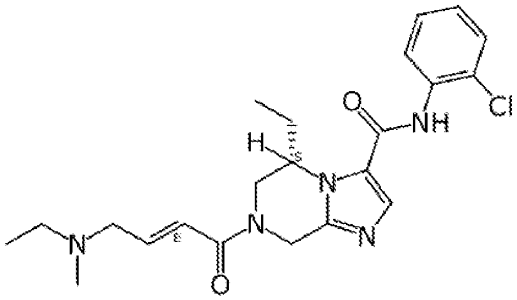
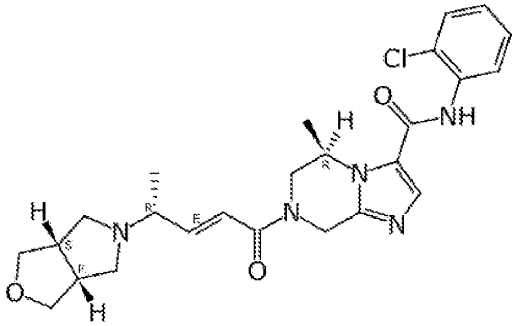
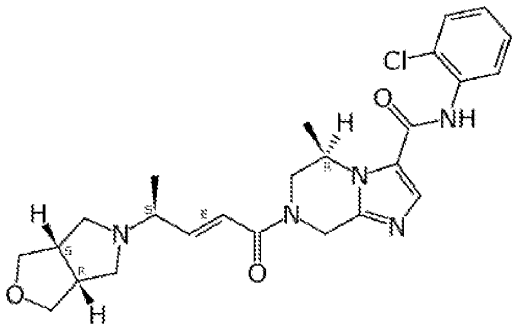
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
196		++++	
197		++++	
198		++	
199		++++	

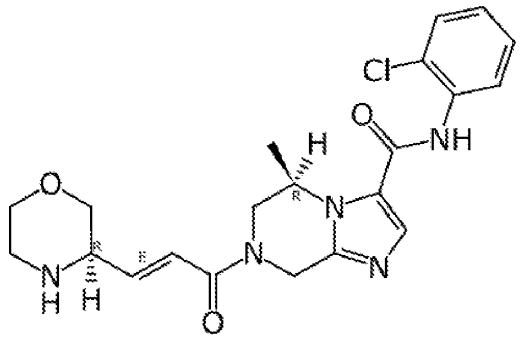
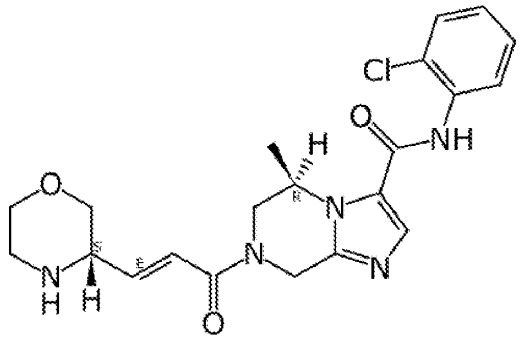
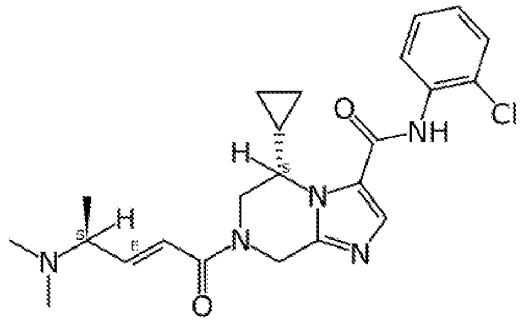
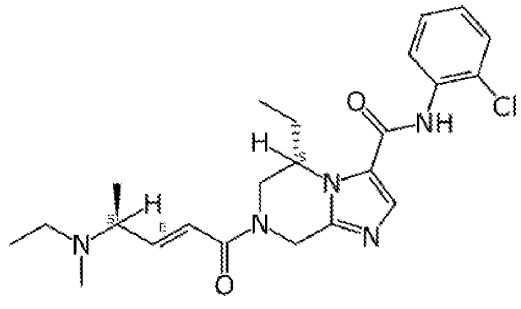
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
200		+++++	
201		++	
202		+	
203		++++	

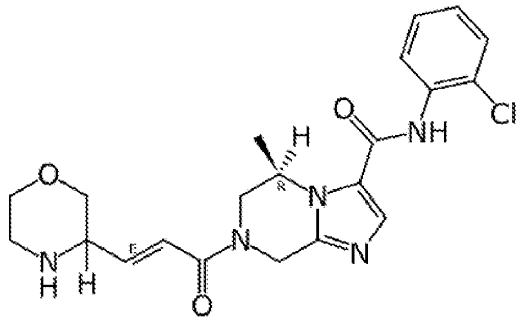
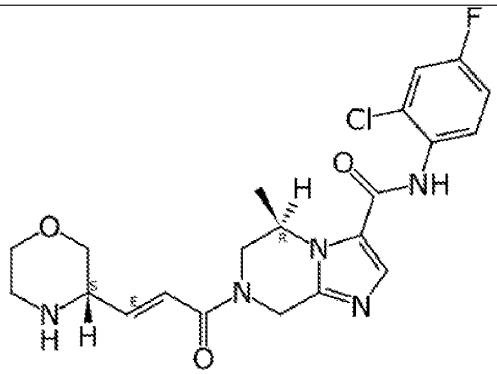
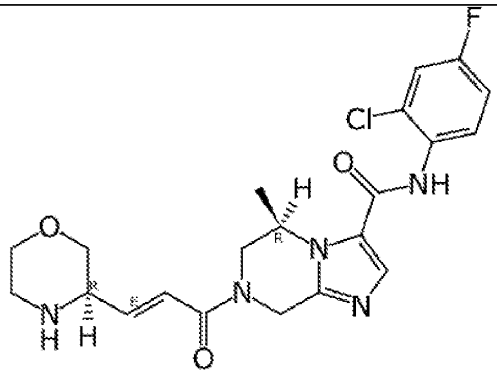
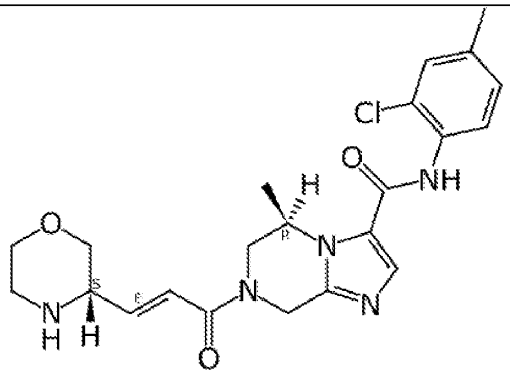
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
204		++++	
205		+++++	
206		+++++	
207		+++	

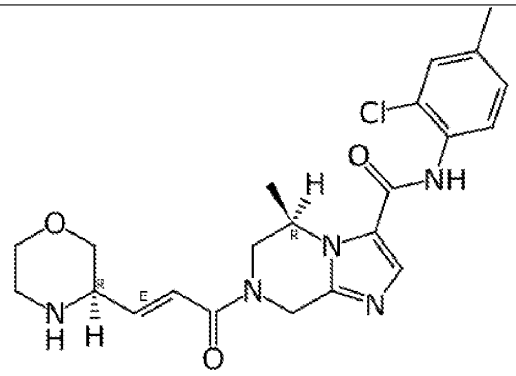
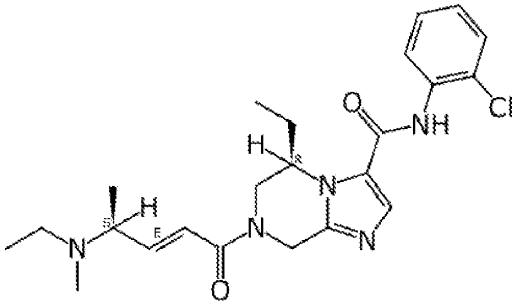
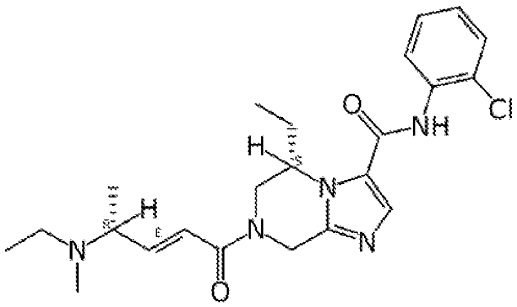
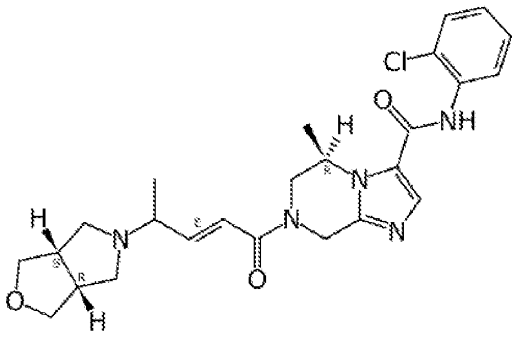
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
208		++	
209		+++++	
210		+	
211		++++	

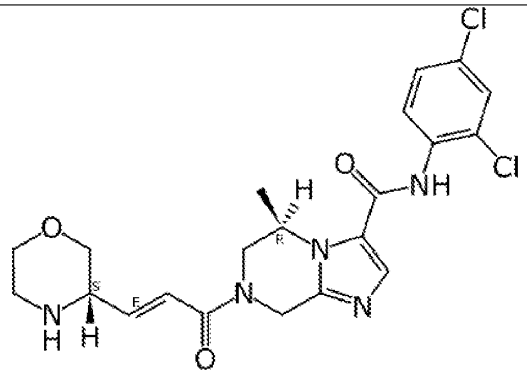
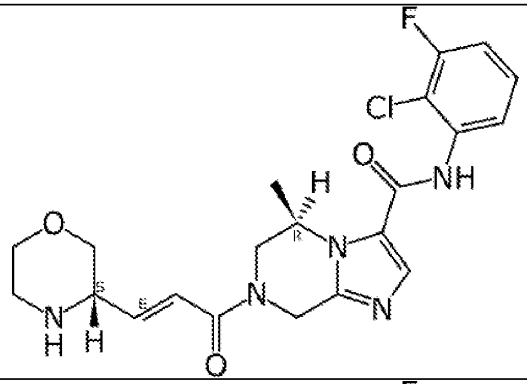
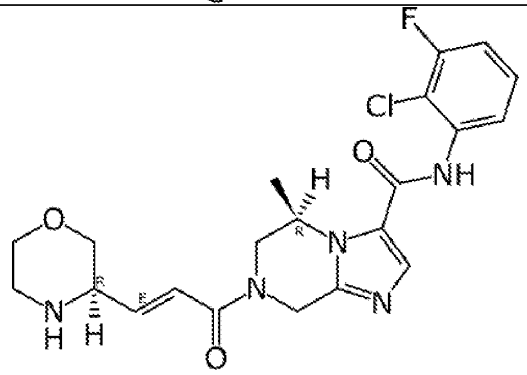
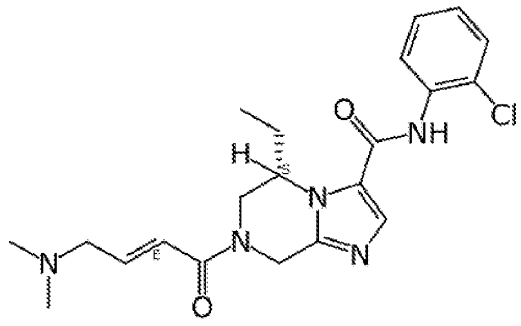
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
212		++++	
213		+++++	
214		+	
215		+++++	

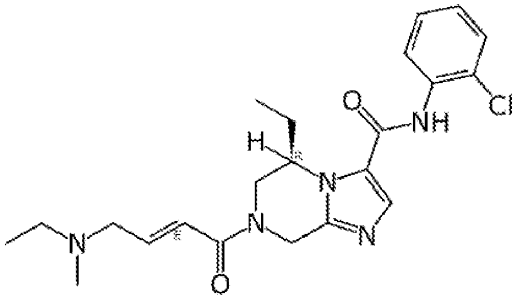
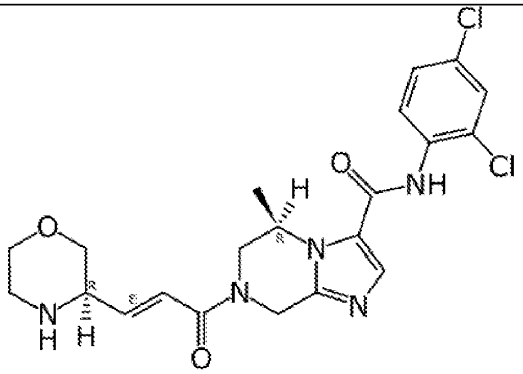
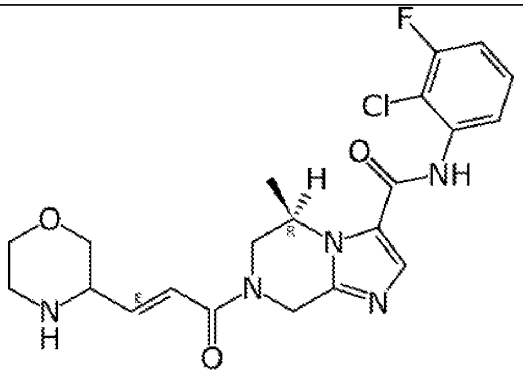
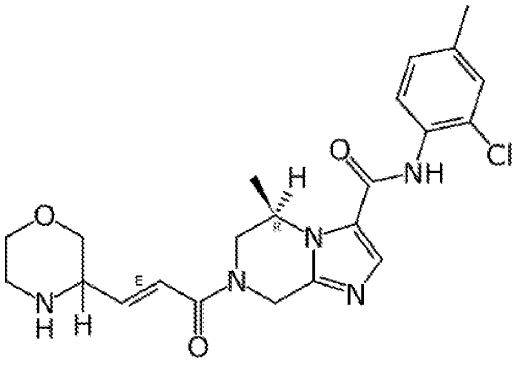
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
216		++++	
217		+++++	
218		+++	
219		++++	

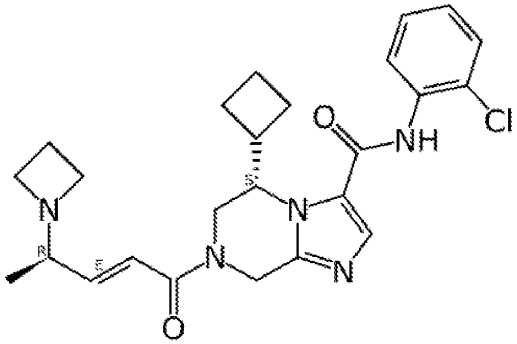
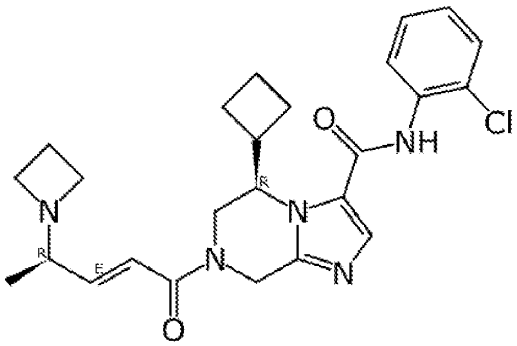
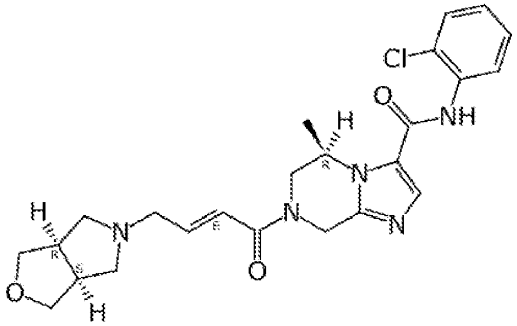
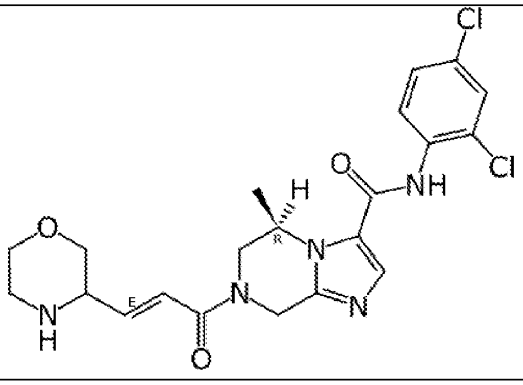
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
220		++++	
221		+++++	
222		+++	
223		++++	

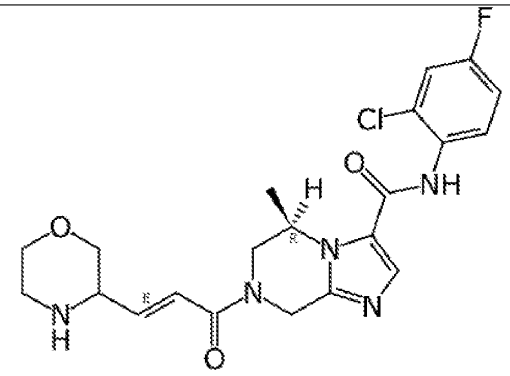
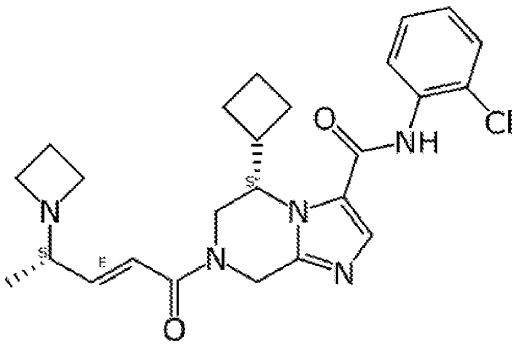
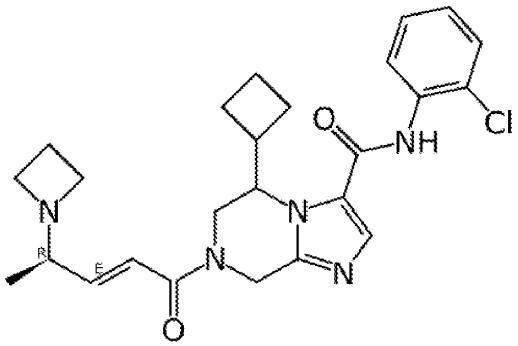
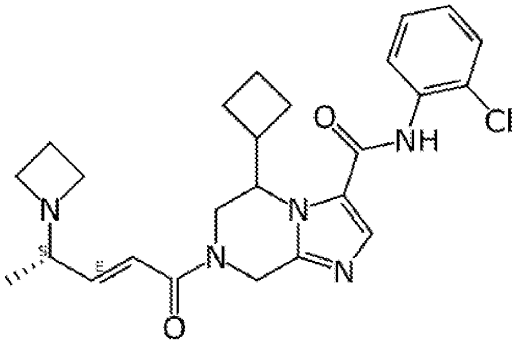
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
224		+++++	
225		++++	
226		+++	
227		+++++	

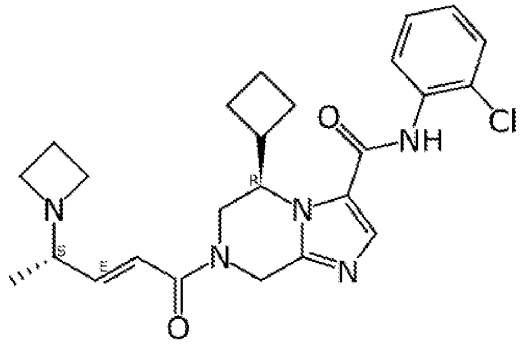
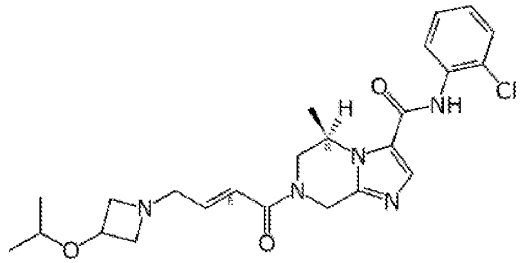
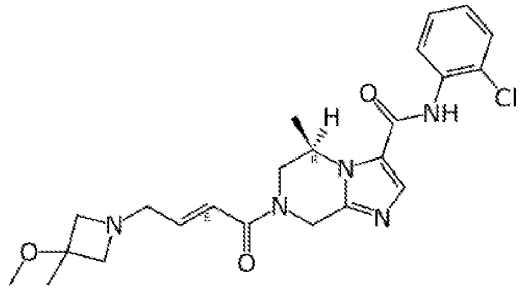
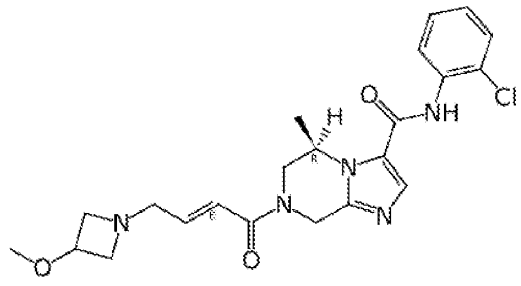
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
228		++++	
229		+++	
230		++++	
231		++++	

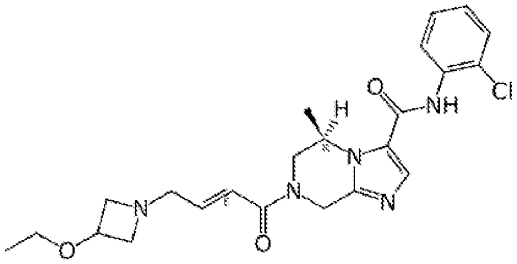
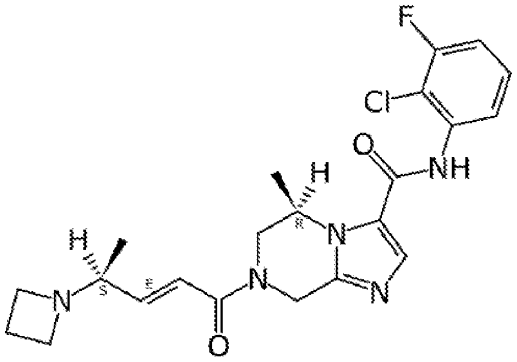
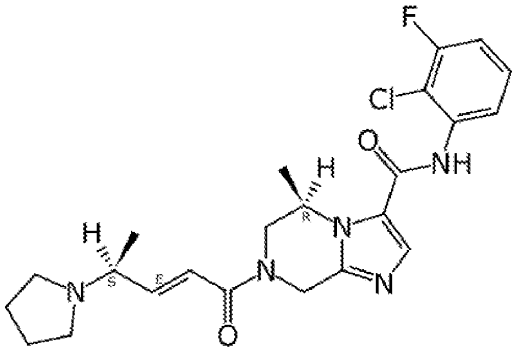
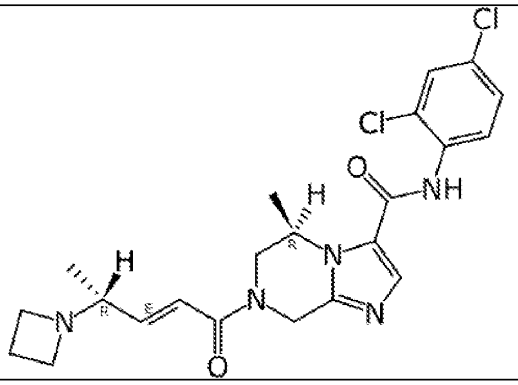
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
232		+++++	
233		+++++	
234		+++++	
235		+++++	

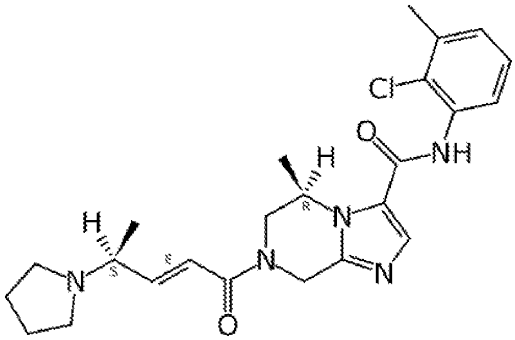
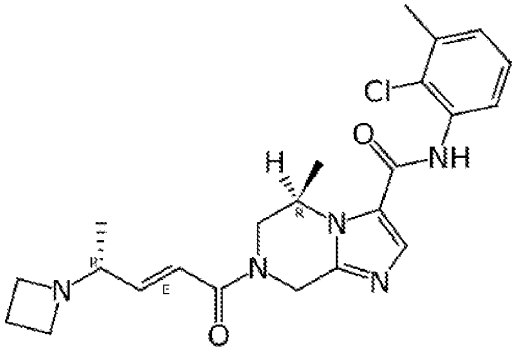
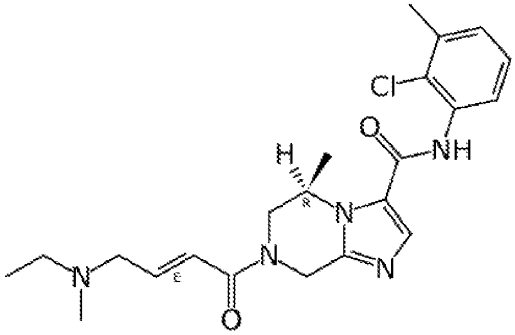
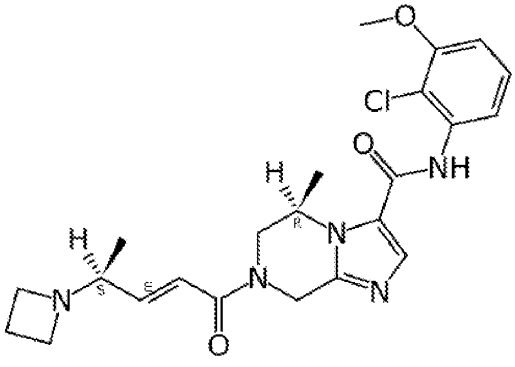
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
236		++++	
237		++++	
238		+++++	
239		+++++	

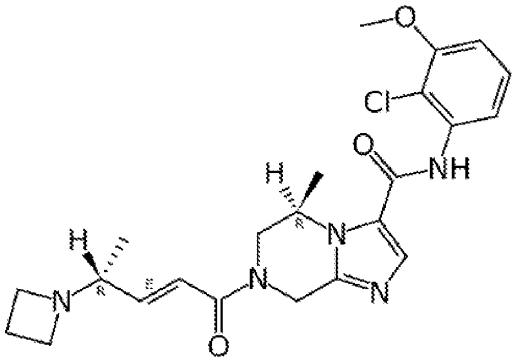
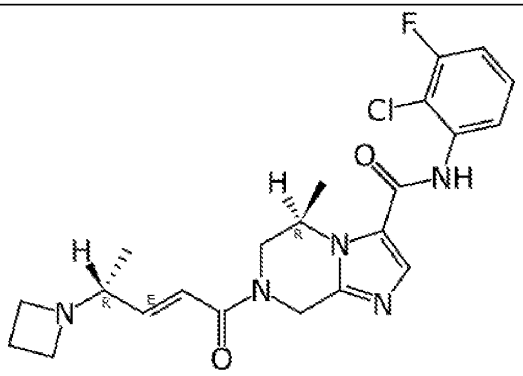
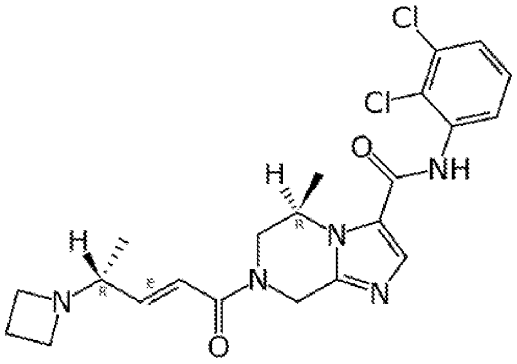
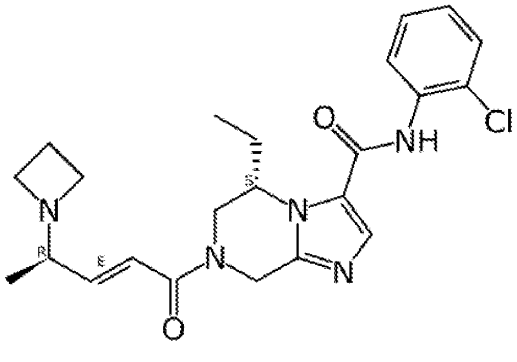
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
240		+++	
241		+++	
242		+++++	
243		+++++	

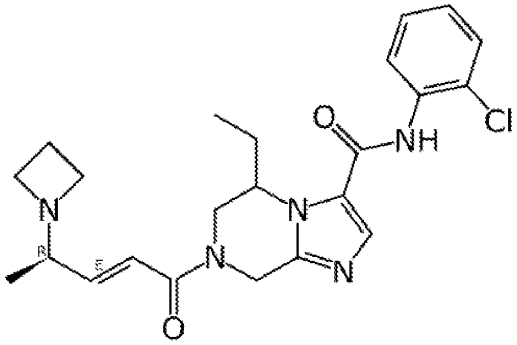
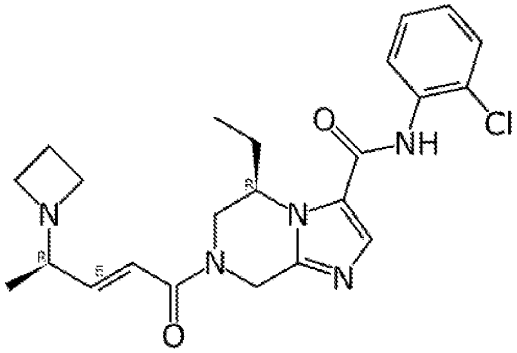
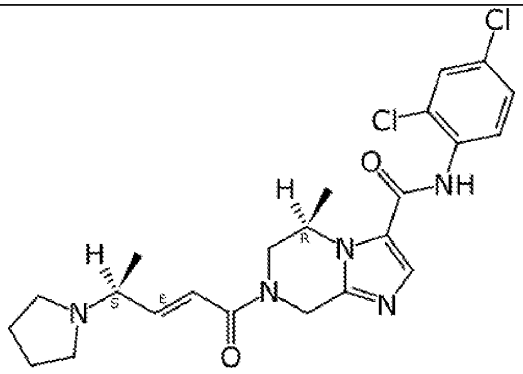
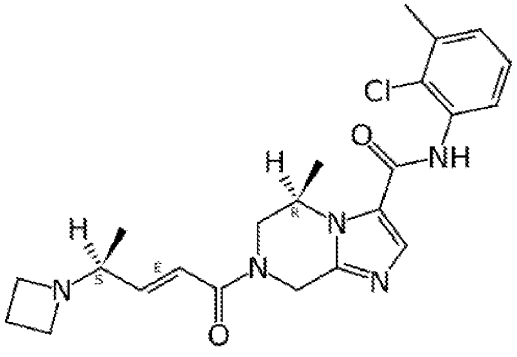
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
244		++++	
245		++	
246		+++	
247		+++	

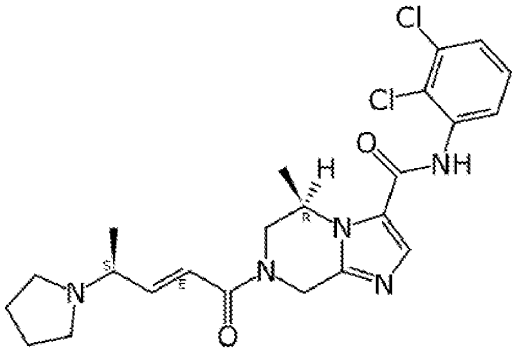
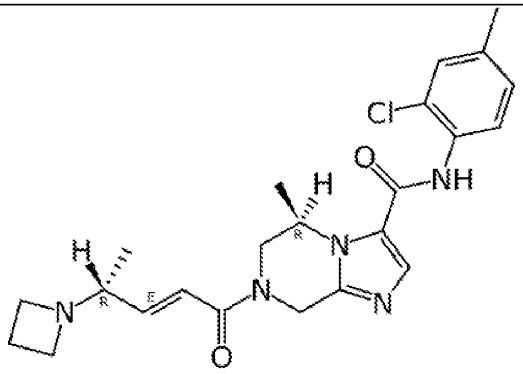
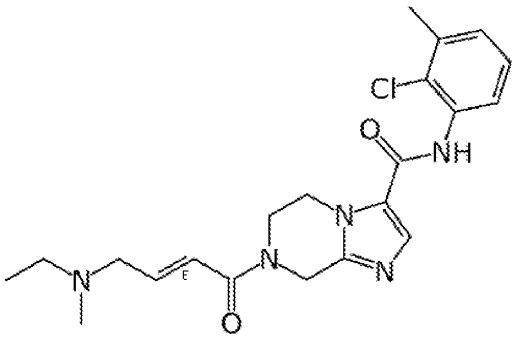
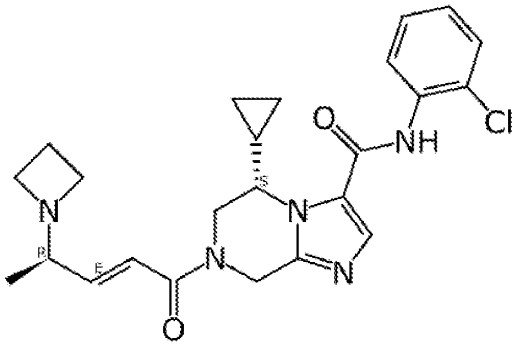
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
248		++	
249		+++++	
250		+++++	
251		+++++	

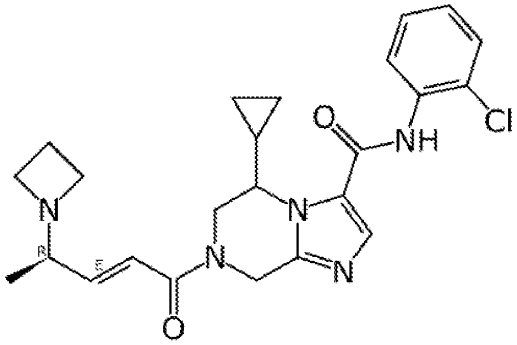
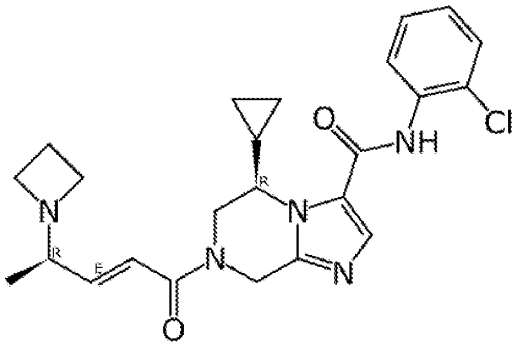
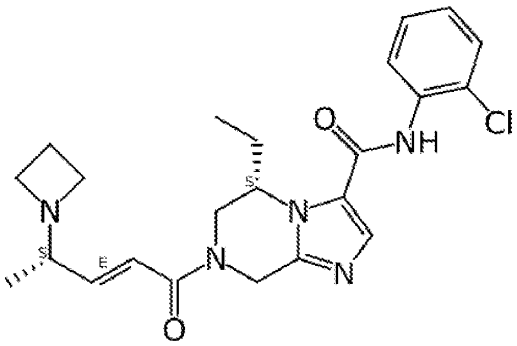
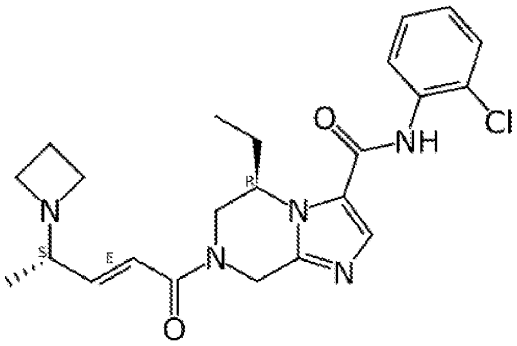
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
252		+++++	
253		+++++	
254		++++	
255		+++++	

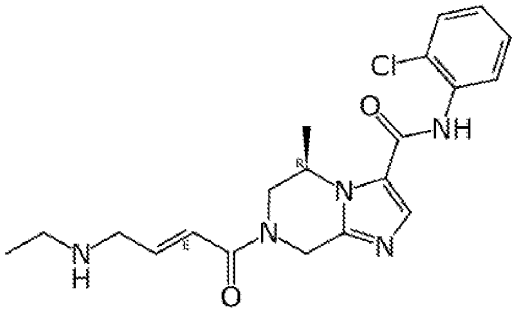
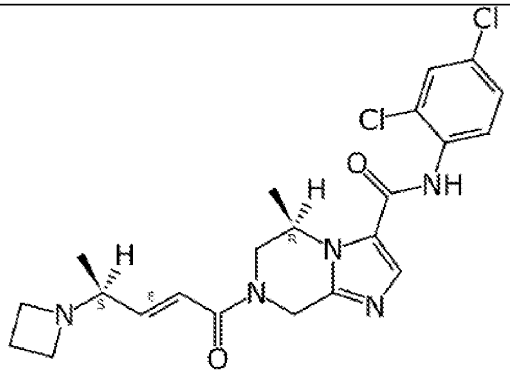
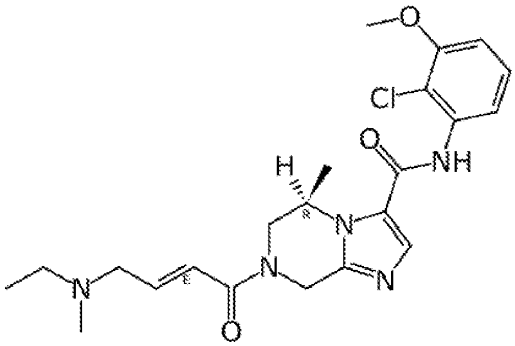
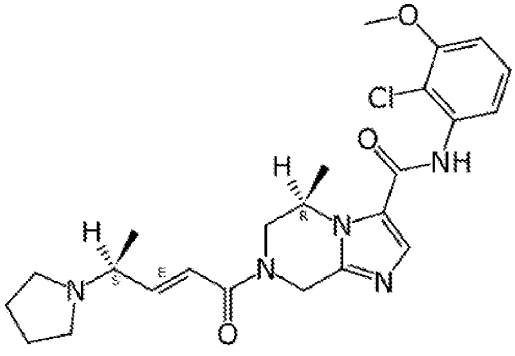
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
256		+	
257		+++	
258		+++	
259		+++	

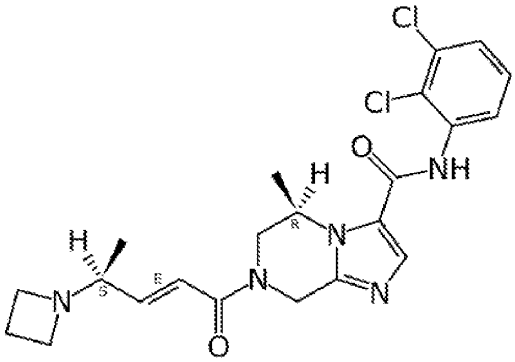
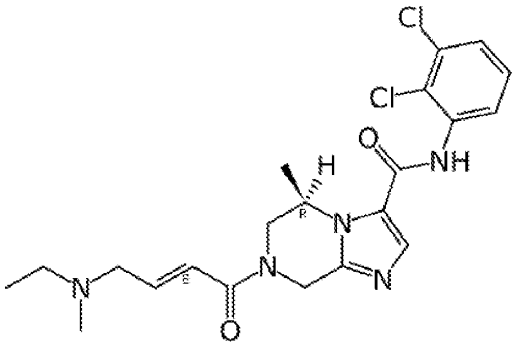
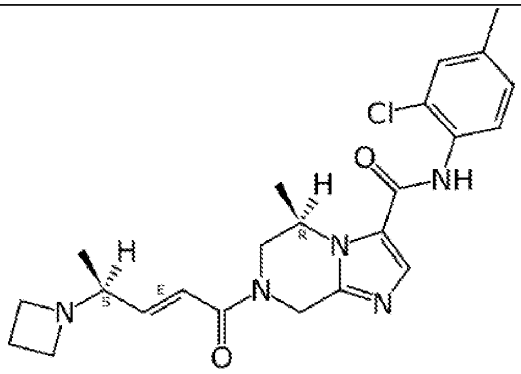
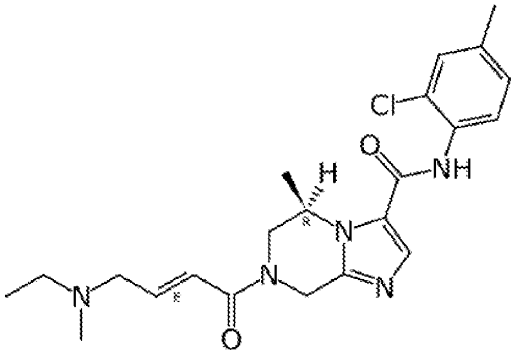
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
260		+++	
261		+++++	
262		++++	
263		++++	

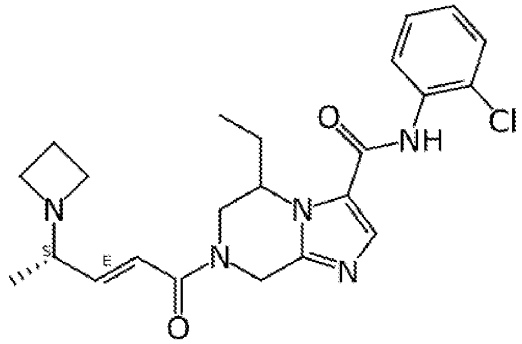
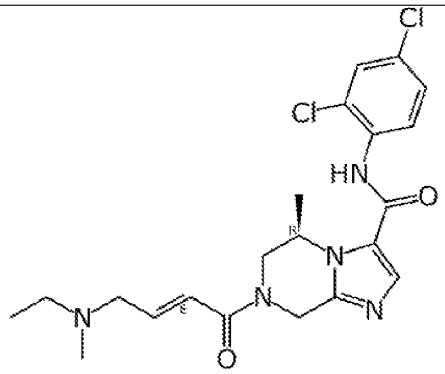
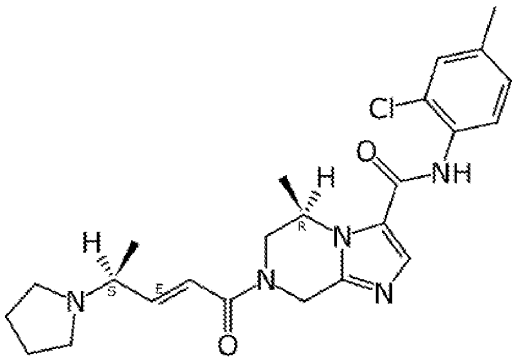
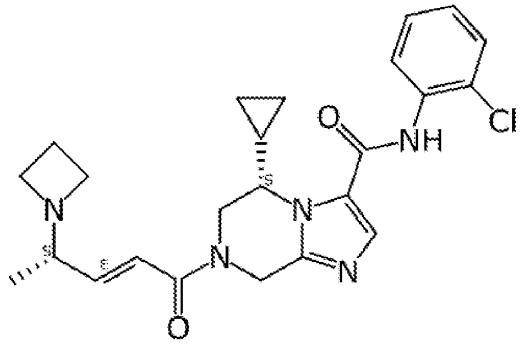
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
264		++++	
265		+++++	
266		++++	
267		++	

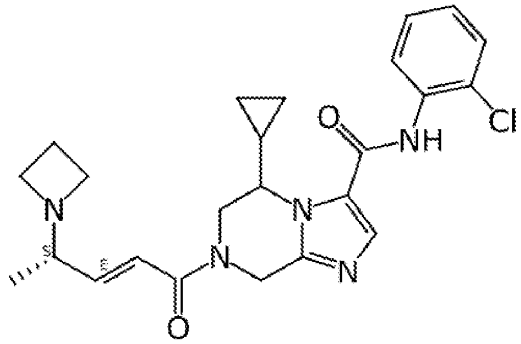
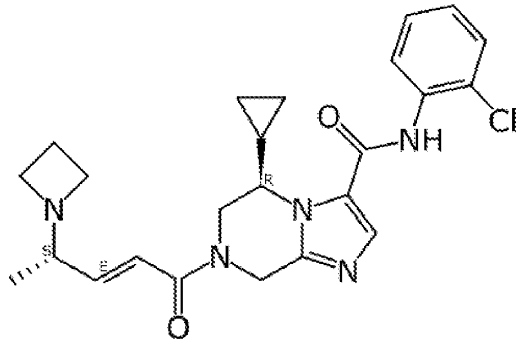
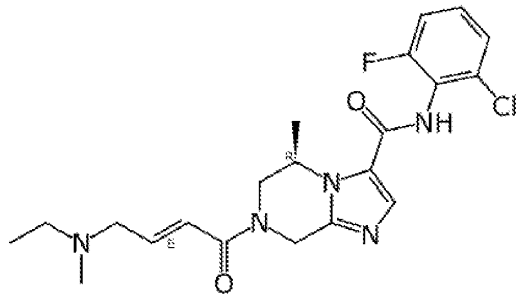
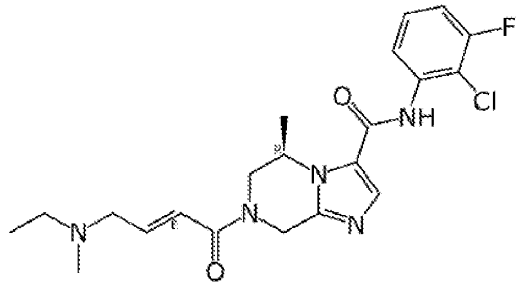
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
268		+++	
269		+++++	
270		++	
271		+++	

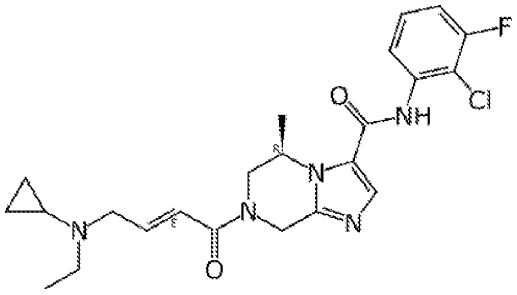
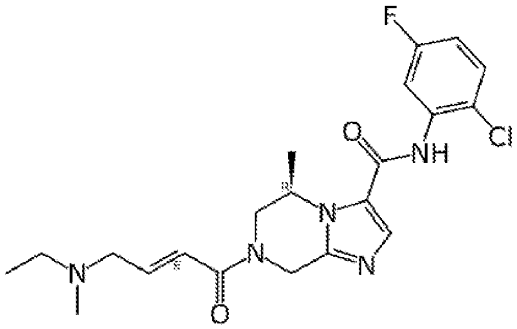
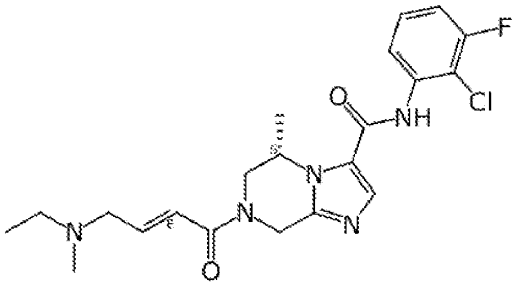
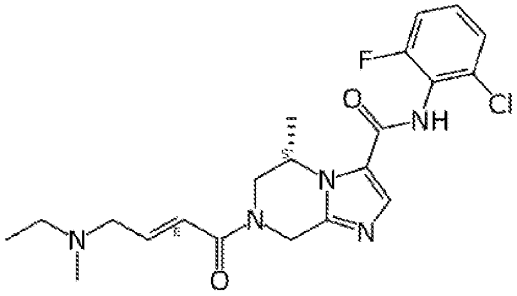
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
272		+++	
273		+++	
274		++++	
275		++++	

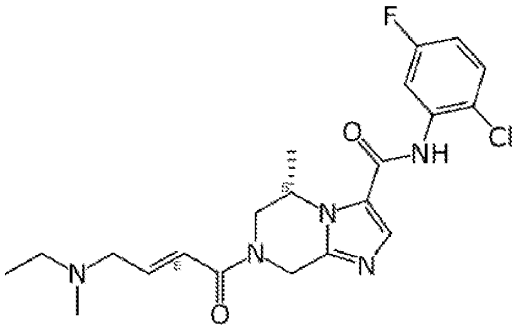
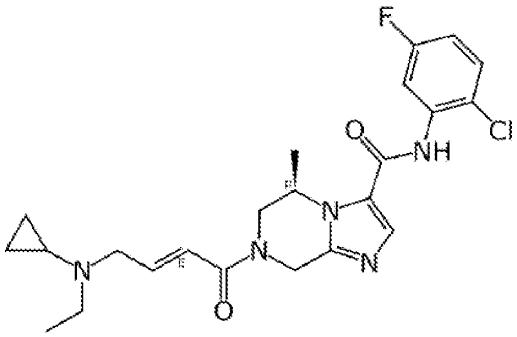
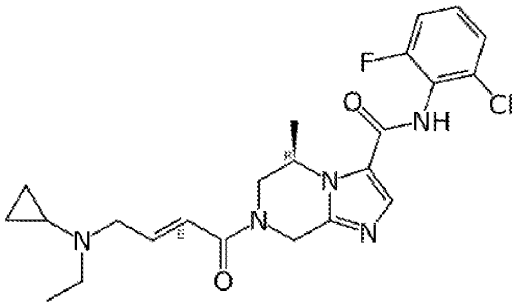
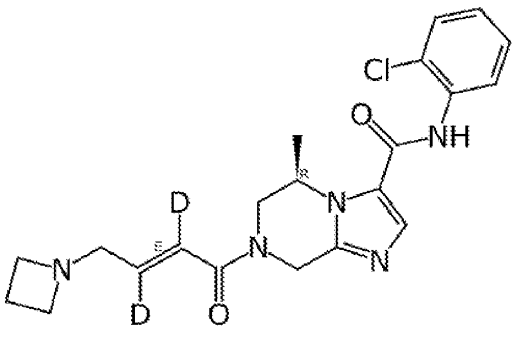
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
276		+++++	
277		+++++	
278		++++	
279		++	

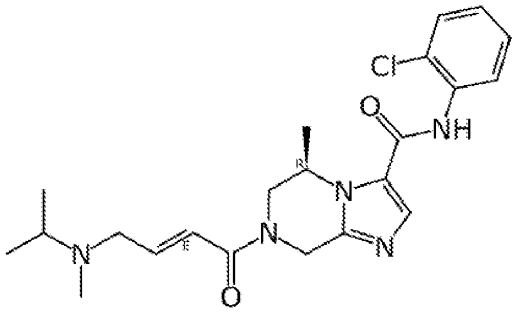
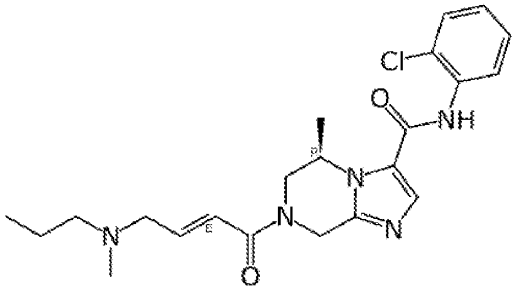
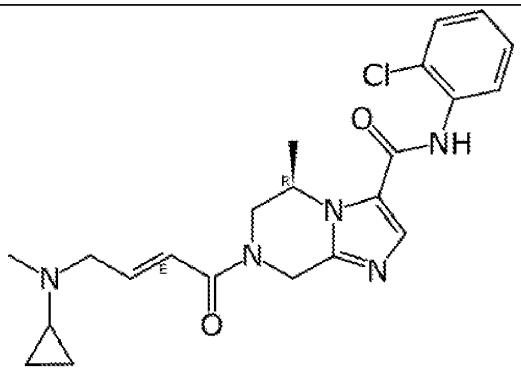
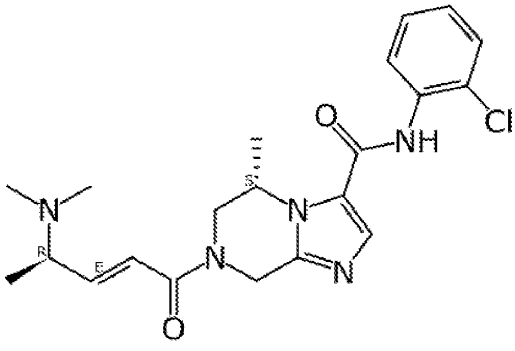
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
280		+++	
281		++++	
282		++++	
283		+++++	

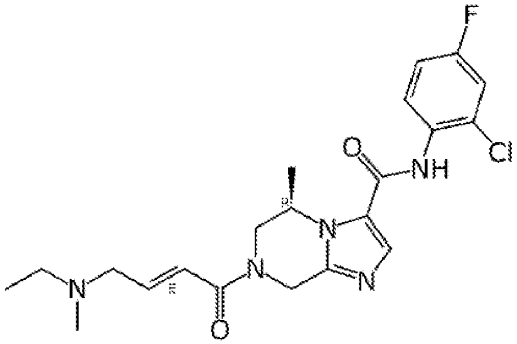
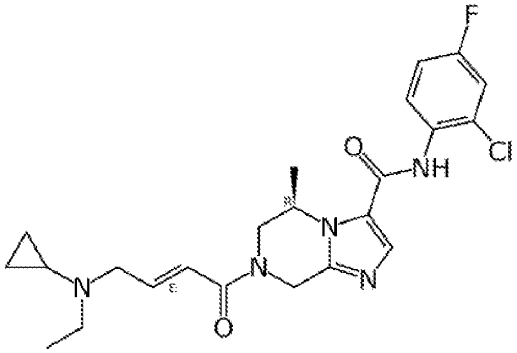
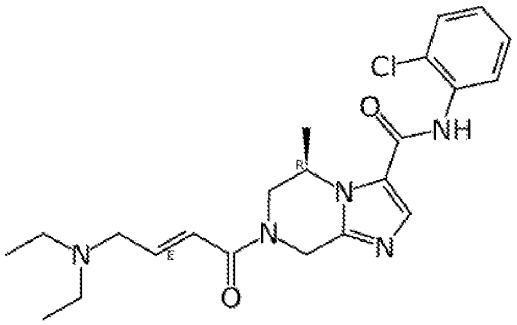
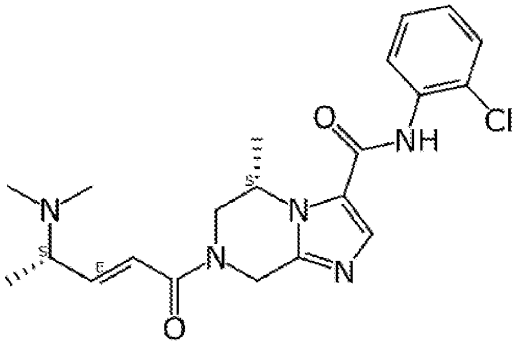
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
284		++++	
285		+++++	
286		++++	
287		+++	

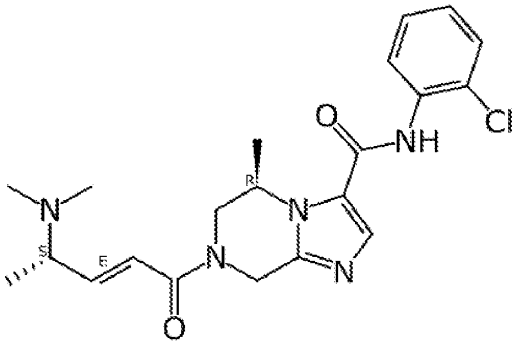
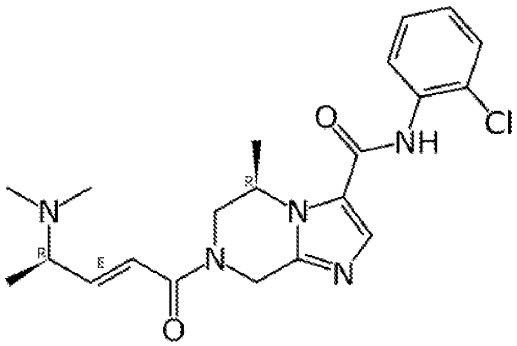
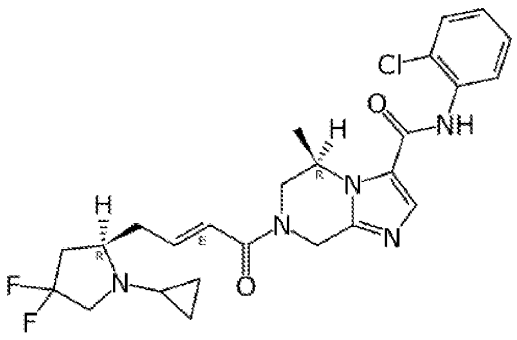
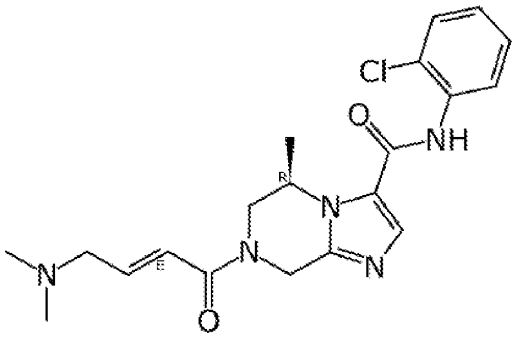
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
288		++	
289		++	
290		+++++	
291		+++++	

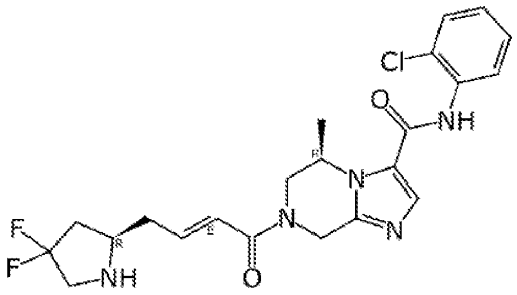
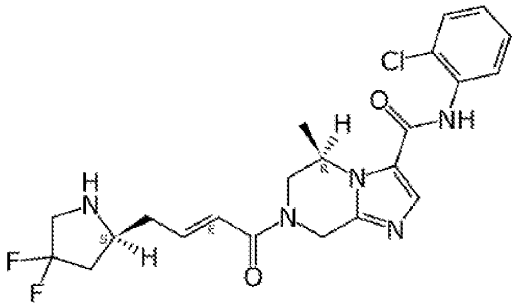
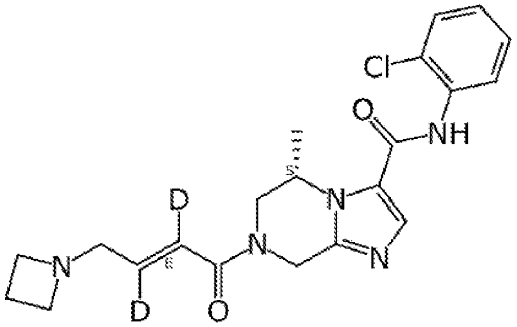
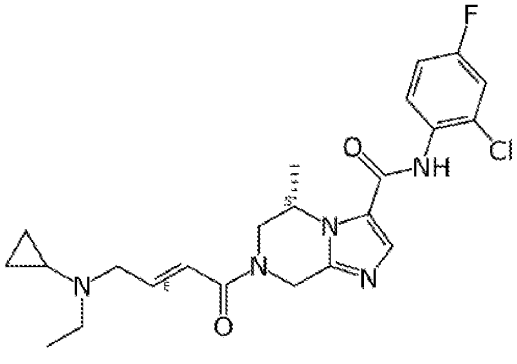
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
292		+++++	
293		+++++	
294		+++	
295		++	

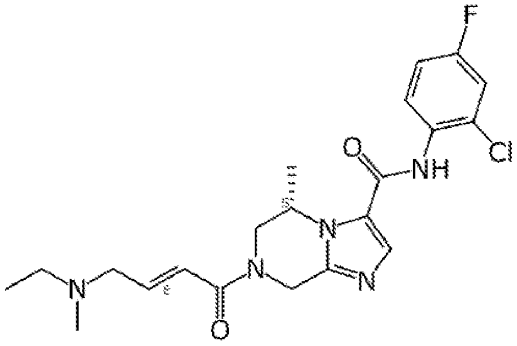
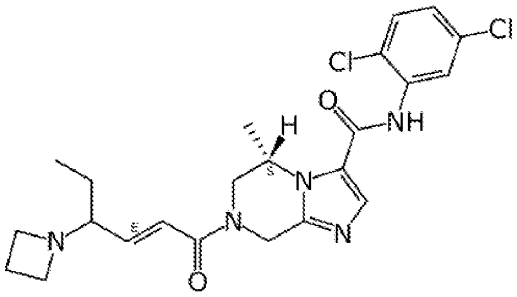
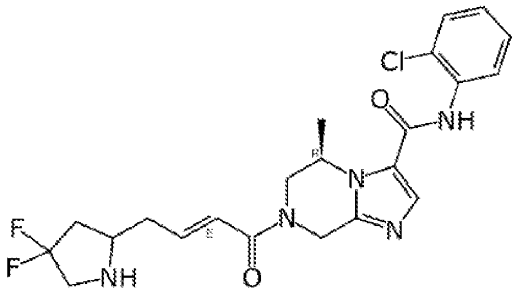
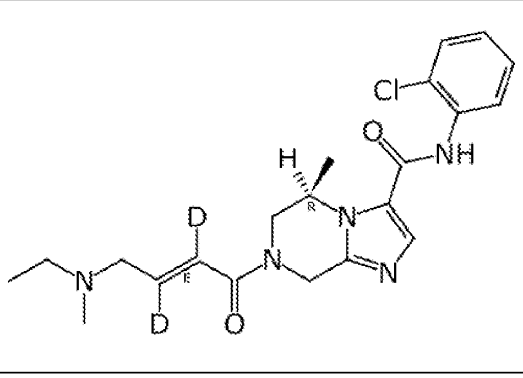
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
296		+++	
297		++++	
298		++++	
299		+++++	

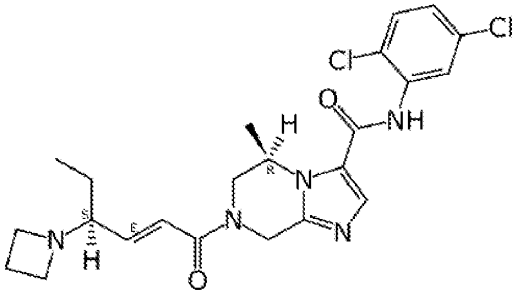
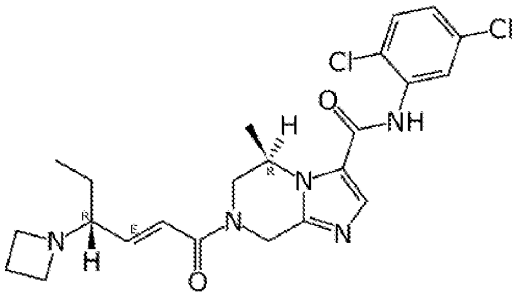
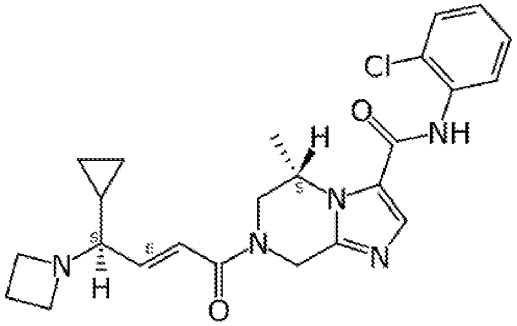
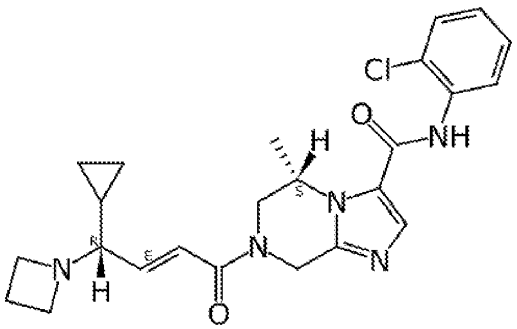
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
300		+++++	
301		+++++	
302		+++++	
303		+	

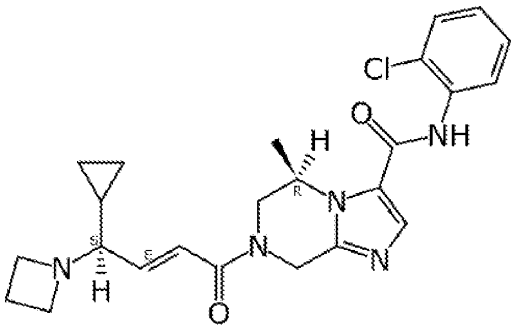
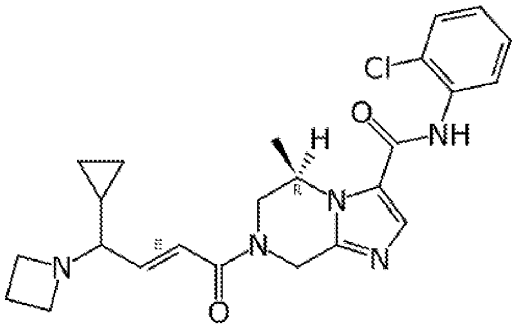
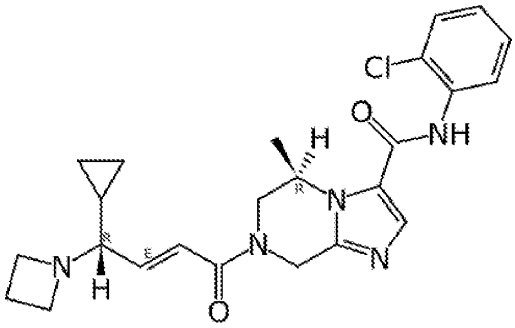
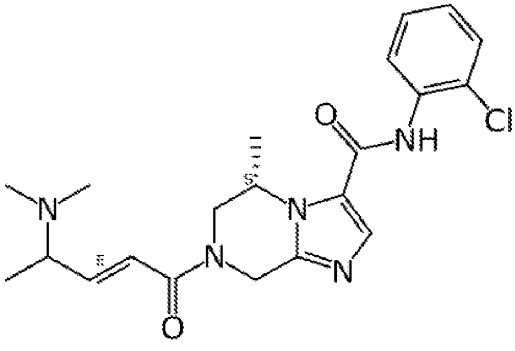
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
304		+++++	
305		++++	
306		+++++	
307		+++	

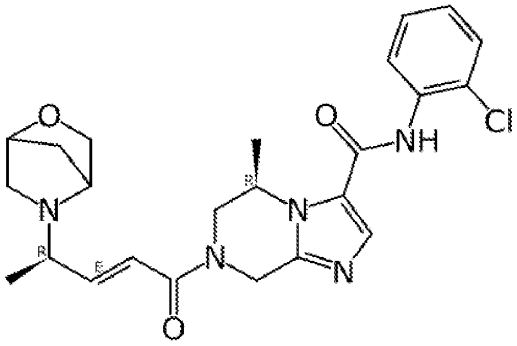
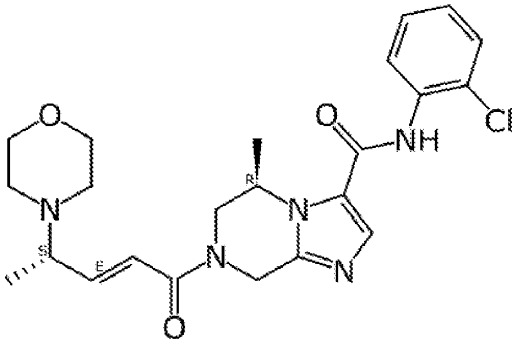
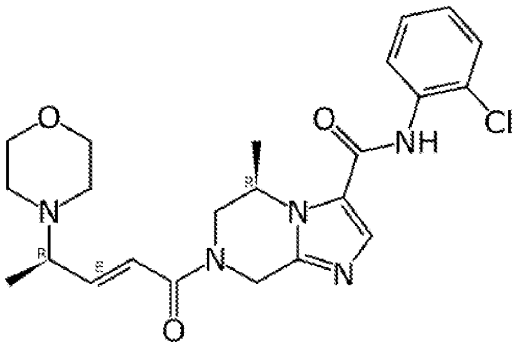
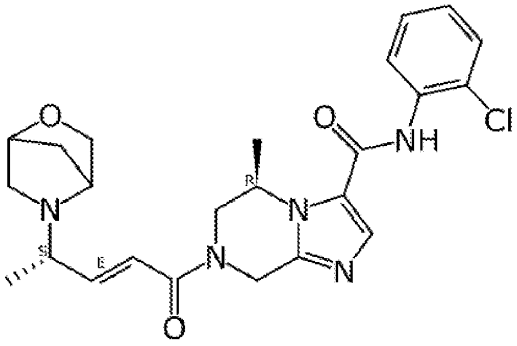
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
308		+++++	
309		++++	
310		+	
311		+++++	

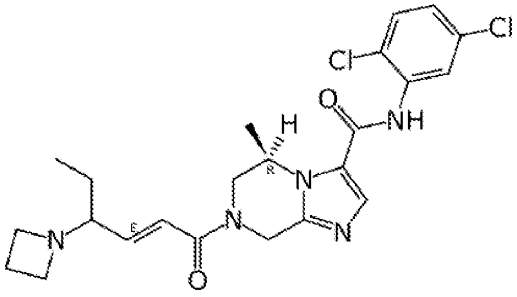
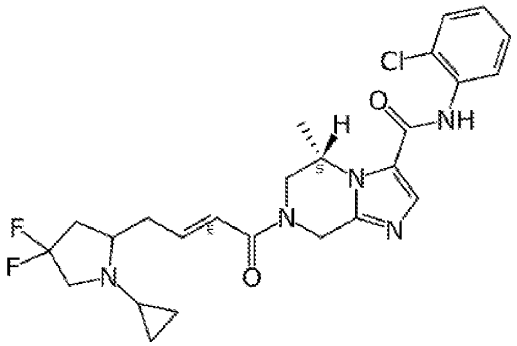
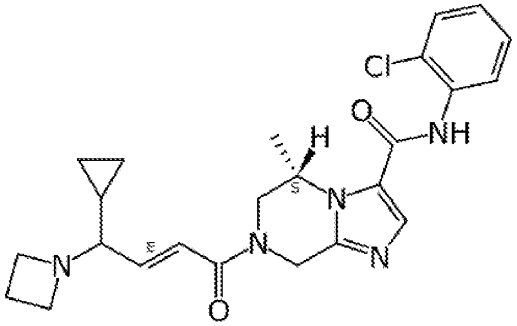
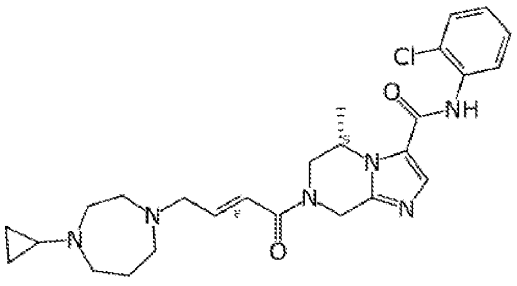
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
312		+++	
313		+++	
314		+++++	
315		++	

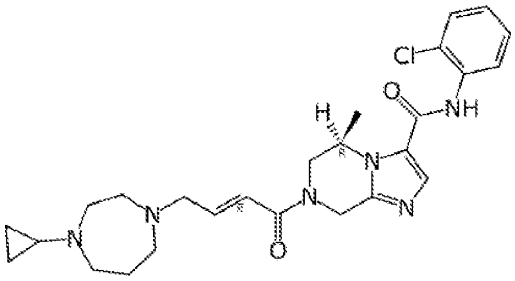
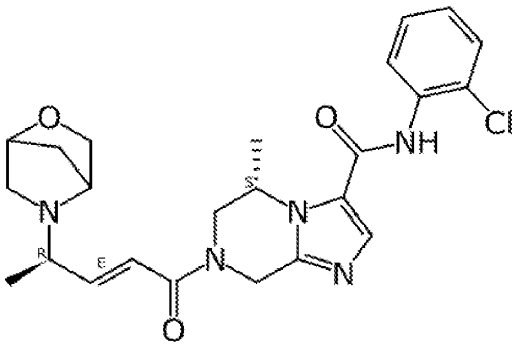
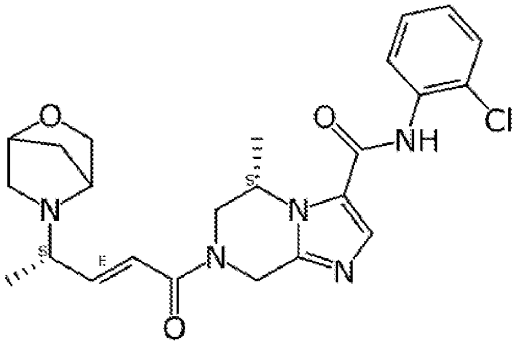
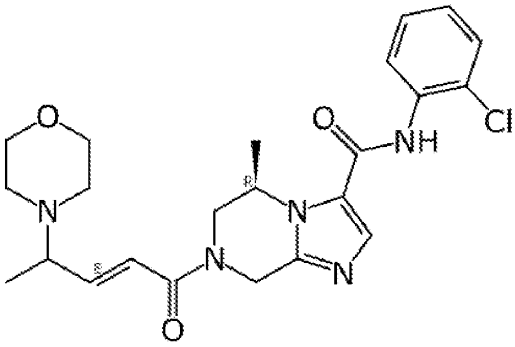
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
316		++	
317		++	
318		++	
319		+++++	
320		++	

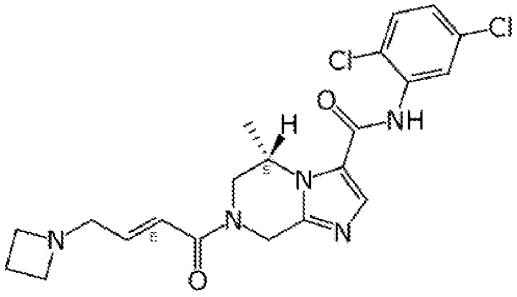
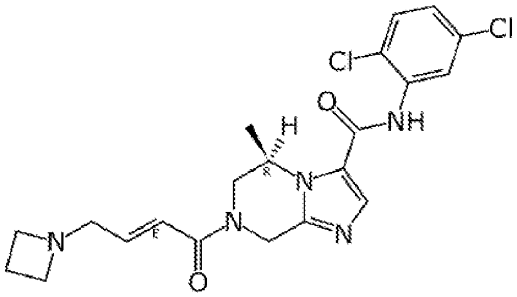
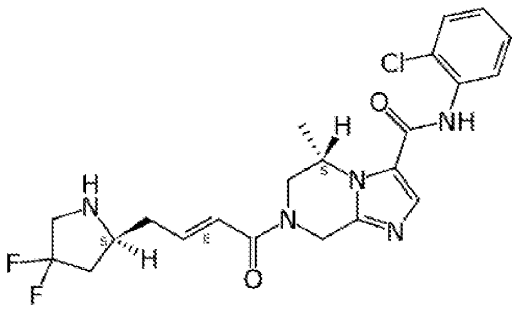
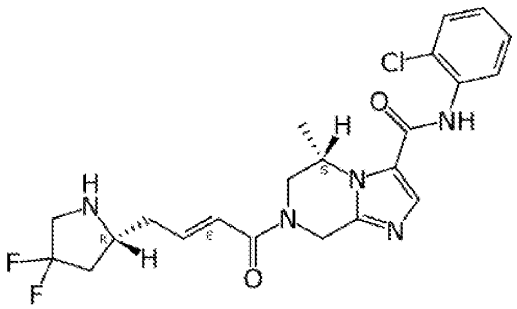
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
321		++	
322		++	
323		+++	
324		+++	
325		++++	

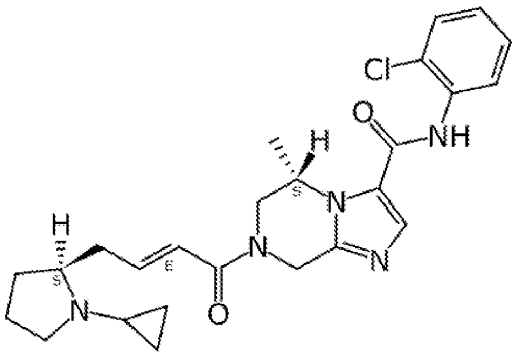
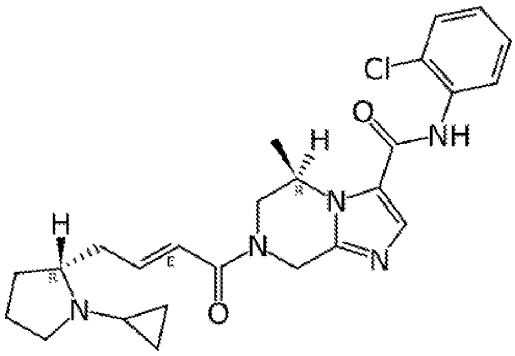
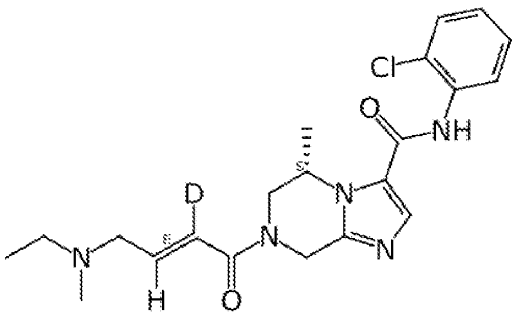
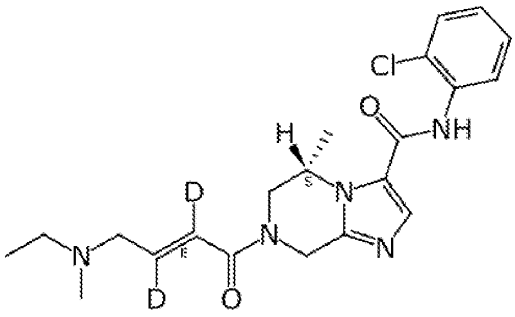
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
326		++	
327		++	
328		++	
329		++	

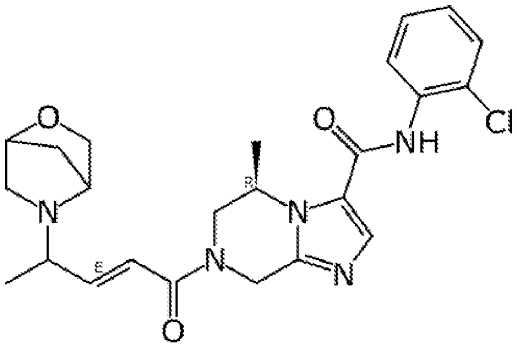
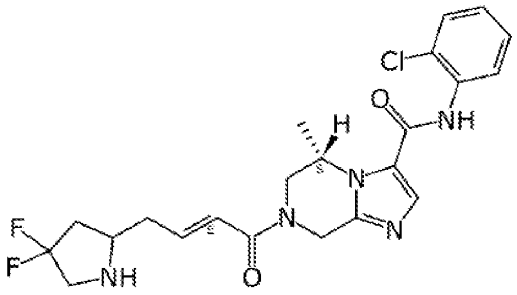
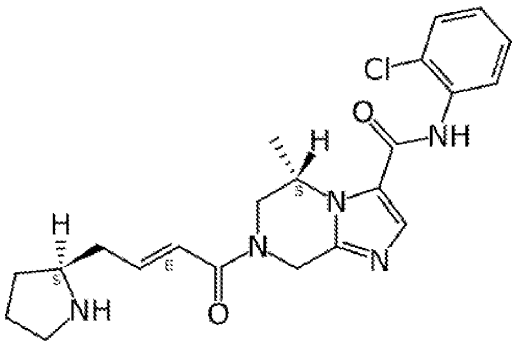
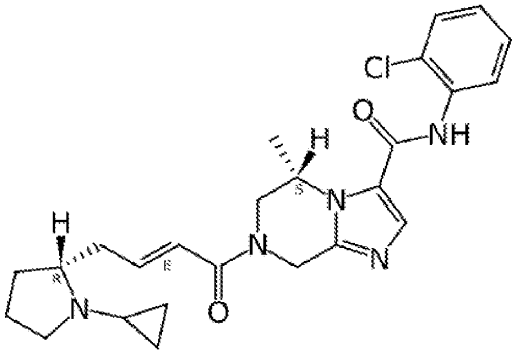
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
330		++	
331		+	
332		++	
333		++	

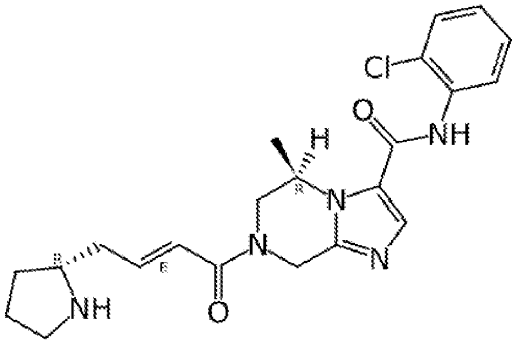
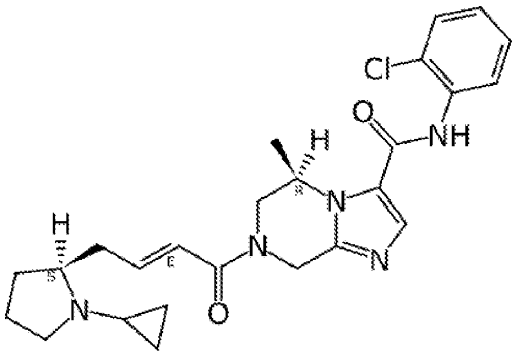
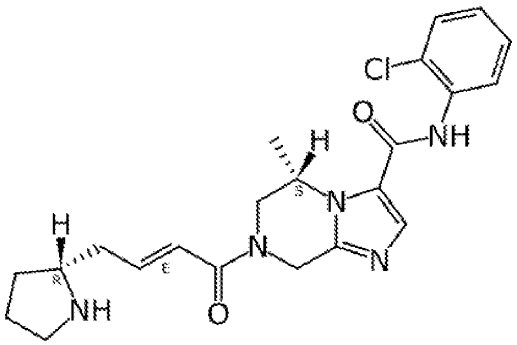
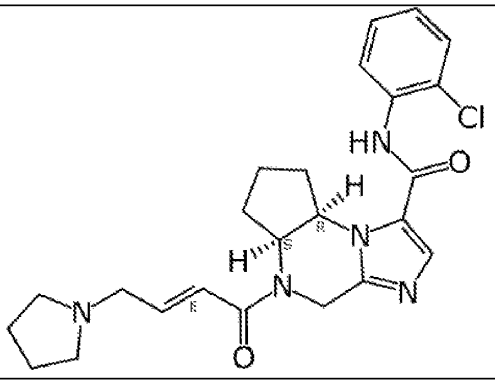
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
334		+	
335		++	
336		+	
337		++	

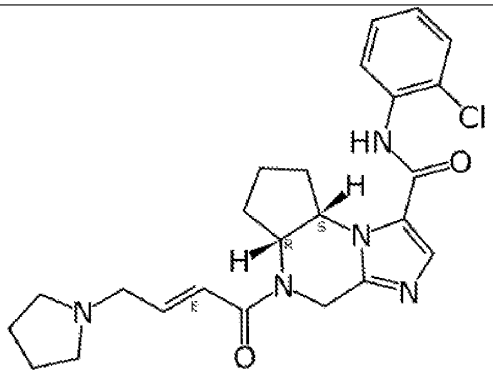
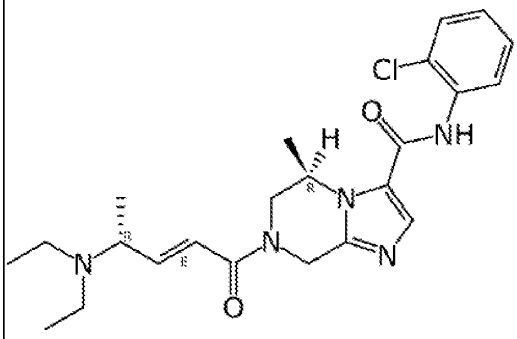
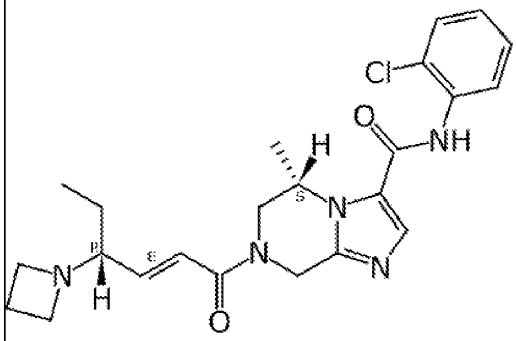
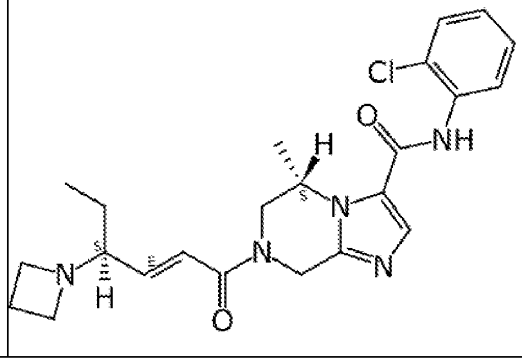
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
338		++++	
339		+	
340		+	
341		++	

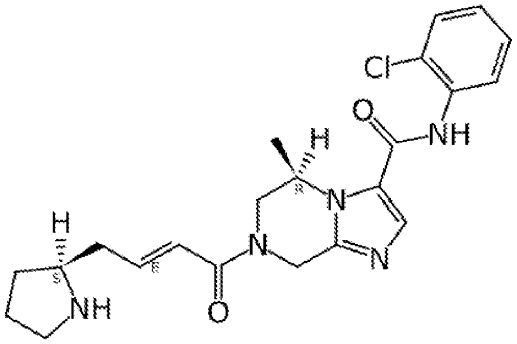
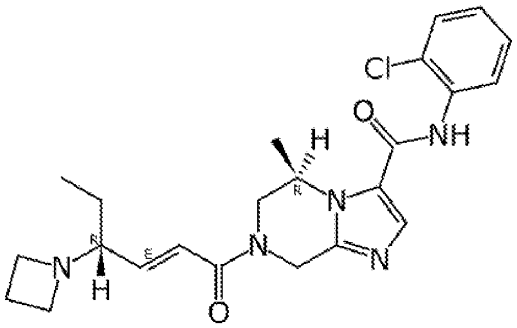
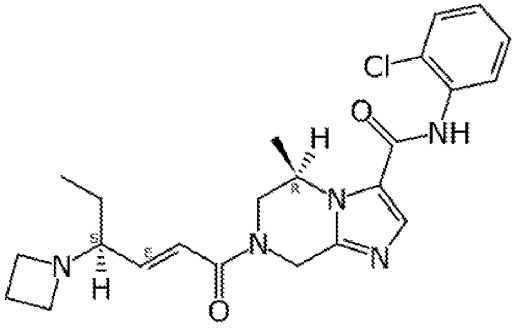
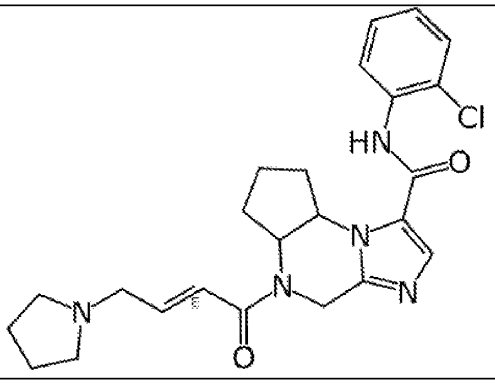
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
342		+++	
343		+++++	
344		++	
345		+	

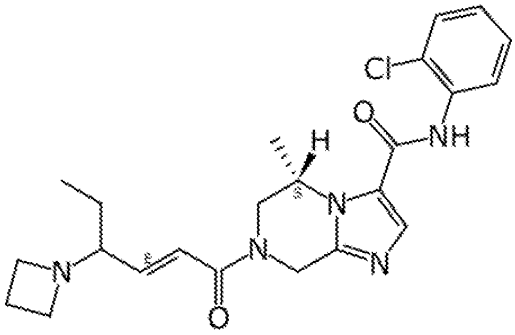
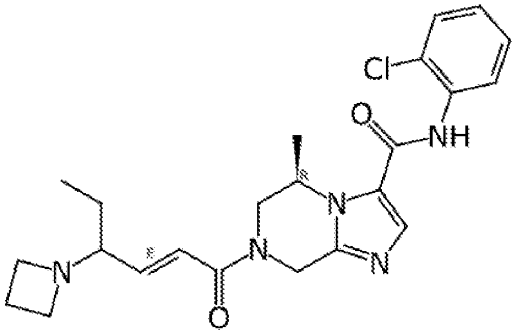
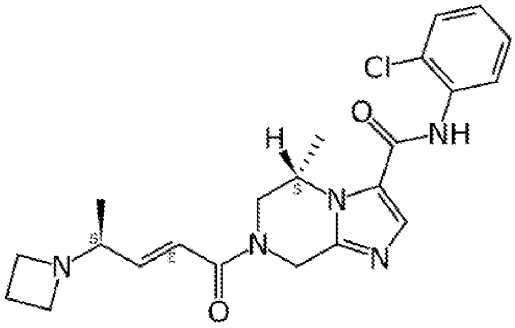
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
346		++	
347		++	
348		++++	
349		++++	

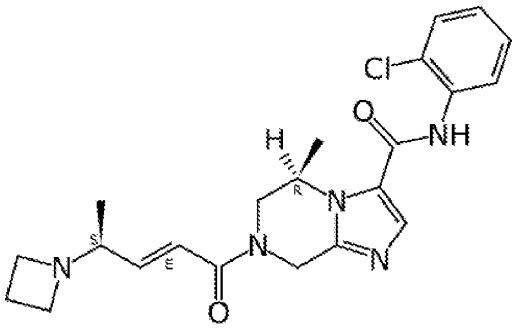
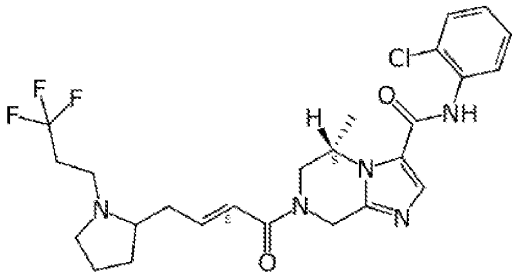
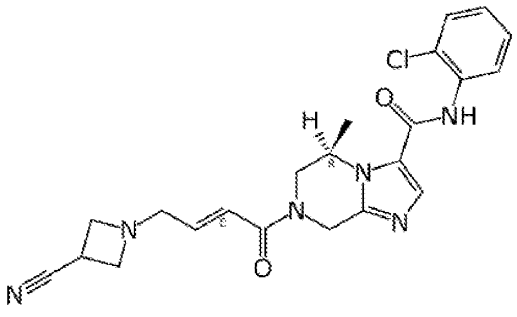
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
350		++	
351		++	
352		+	
353		++	

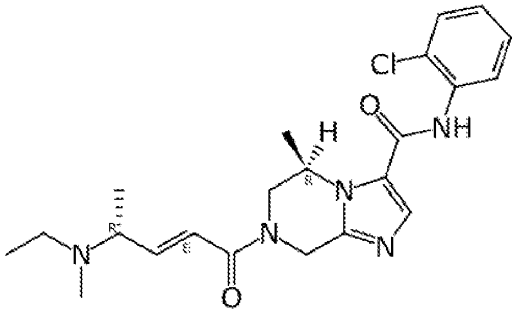
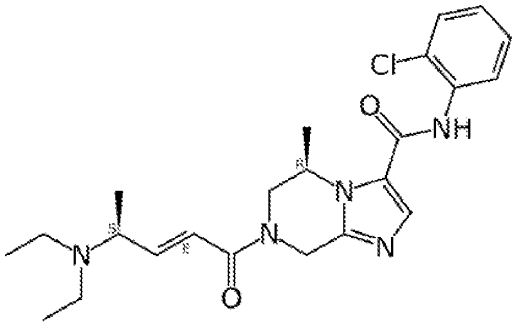
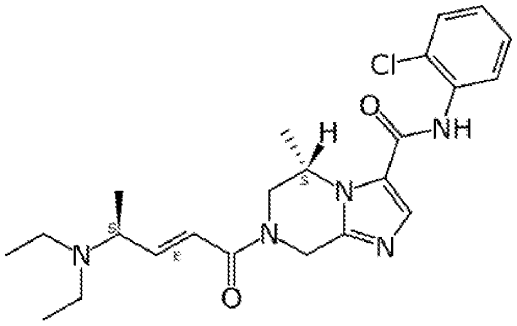
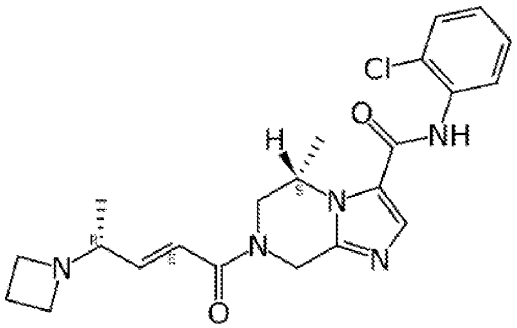
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
354		+++	
355		++	
356		++	
357		++++	

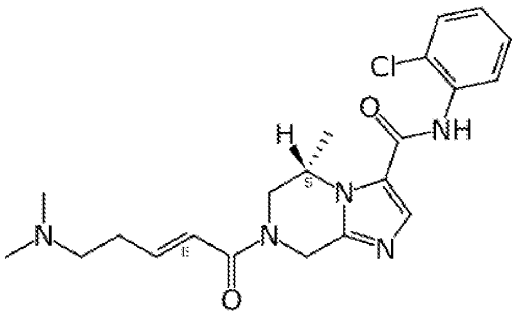
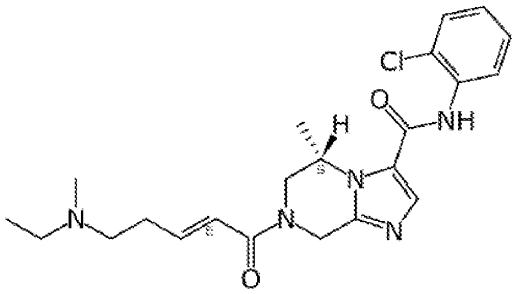
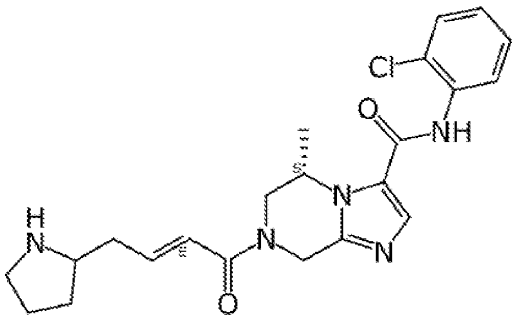
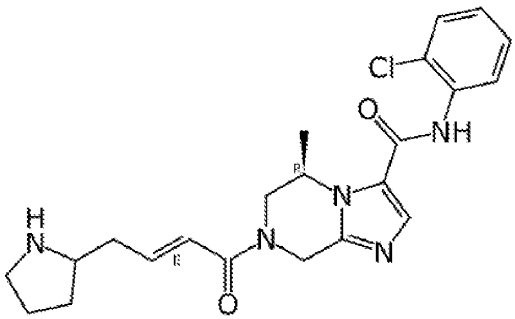
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
358		+	
359		+++	
360		+	
361		++	

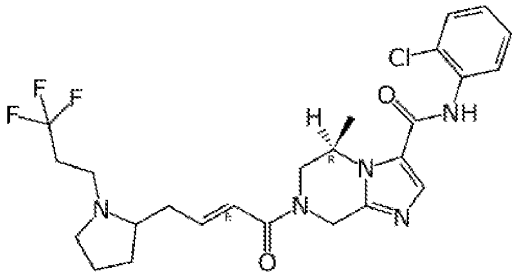
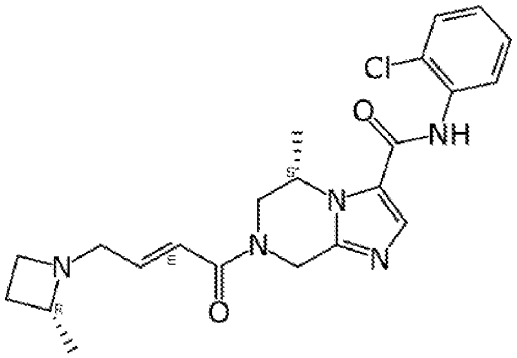
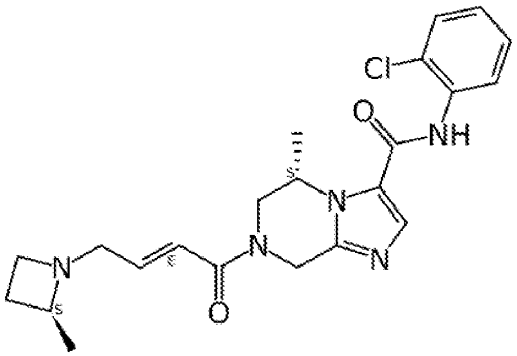
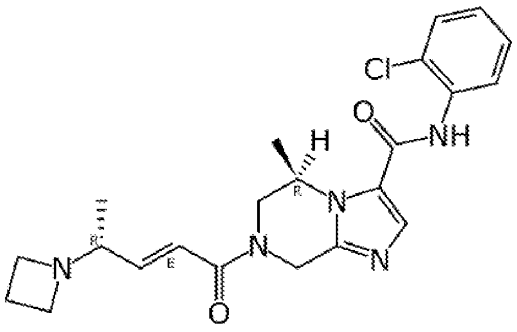
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
362		+++	
363		+++	
364		+++	
365		+++	

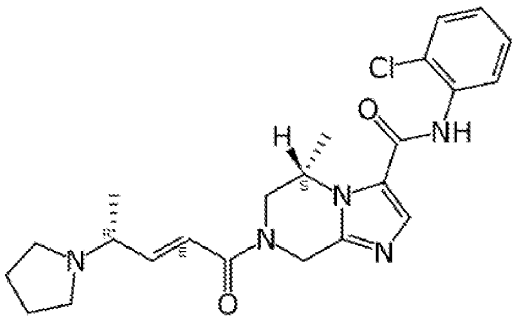
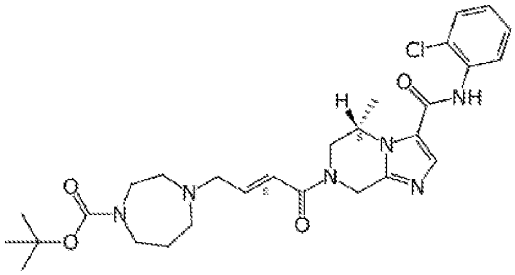
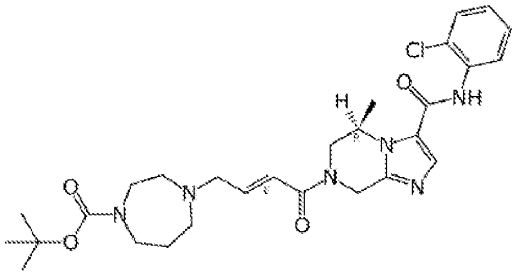
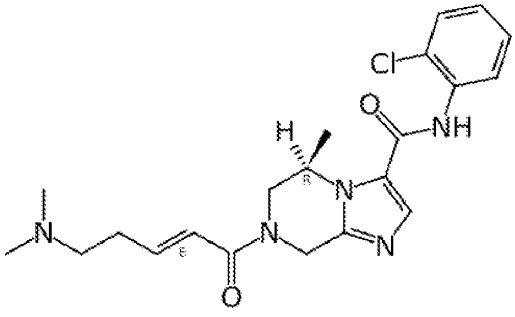
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
366		+	
367		+++	
368		++	

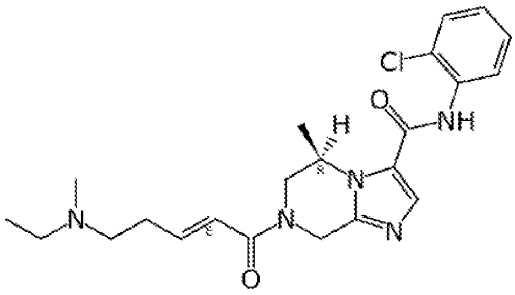
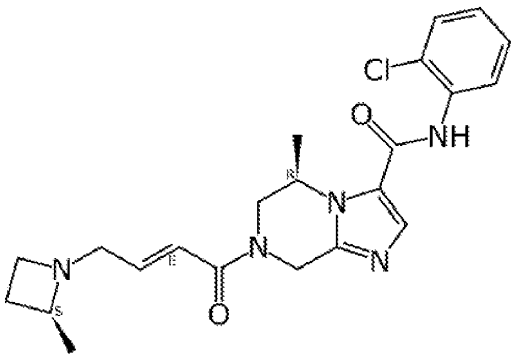
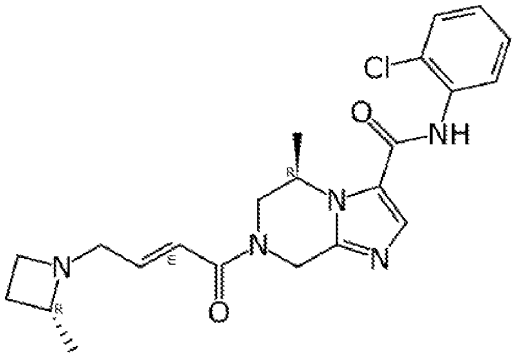
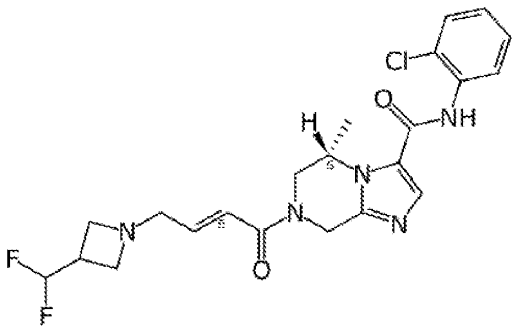
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
369		+++++	
370		+	
371		+++	

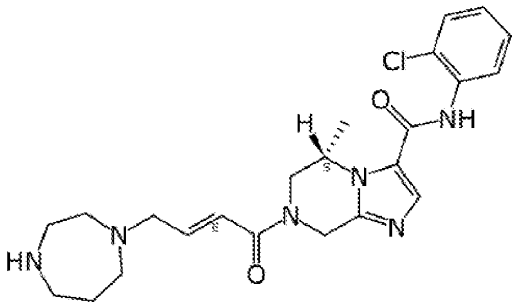
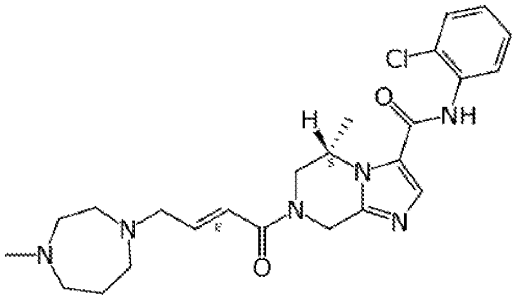
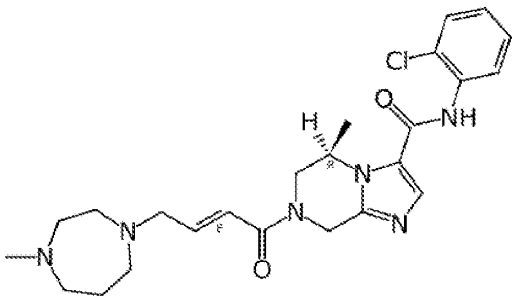
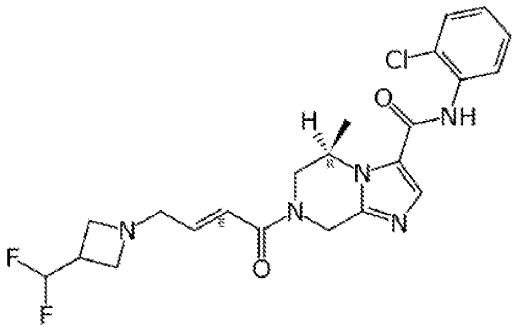
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
372		++++	
373		+++	
374		++	
375		+++	

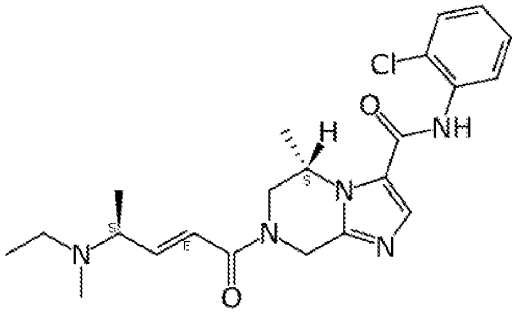
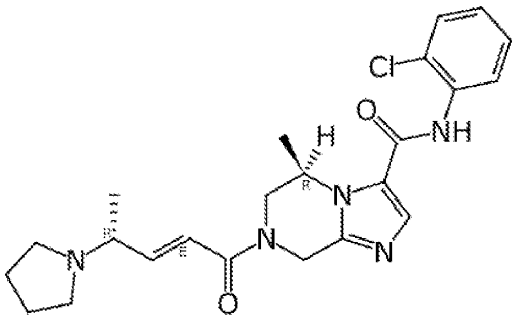
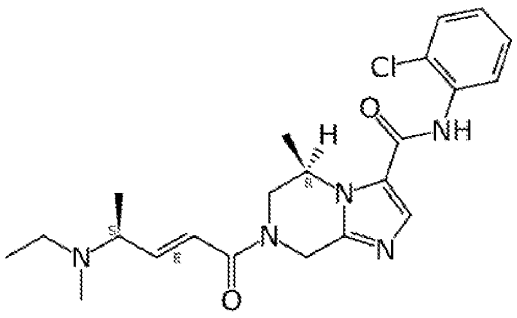
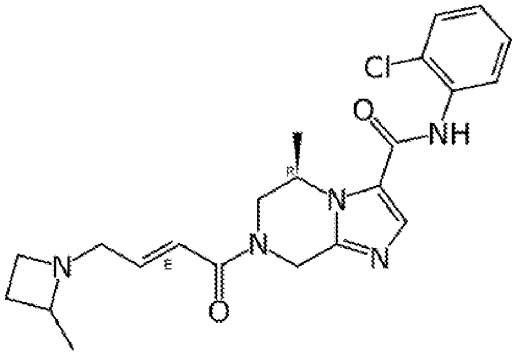
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
376		++	
377		++	
378		+	
379		+++	

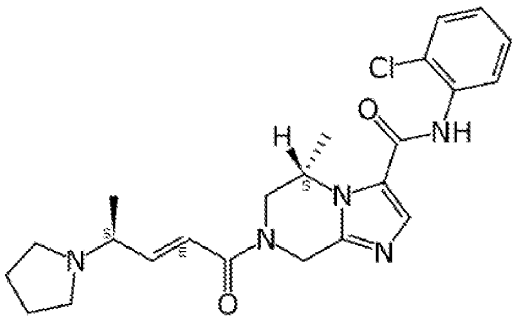
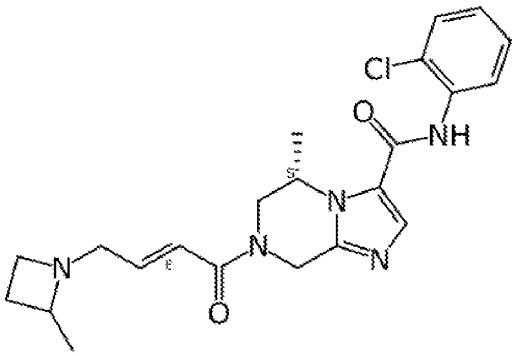
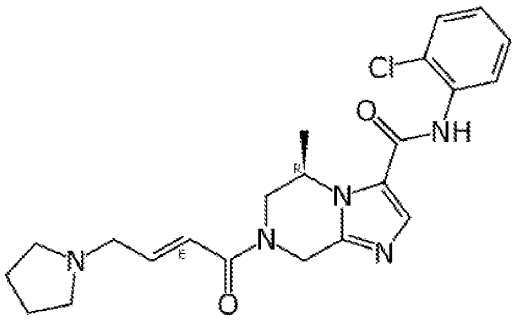
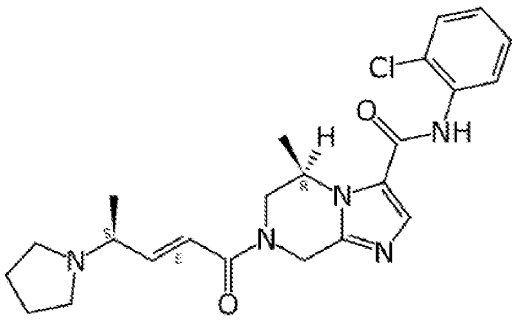
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
380		++	
381		++++	
382		++++	
383		+++++	

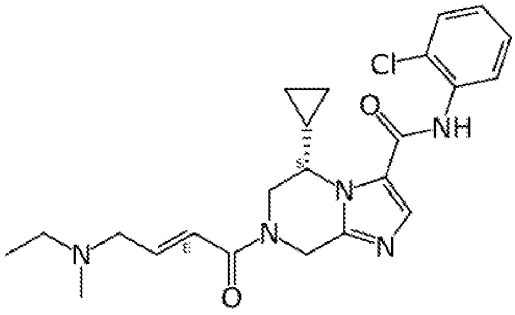
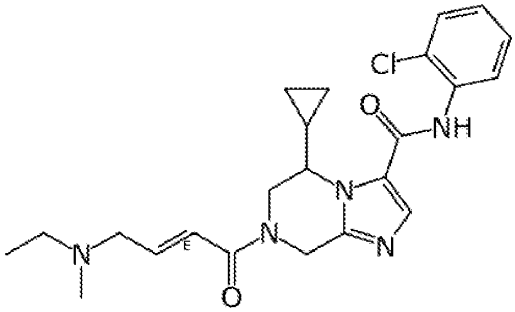
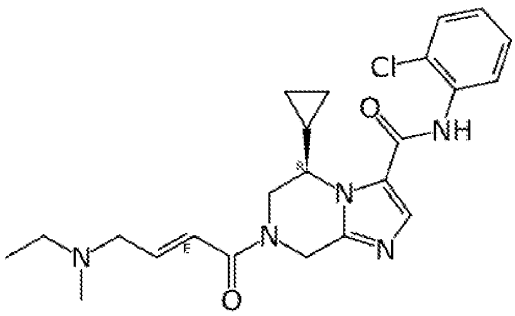
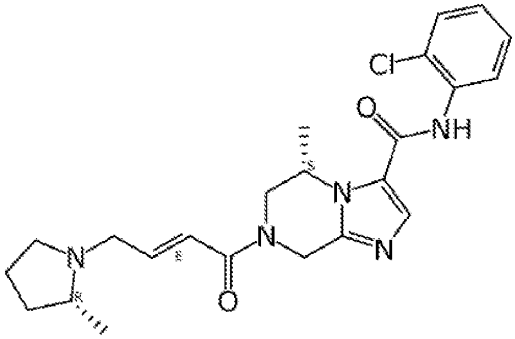
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
384		++	
385		++	
386		+++++	
387		++++	

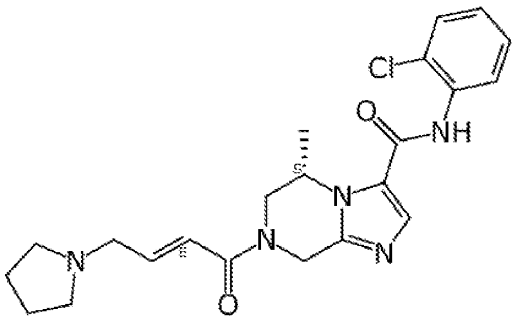
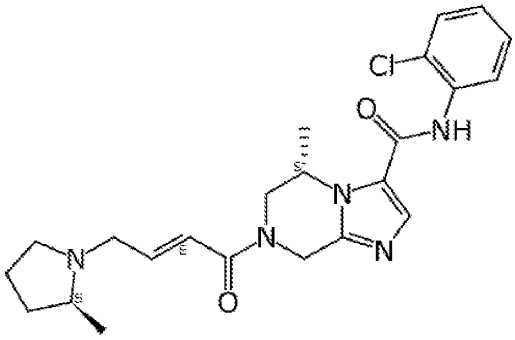
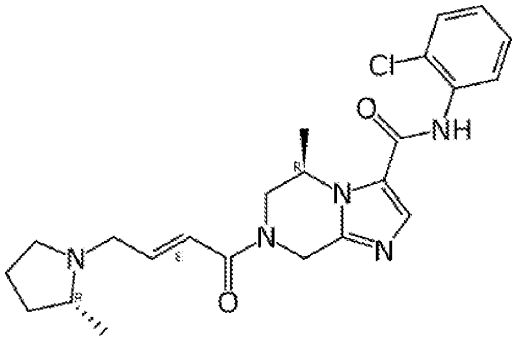
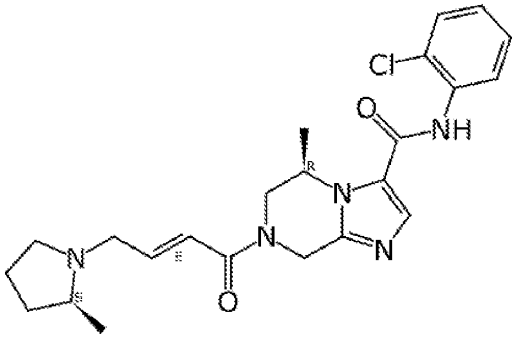
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
388		++++	
389		+++++	
390		+++++	
391		++++	

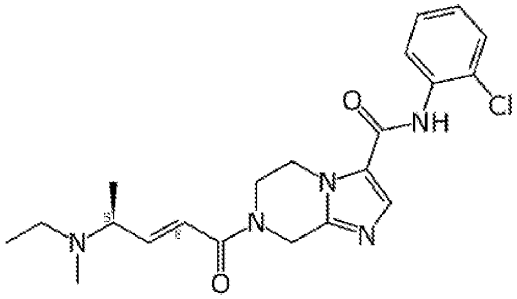
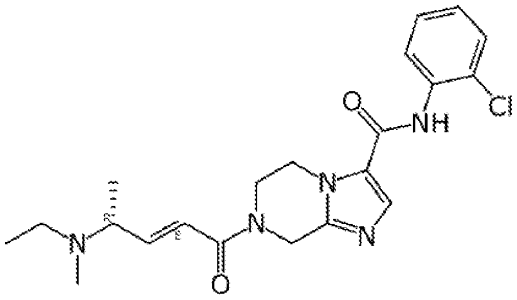
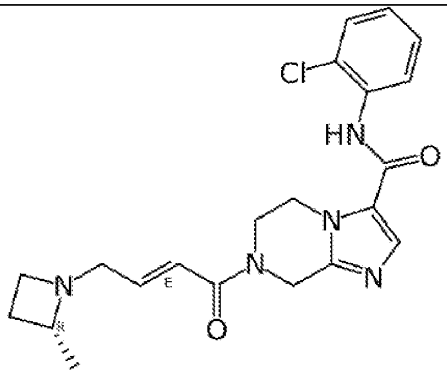
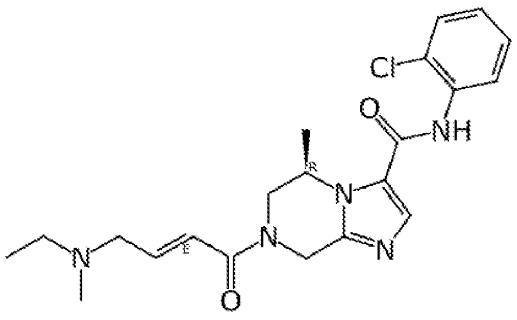
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
392		+	
393		+	
394		+++	
395		+++++	

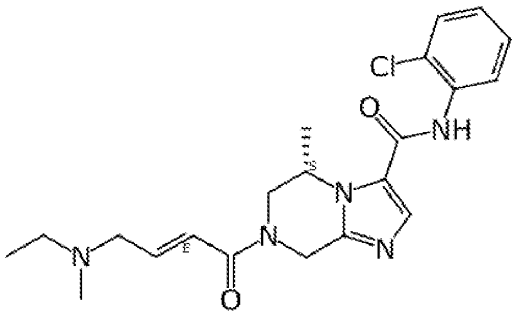
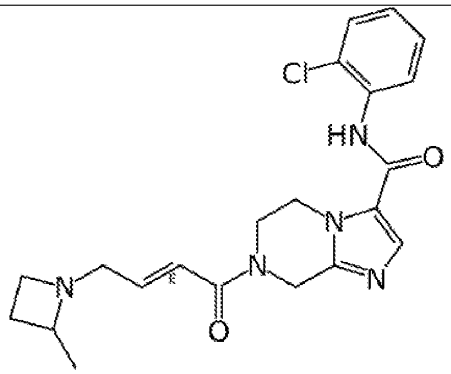
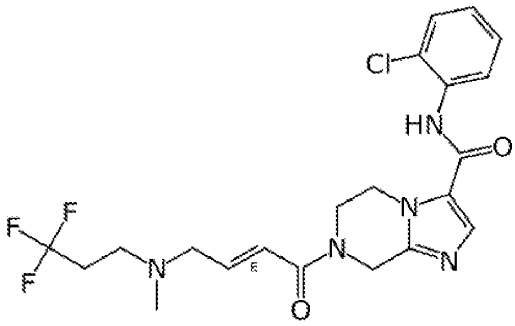
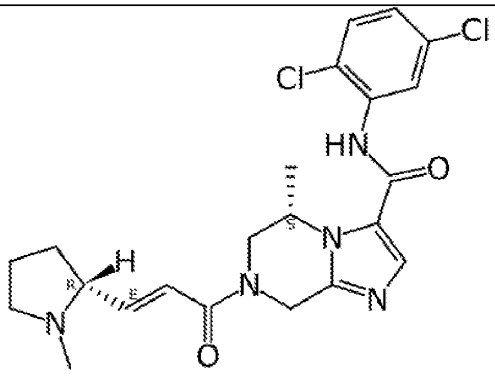
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
396		++	
397		+++	
398		++++	
399		+++++	

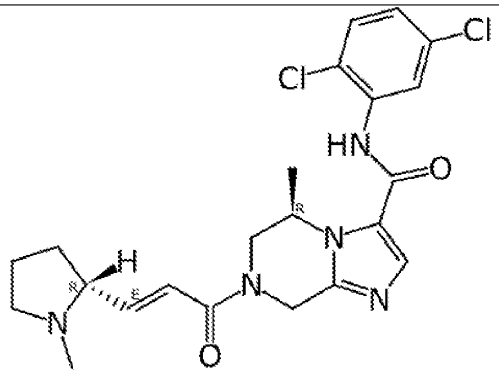
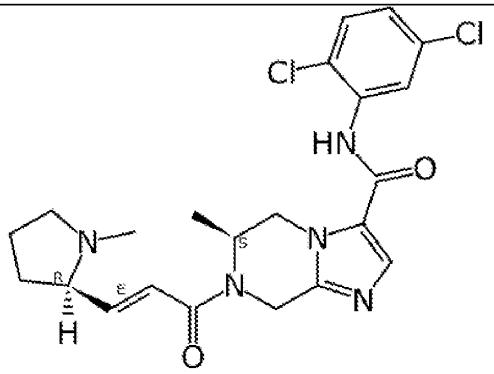
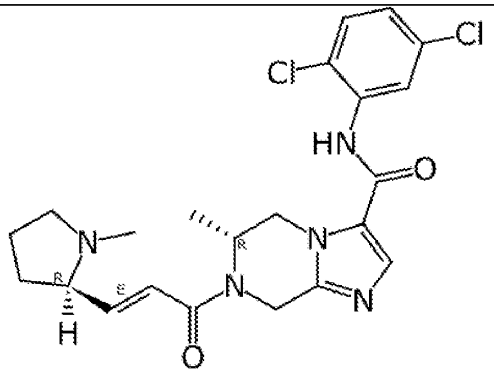
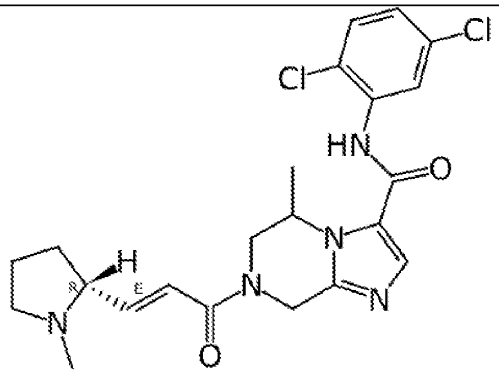
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
400		+++	
401		++++	
402		+++++	
403		++++	

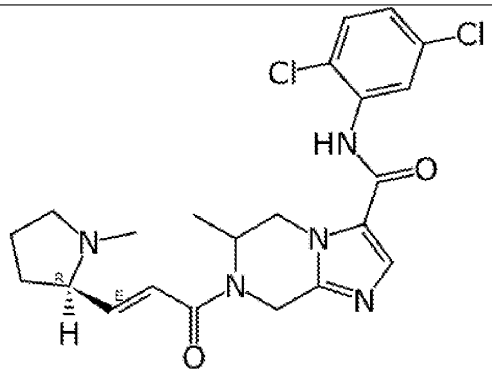
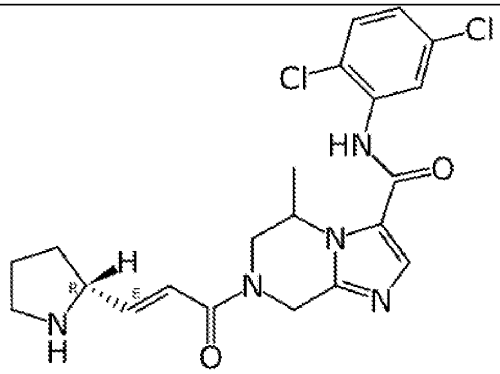
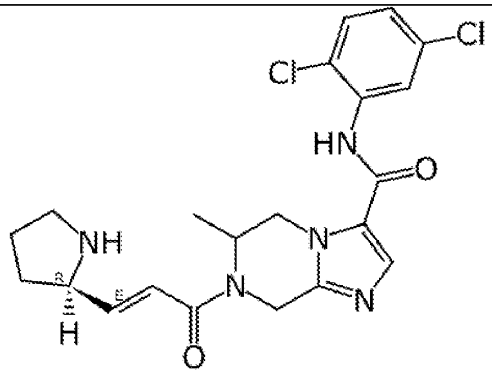
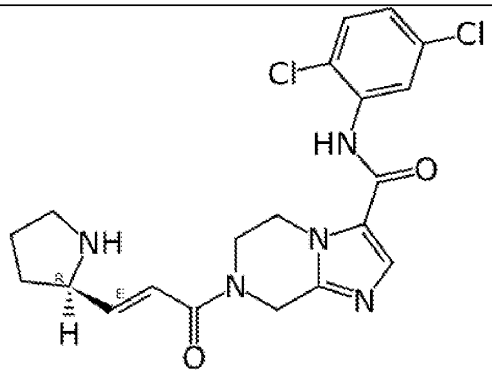
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
404		+++	
405		++++	
406		++++	
407		+++++	

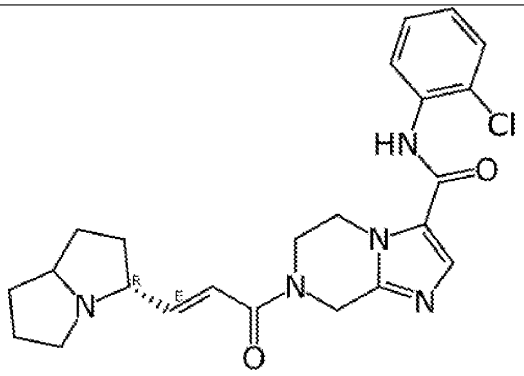
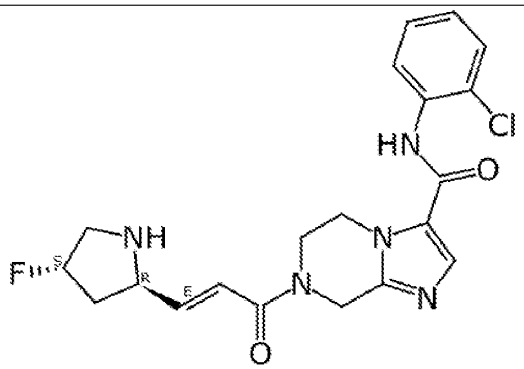
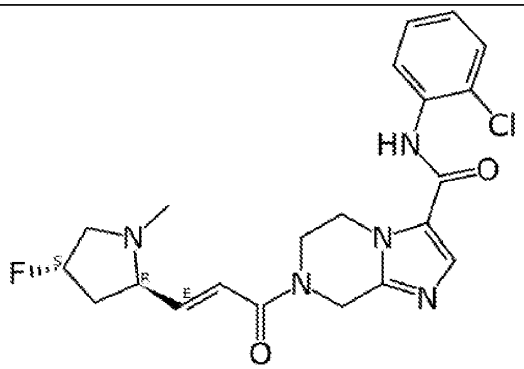
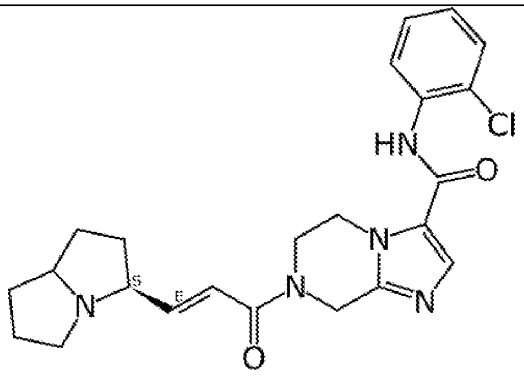
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
408		++++	
409		++	
410		+++	
411		++	
412		+++++	

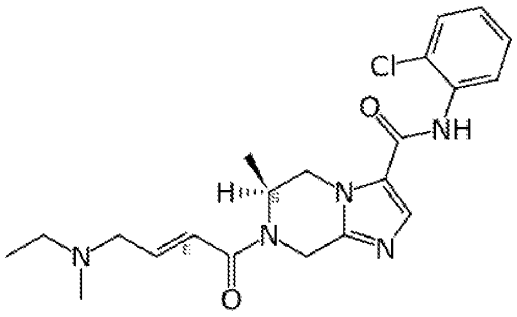
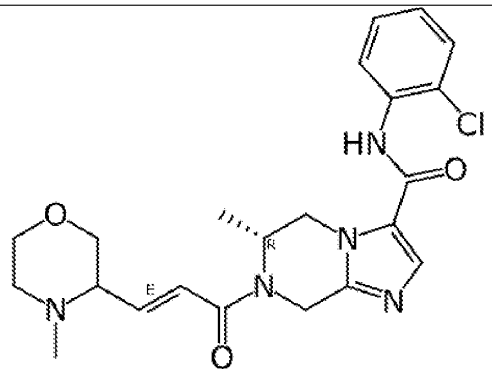
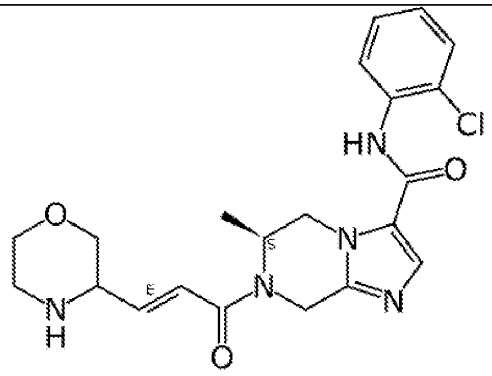
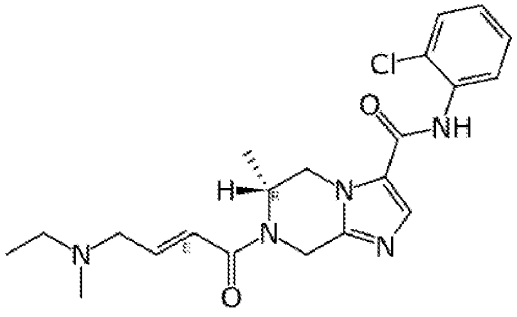
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
413		++	
414		+++	
415		+++++	
416		+++++	

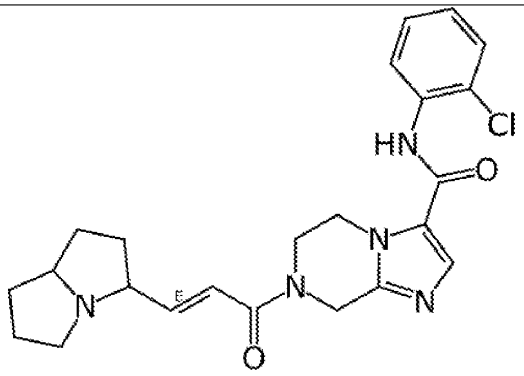
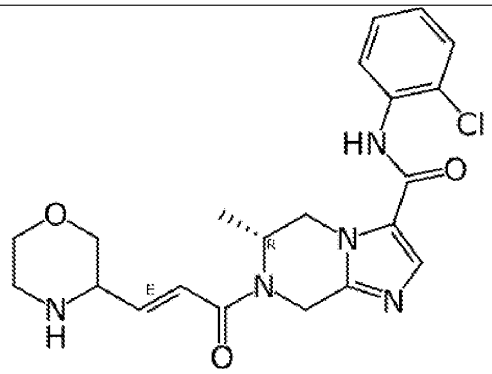
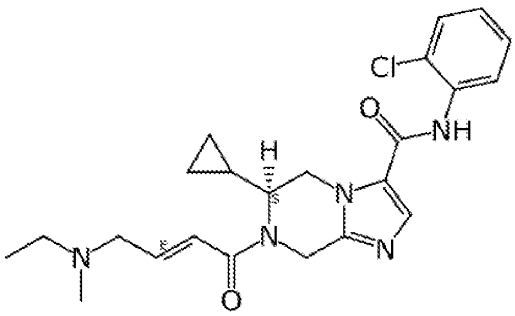
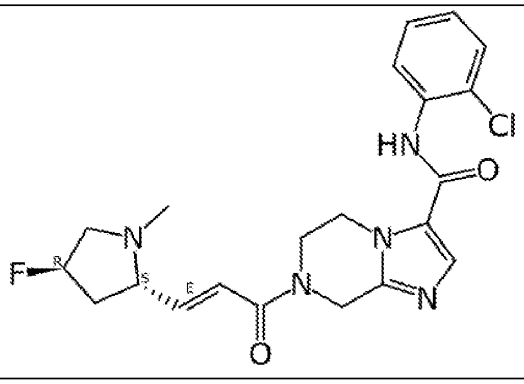
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
417		++	
418		+++++	
419		+++	
420		+++++	

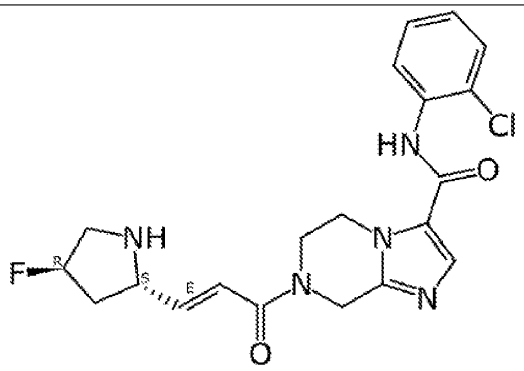
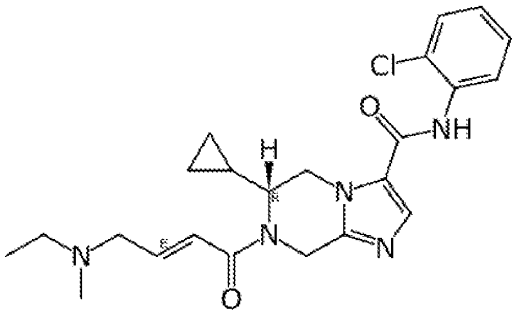
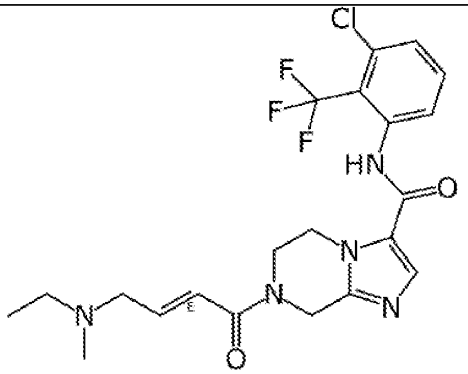
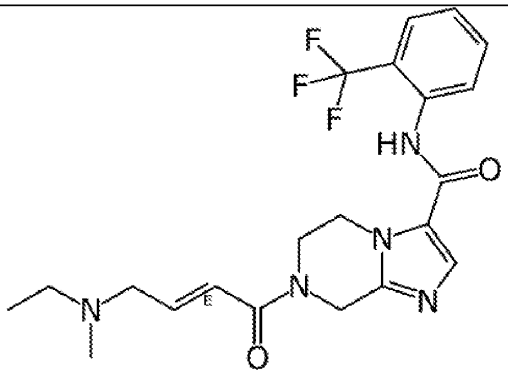
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
421		++	
422		+	
423		++++	
424		+++++	

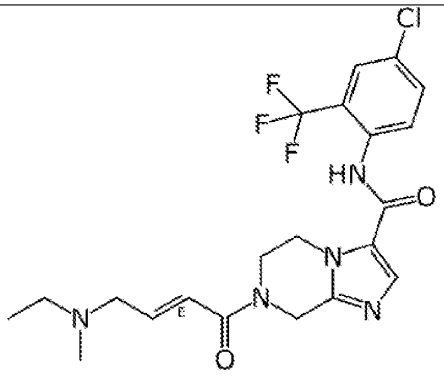
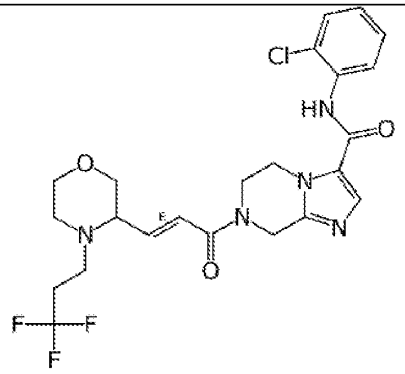
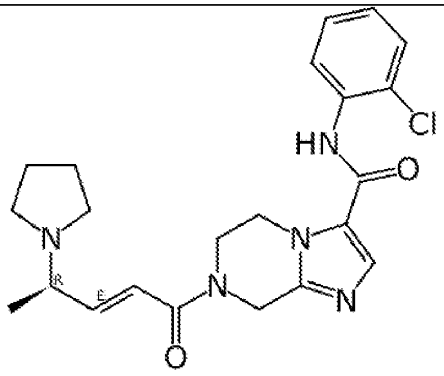
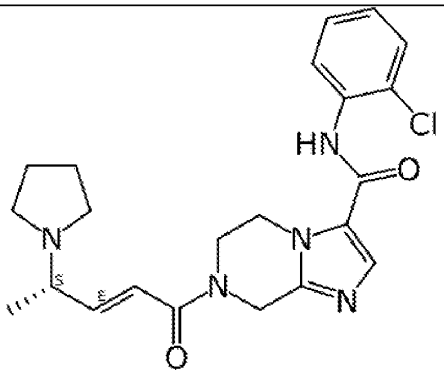
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
425		++++	
426		+++++	
427		+++	
428		+++	

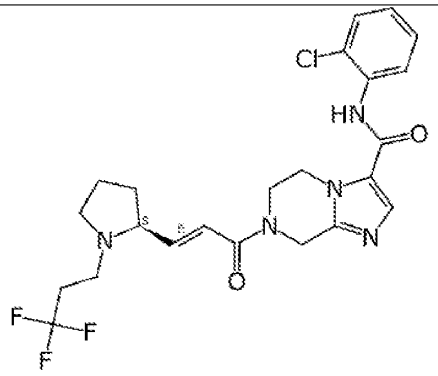
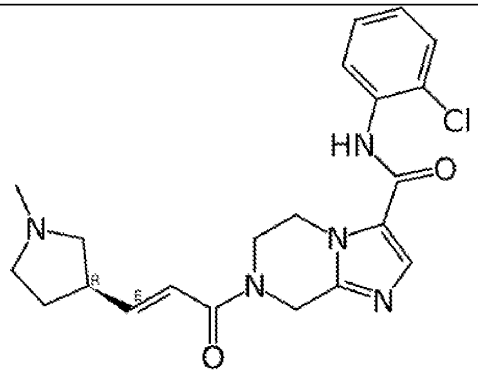
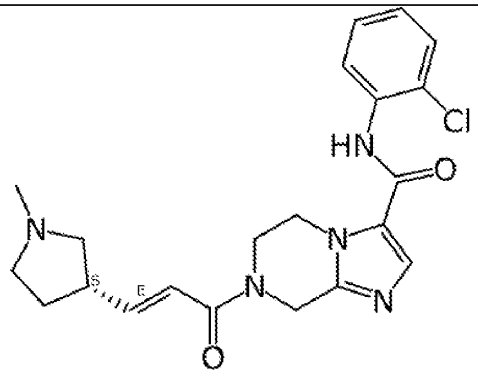
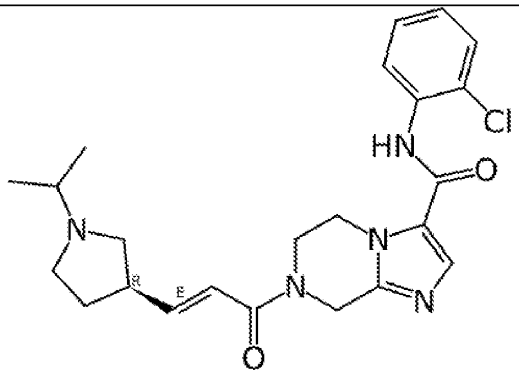
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
429		+++++	
430		+++++	
431		+++++	
432		+++++	

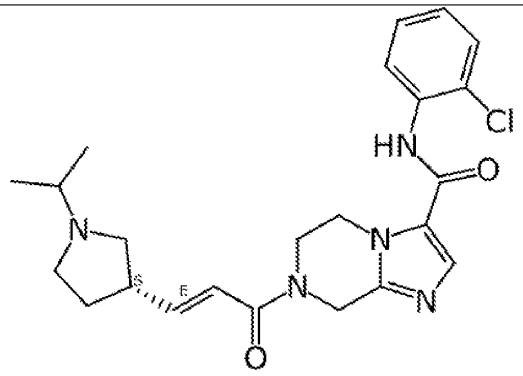
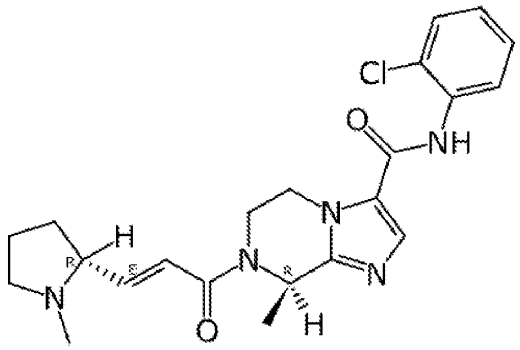
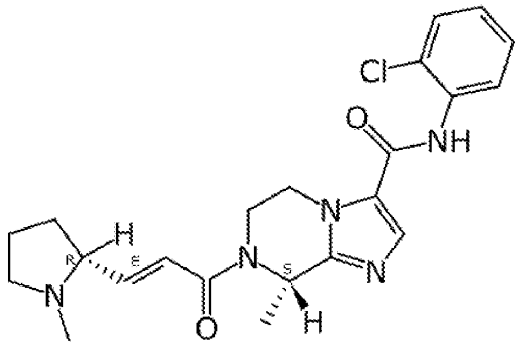
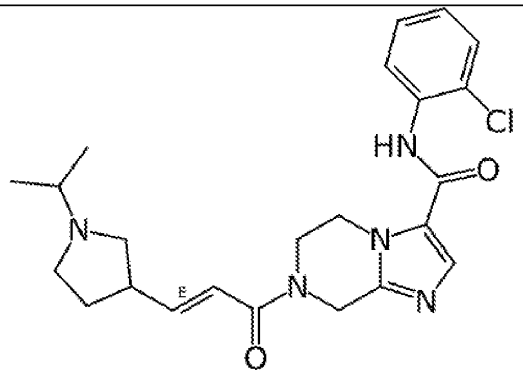
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
433		+++	
434		+	
435		+++	
436		+++++	

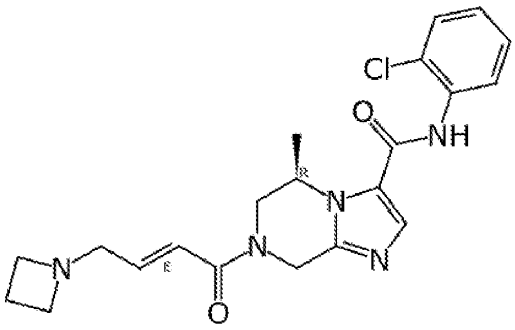
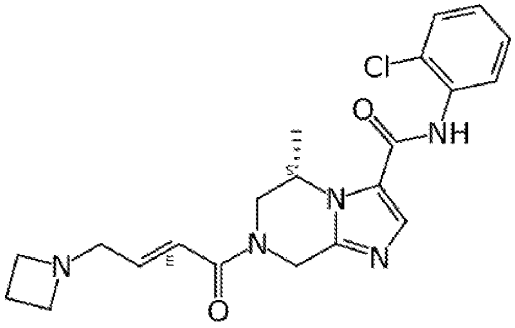
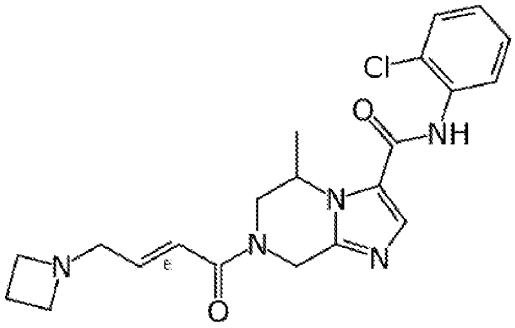
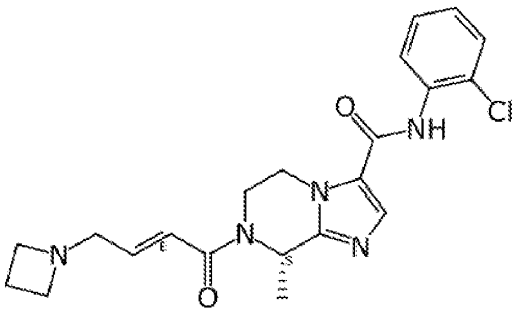
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
437		+++++	
438		+++++	
439		++	
440		+++++	

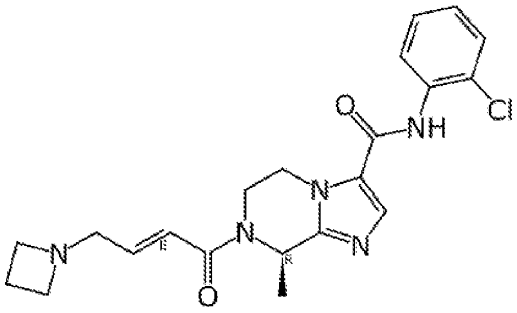
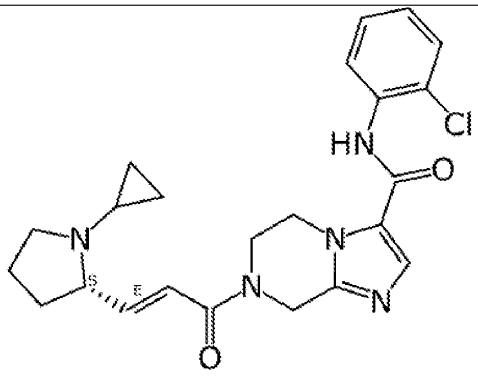
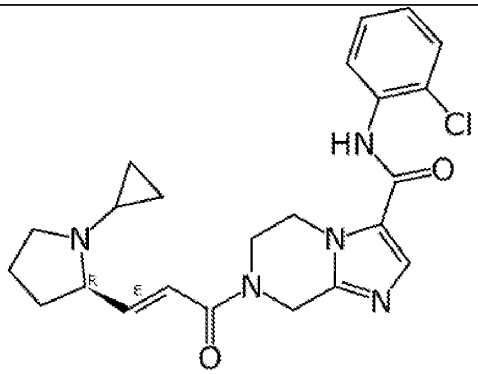
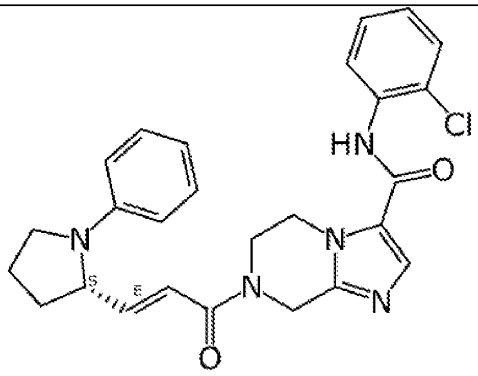
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
441		+++++	
442		++++	
443		++	
444		++	

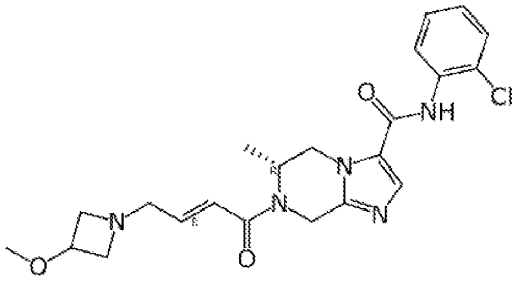
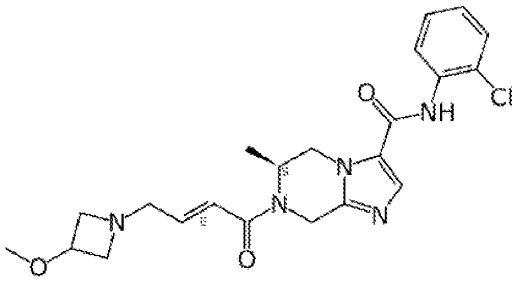
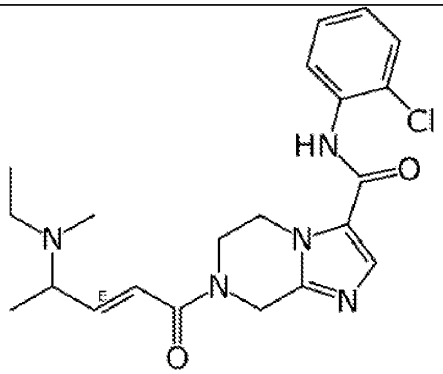
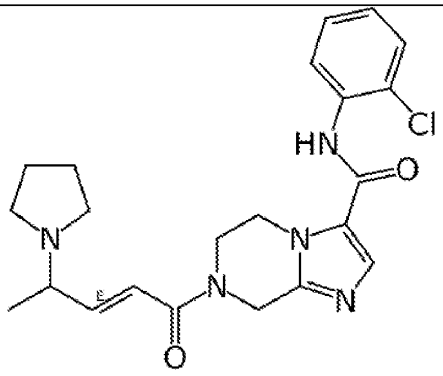
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
445		++	
446		+	
447		++	
448		+++	

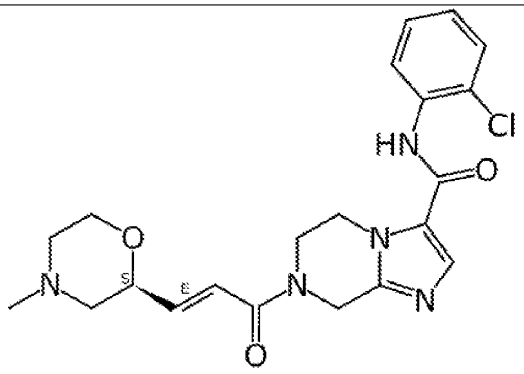
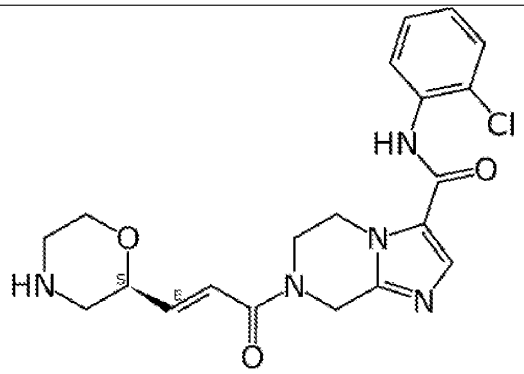
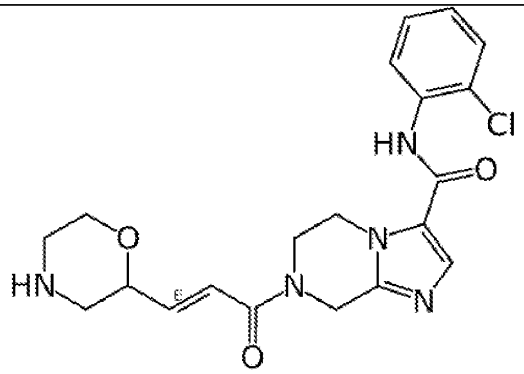
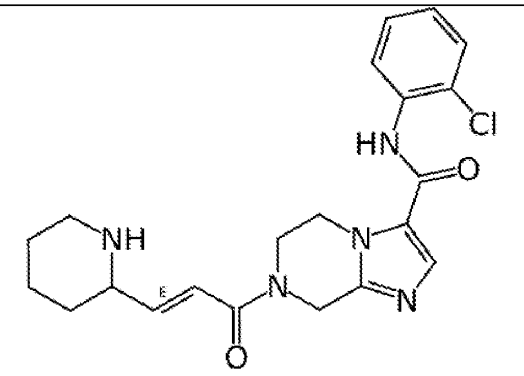
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
449		++++	
450		++	
451		+	
452		++	

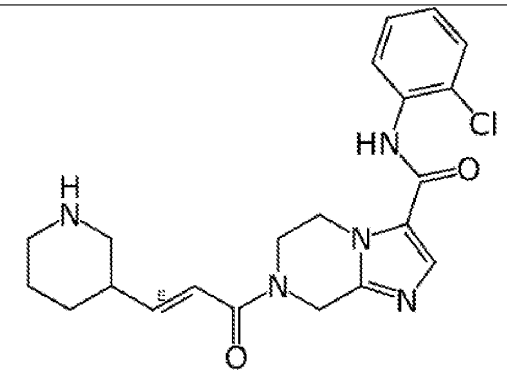
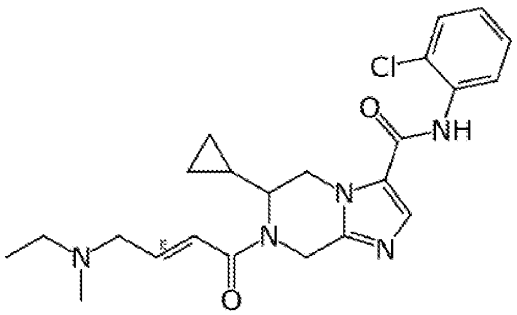
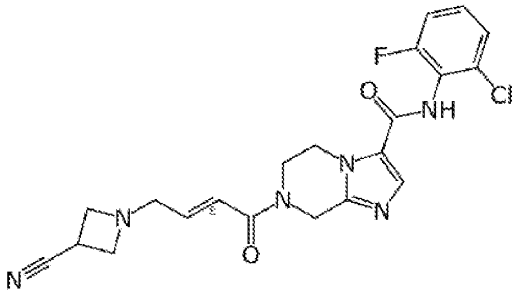
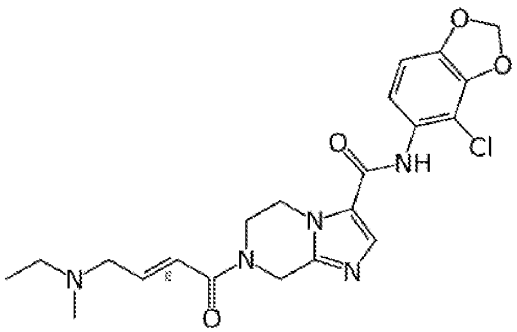
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
453		++	
454		++++	
455		+	
456		+	

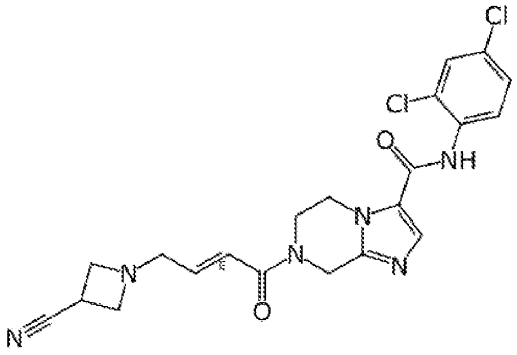
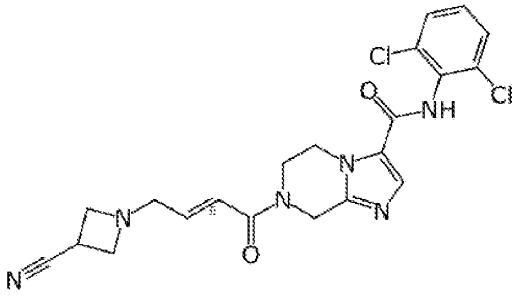
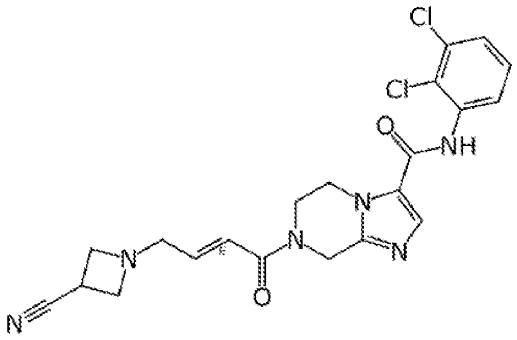
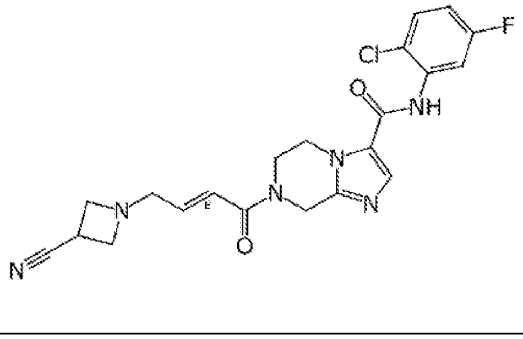
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
457		+++++	
458		++	
459		++++	
460		+++++	
461		++	
462		+++++	
463		++++	

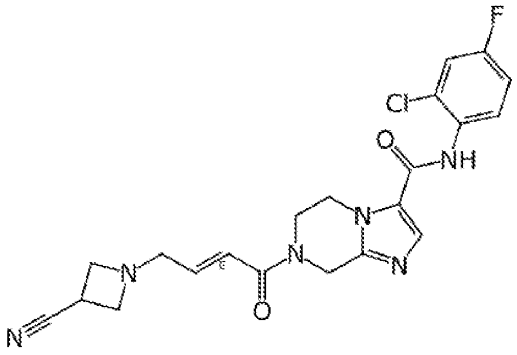
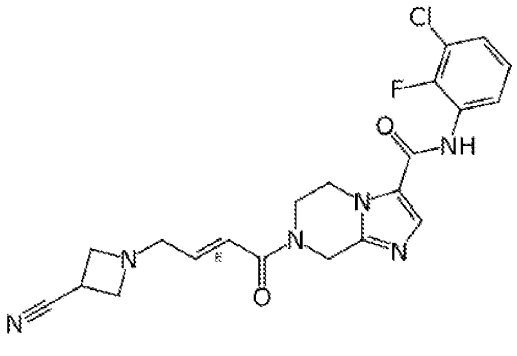
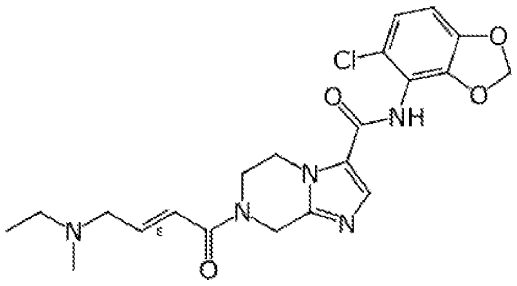
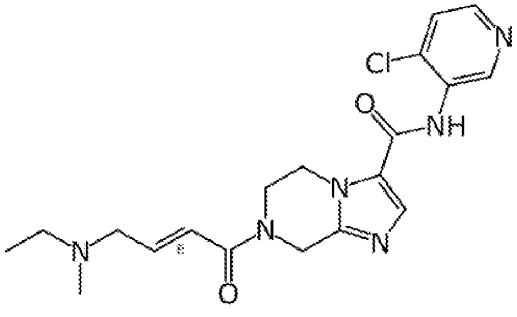
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
464		+	
465		+++	
466		+++	
467		+	

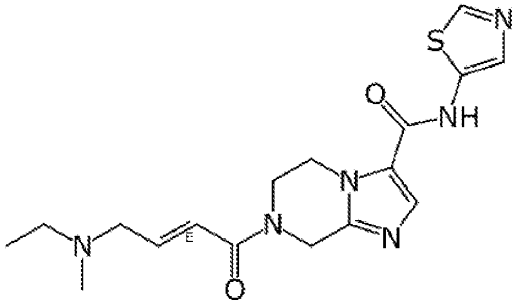
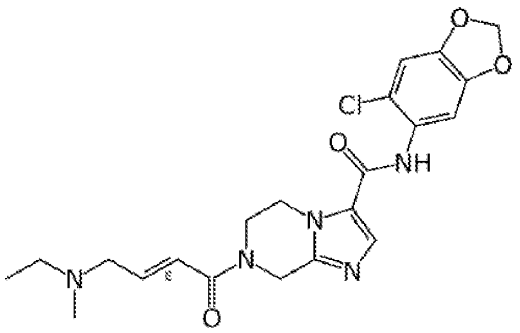
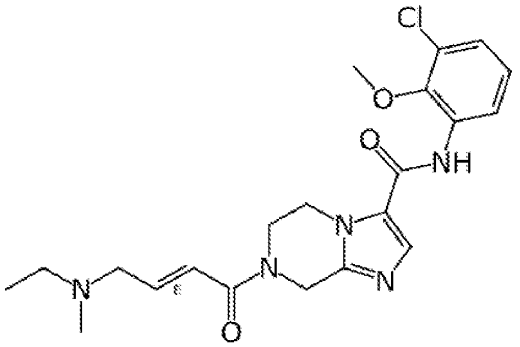
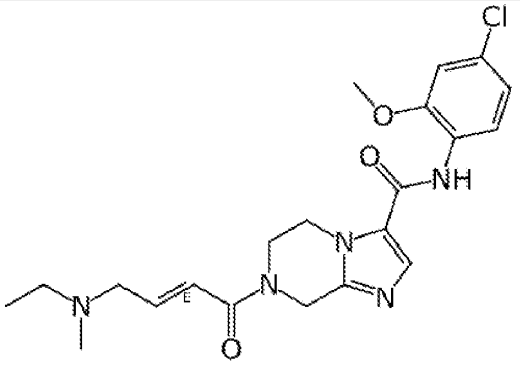
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
468		++++	+
469		+++++	+++
470		+++	
471		+++	+

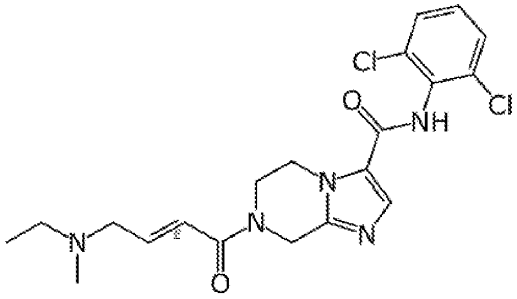
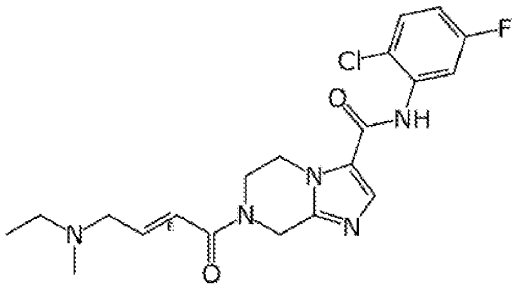
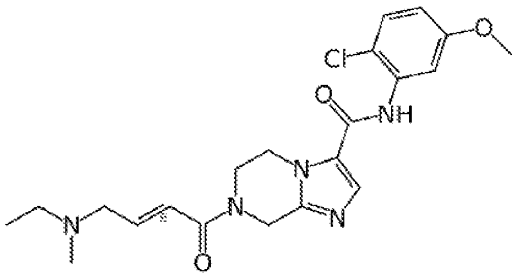
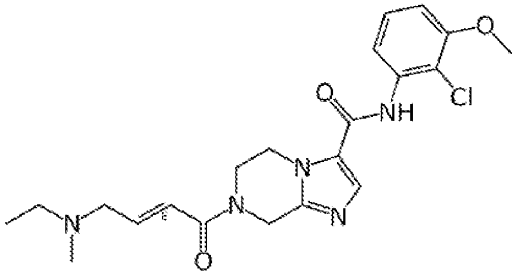
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
472		++	
473		++	
474		++	
475		++++	

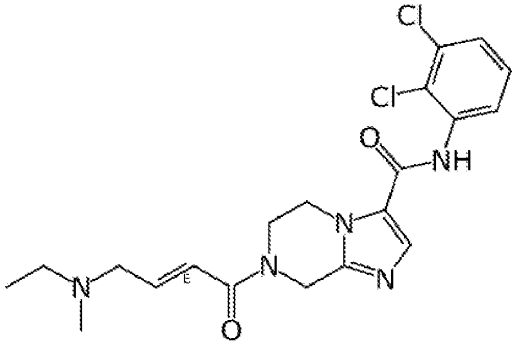
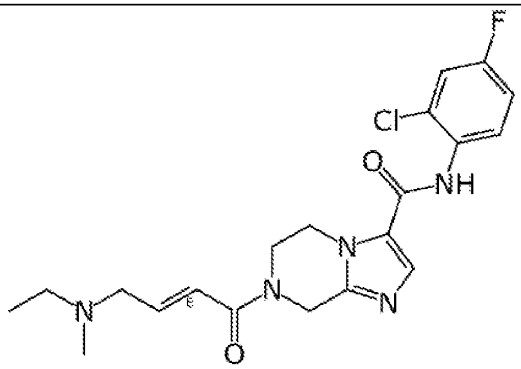
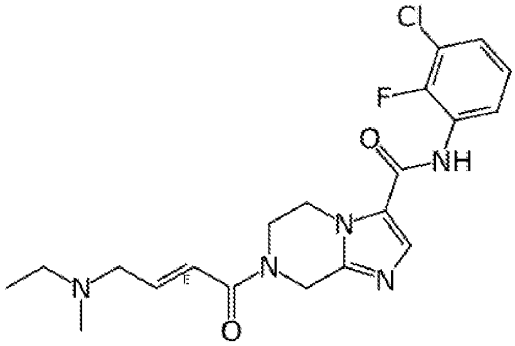
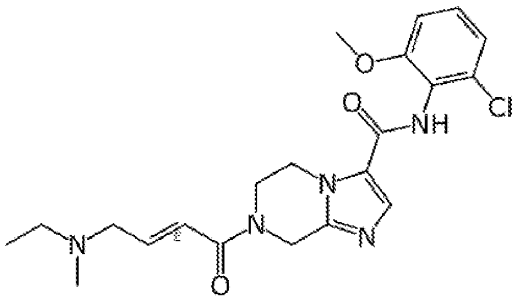
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
476		+	
477		++++	
478		+++	
479		+++	+

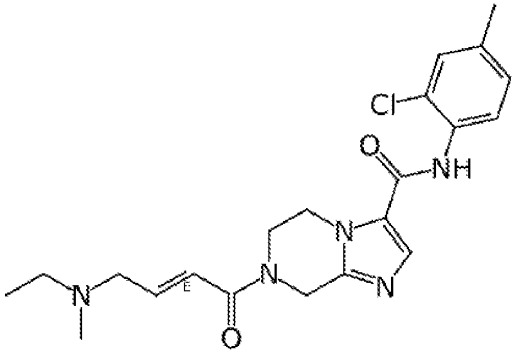
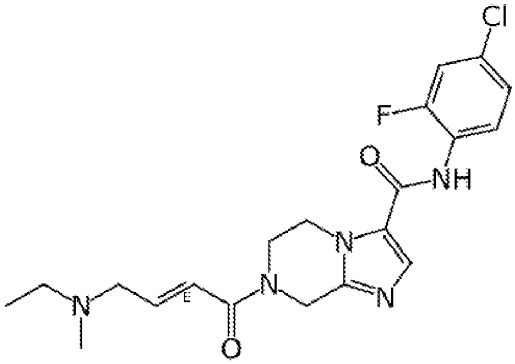
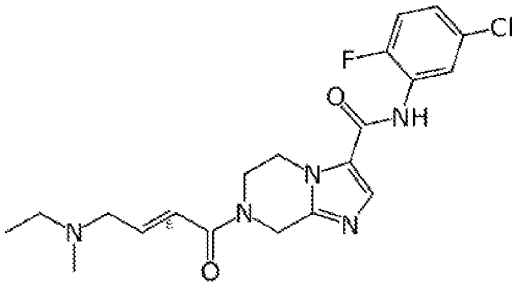
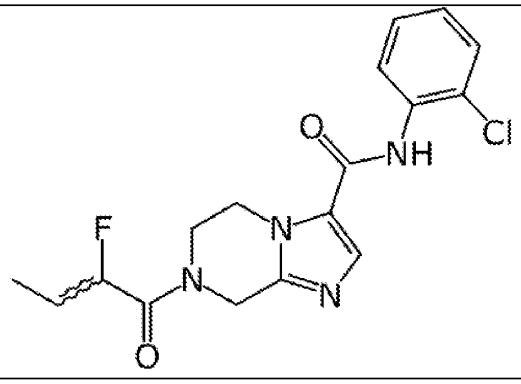
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
480		+++	
481		+++	
482		+	
483		++	

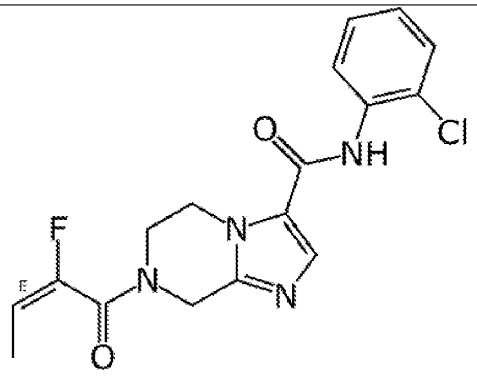
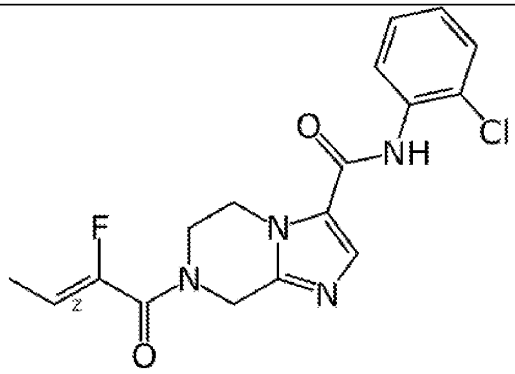
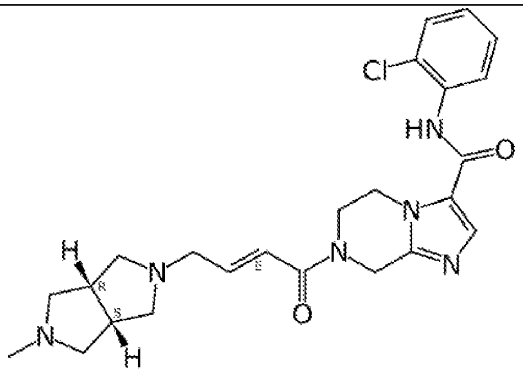
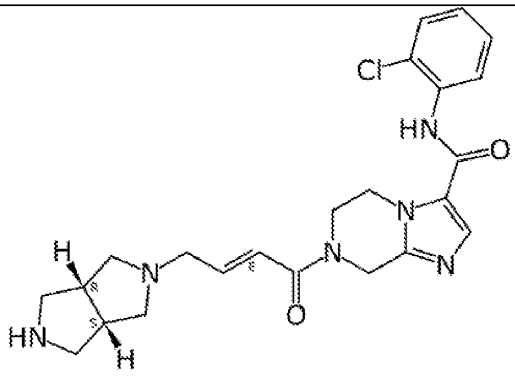
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
484		++	
485		+	
486		+++	
487		+	

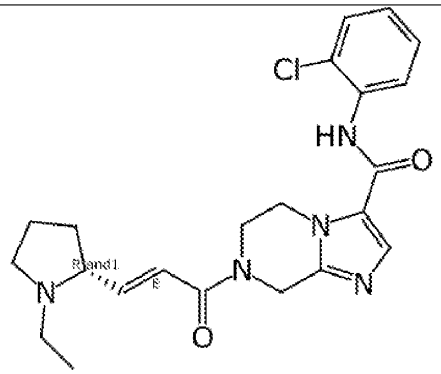
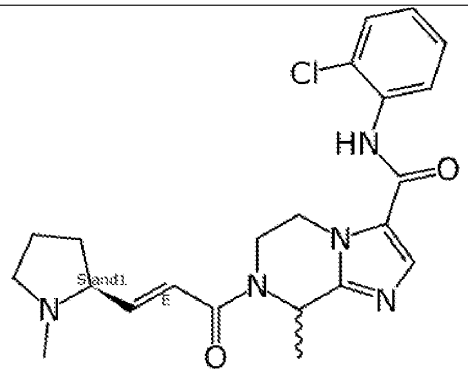
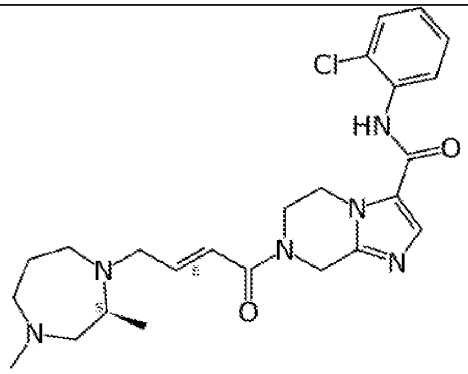
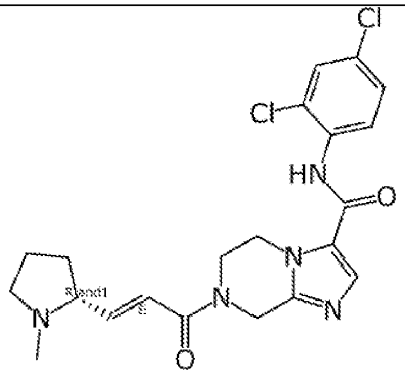
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
488		+	
489		++	
490		++	
491		+	

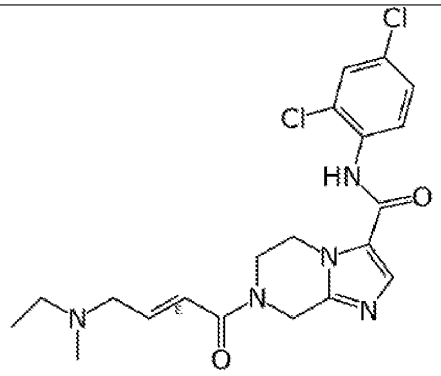
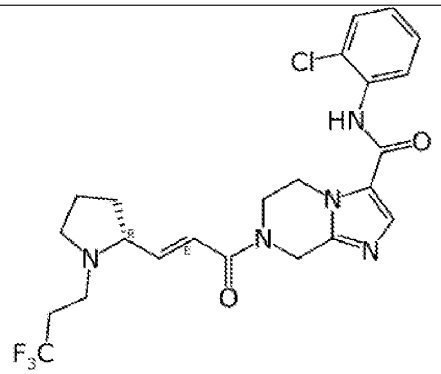
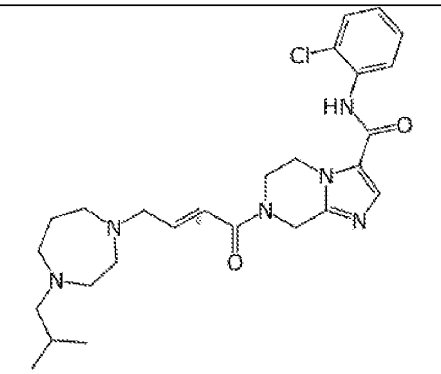
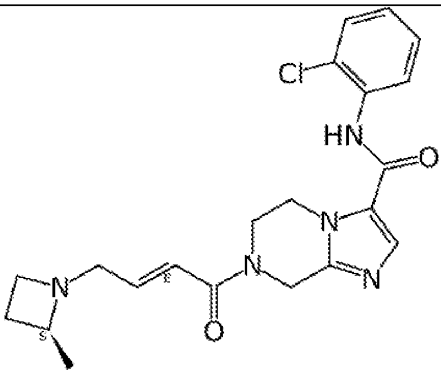
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
492		+++++	+
493		++++	
494		+	+
495		+++	+

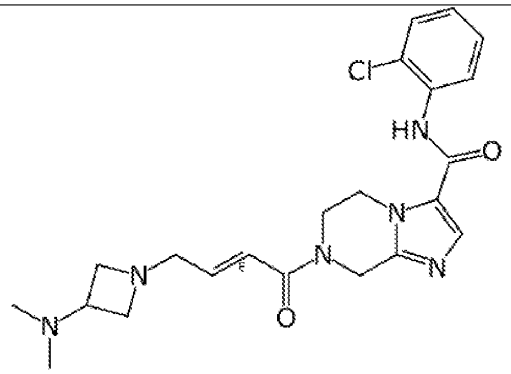
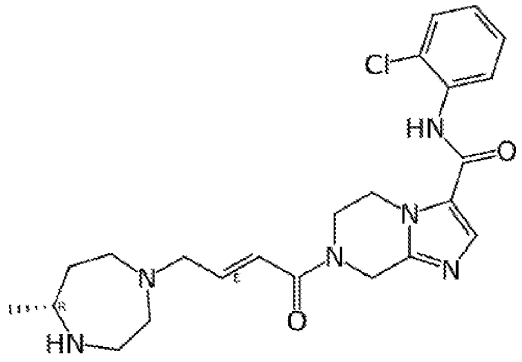
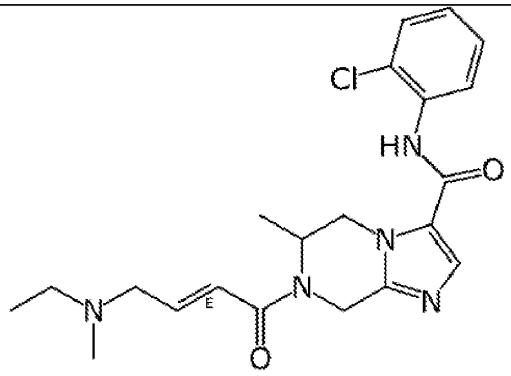
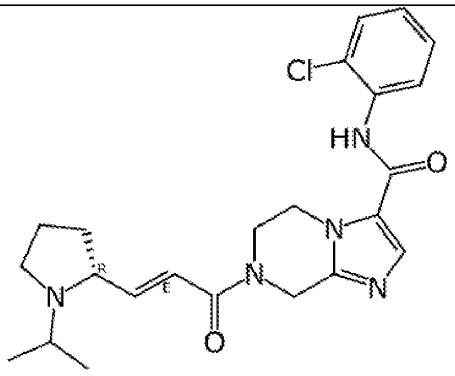
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
496		+++	+
497		++++	+
498		+	+
499		+++	+

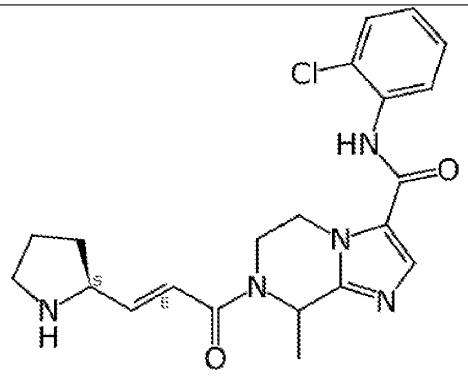
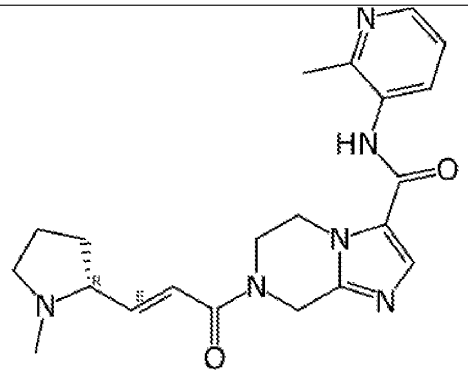
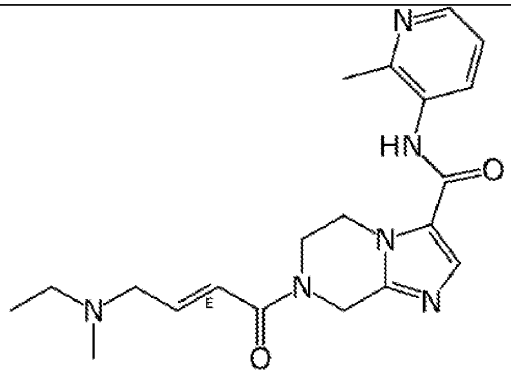
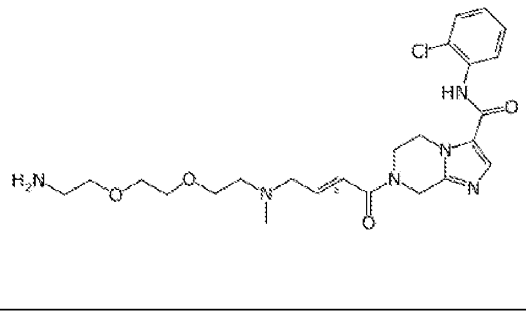
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
500		+++++	+
501		++++	
502		++	+
503		+	+
504		+	

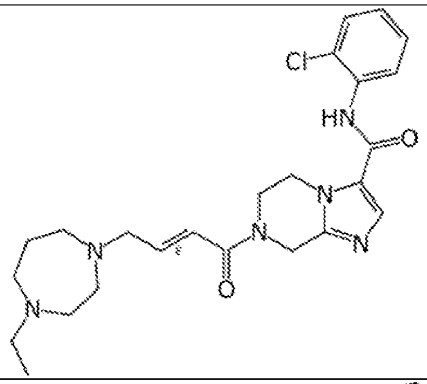
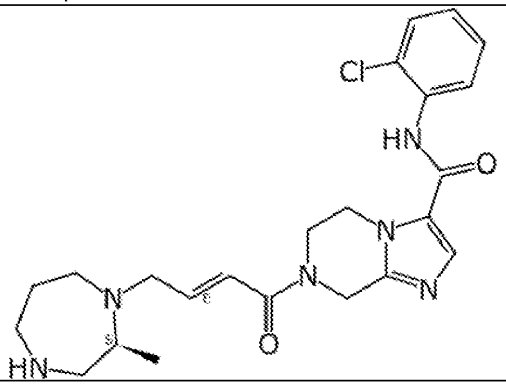
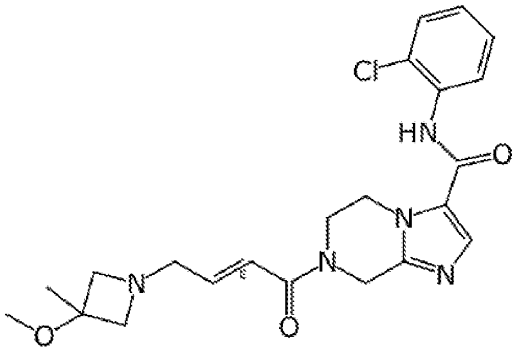
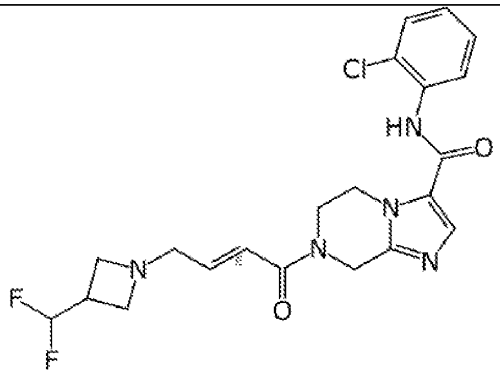
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
505		+	+
506		+	+
507		+++	
508		+	

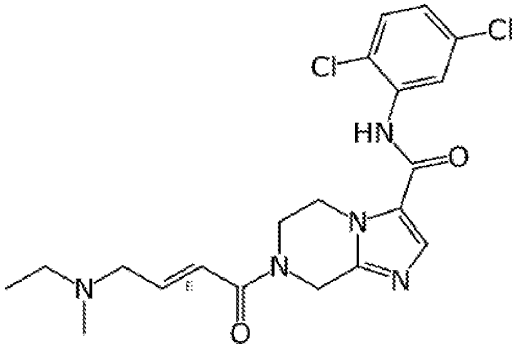
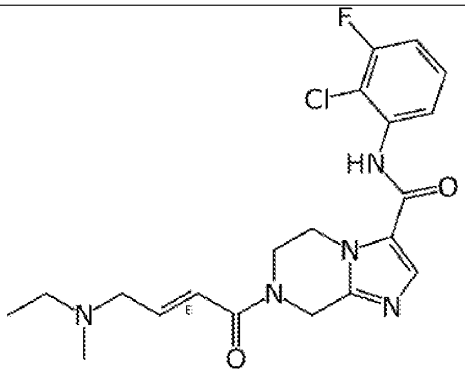
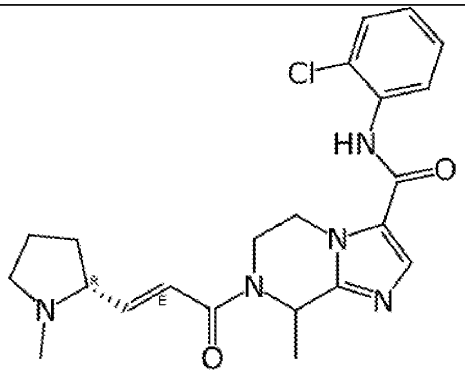
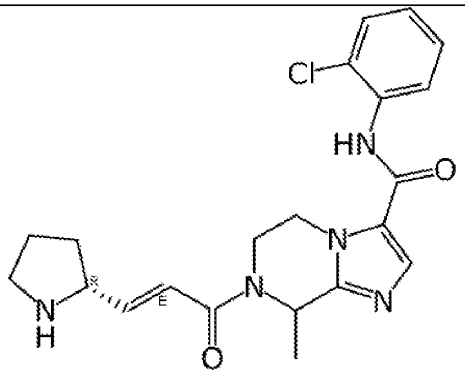
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
509		++++	
510		++	
511		++	
512		+++++	

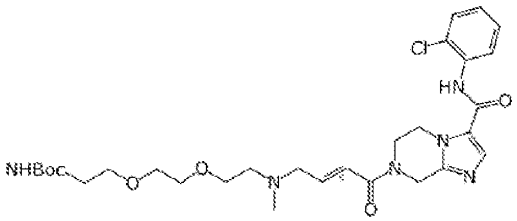
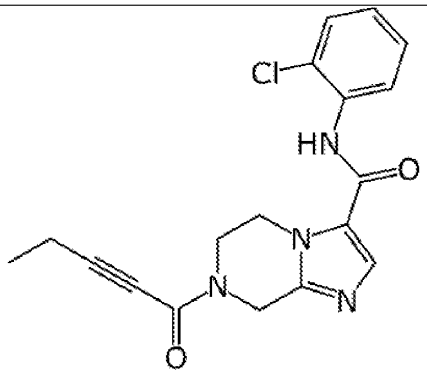
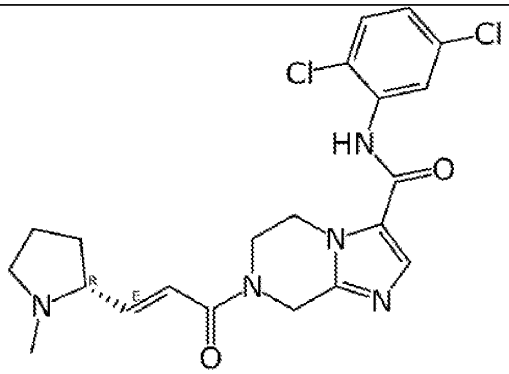
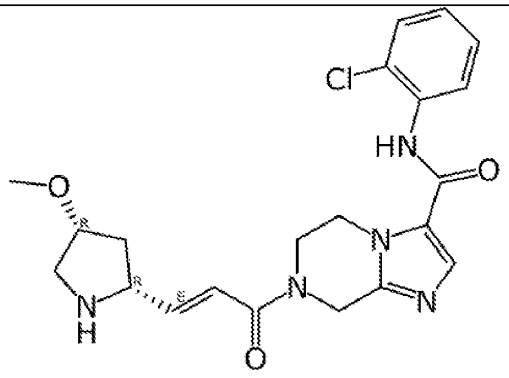
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
513		+++++	+
514		++++	
515		+++	
516		++	
517		+++++	

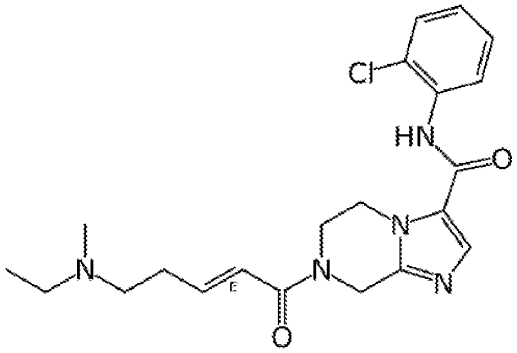
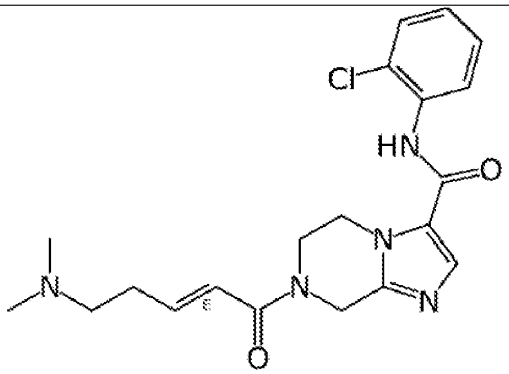
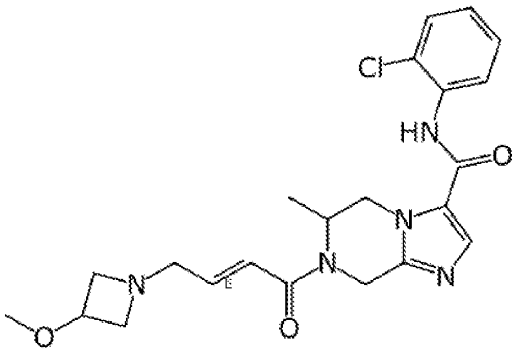
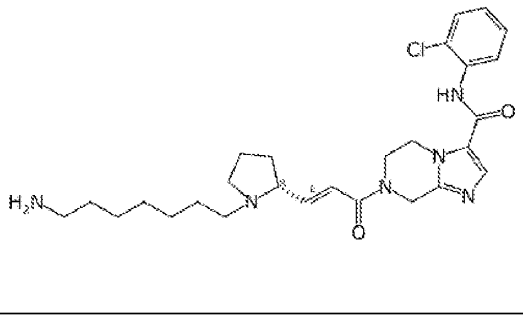
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
518		+++++	
519		+	
520		++++	
521		++++	

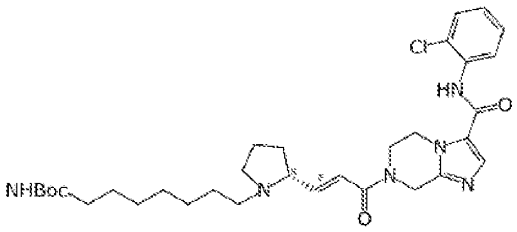
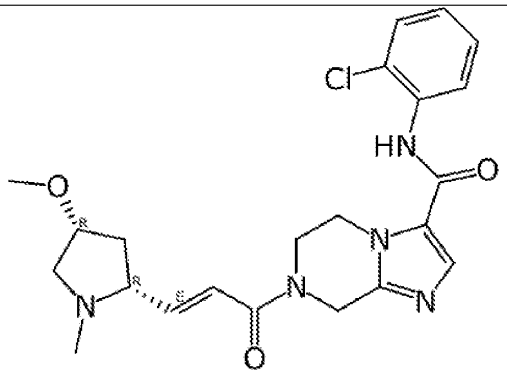
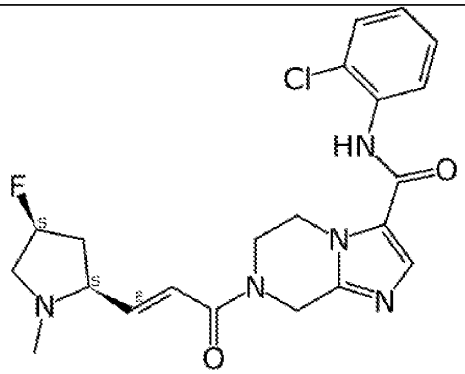
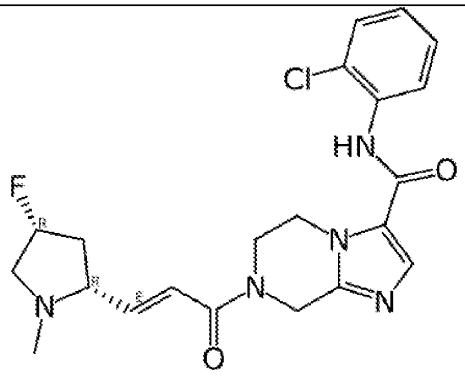
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
522		+++	
523		++	
524		+	
525		+++++	

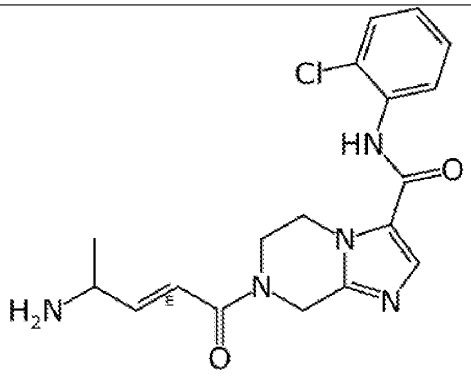
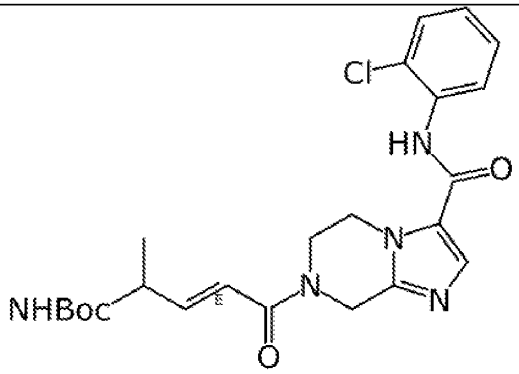
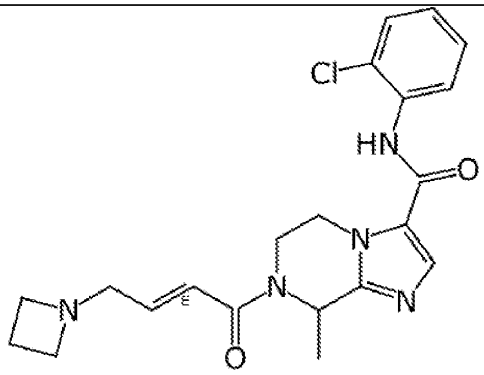
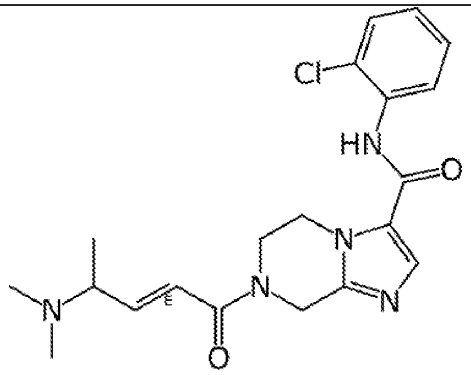
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
526		++	
527		++	
528		++++	
529		+++++	+

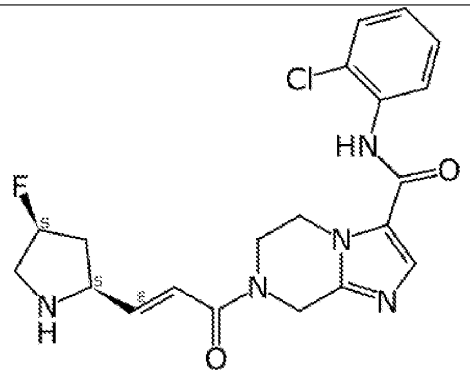
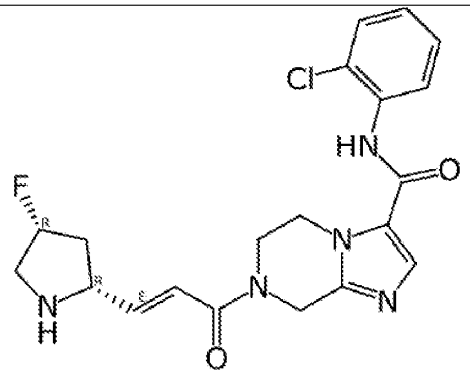
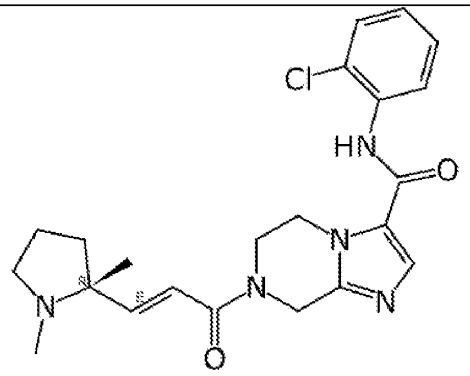
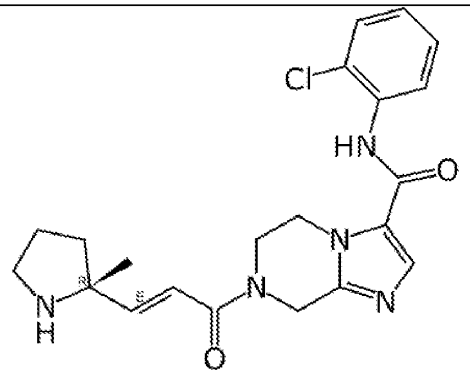
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
530		+++	+
531		++++	
532		++++	+
533		++++	+

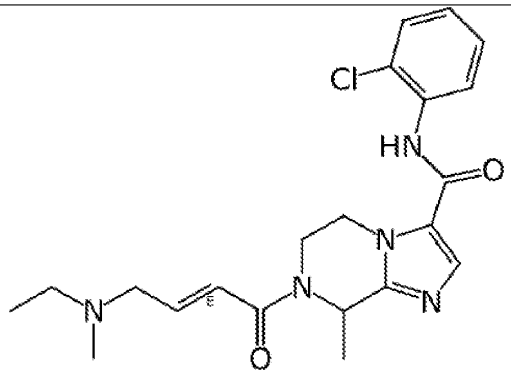
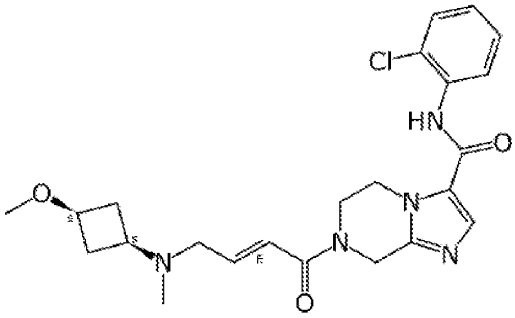
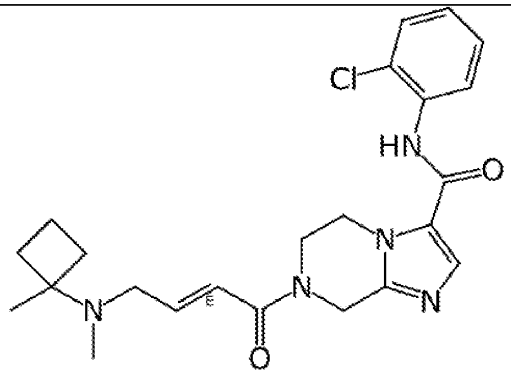
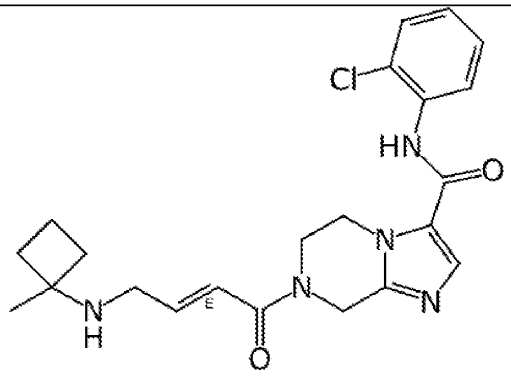
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
534		++++	+
535		+++	+
536		++++	+
537		+++++	+

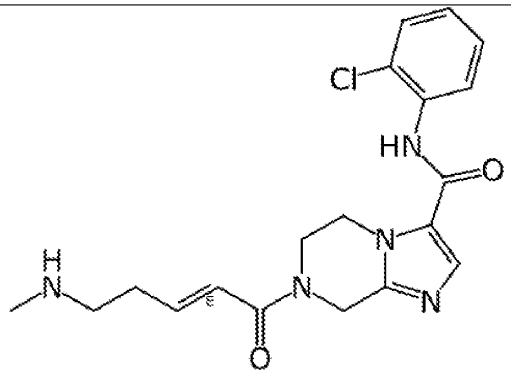
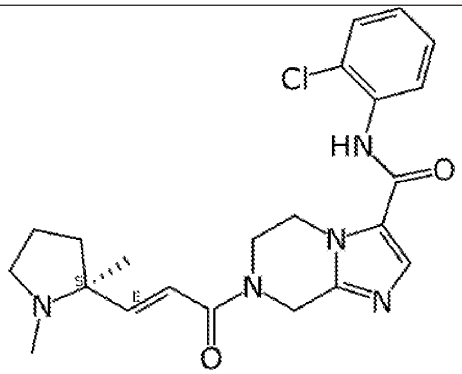
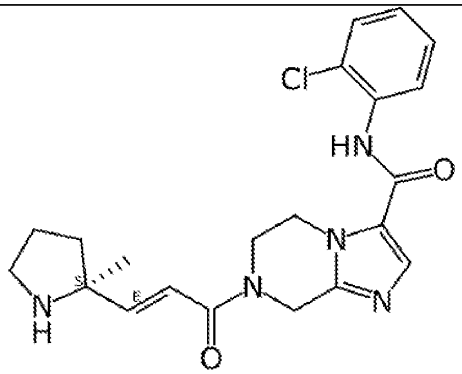
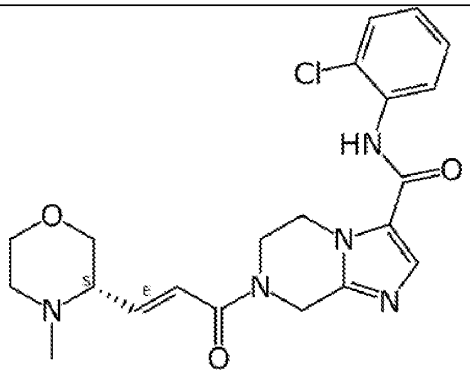
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
538		+++	+
539		++	+
540		+++++	+
541		+++++	++

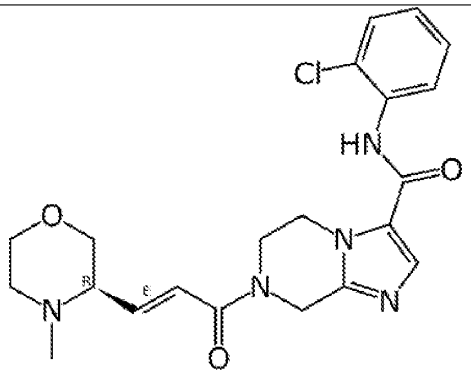
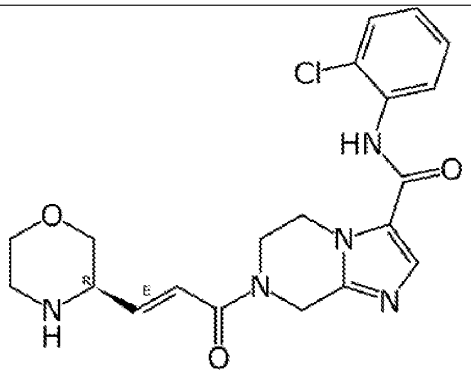
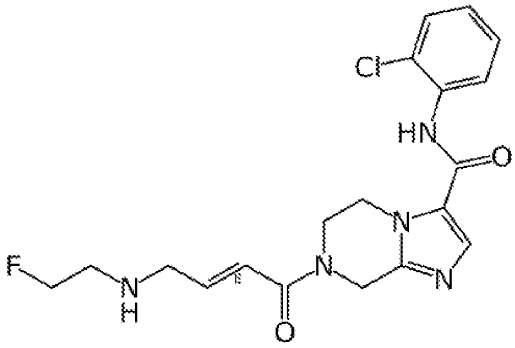
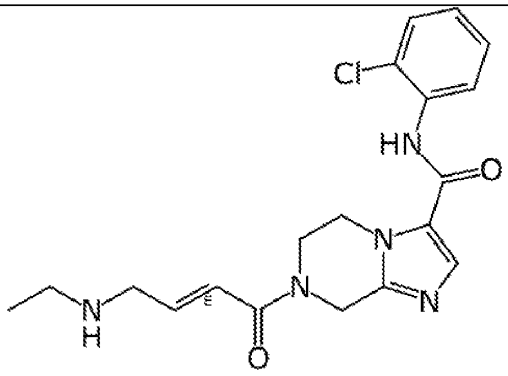
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
542		++++	+
543		+++++	+
544		++++	+
545		+++++	+

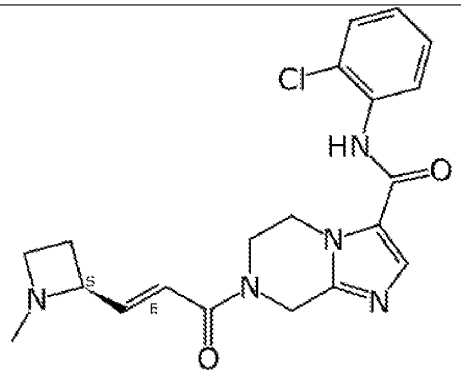
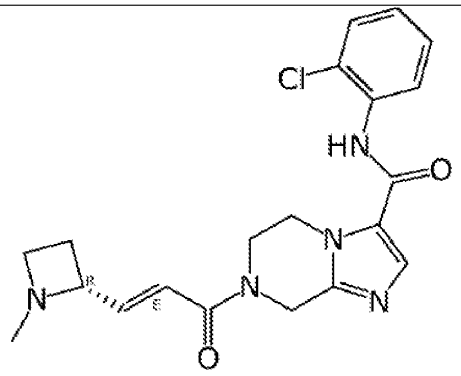
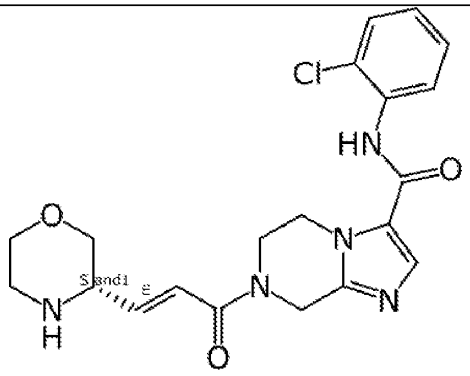
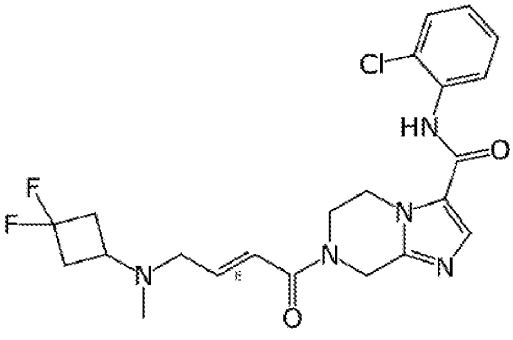
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
546		+++++	+
547		+	+
548		++++	+
549		++++	+

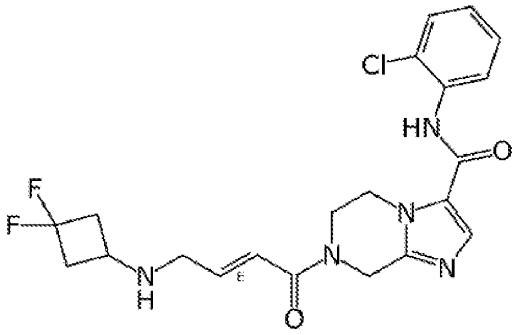
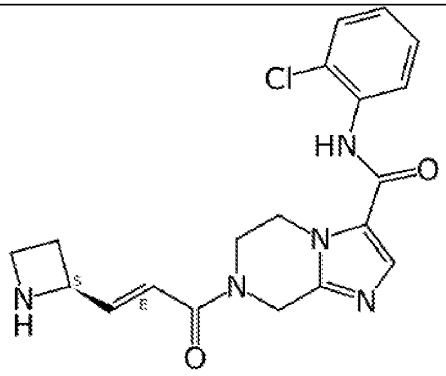
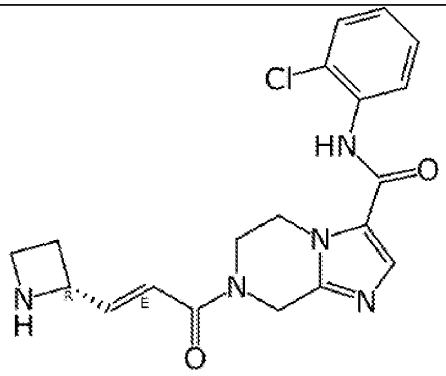
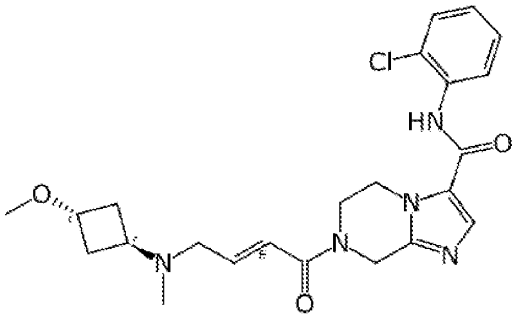
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
550		+++++	+
551		+++++	+
552		++++	+
553		++++	+

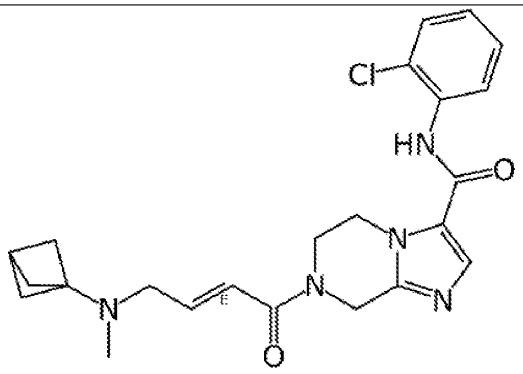
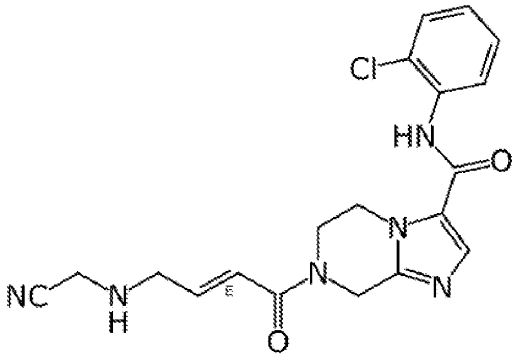
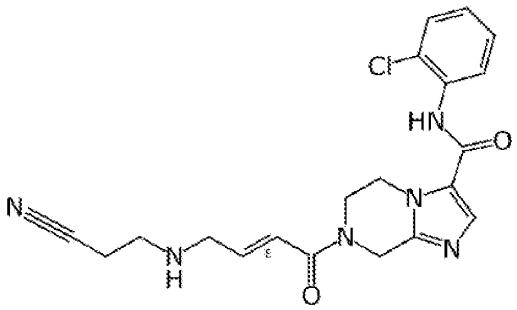
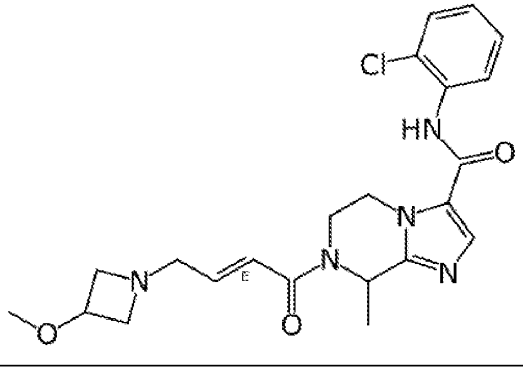
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
554		+++	+
555		++++	+
556		++++	+
557		++++	+

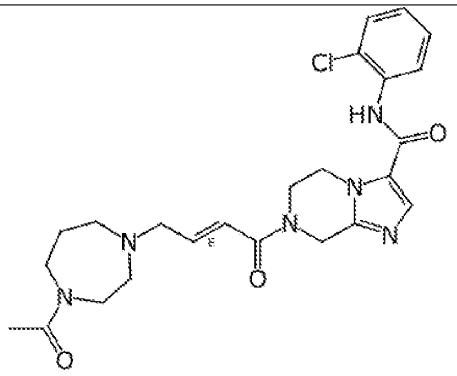
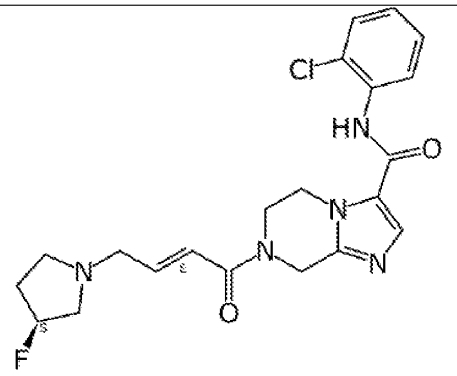
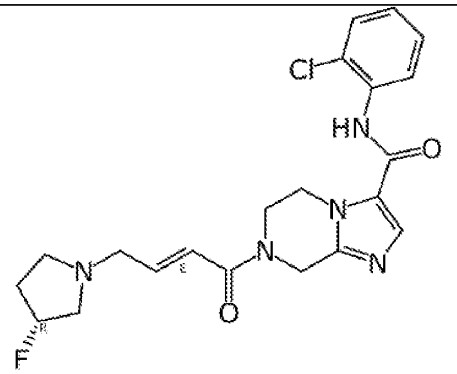
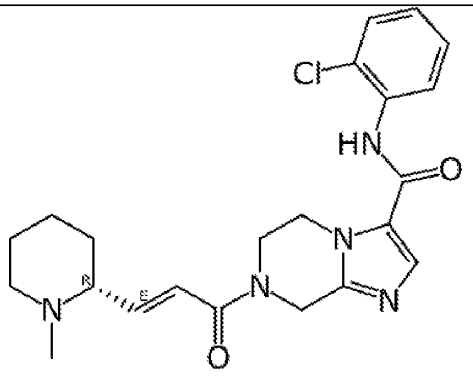
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
558		+++	+
559		+++	+
560		+++++	+
561		+	+

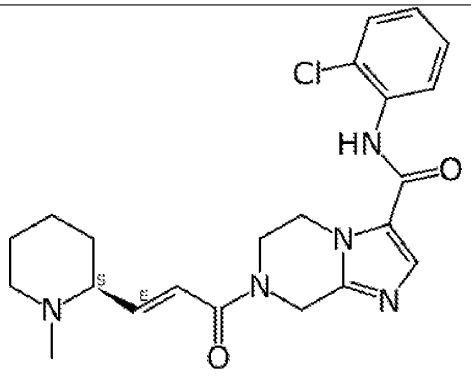
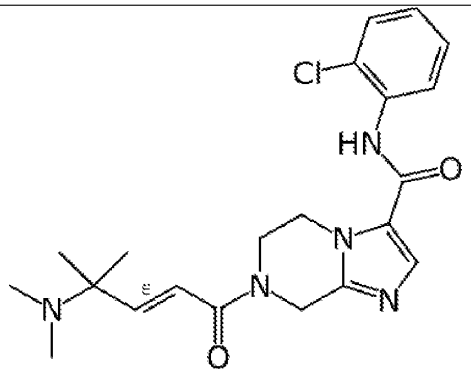
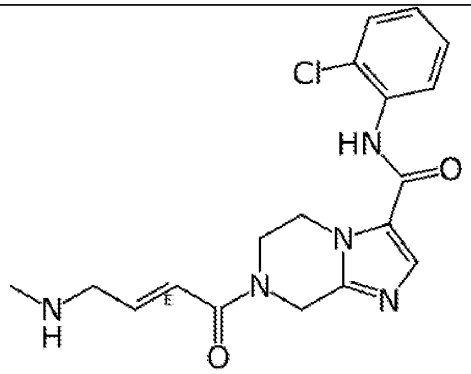
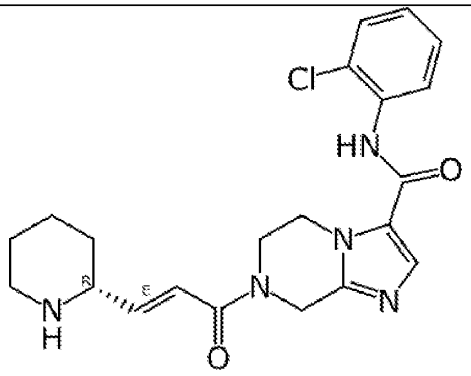
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
562		+	+
563		+++++	+
564		+++++	+
565		+++++	+

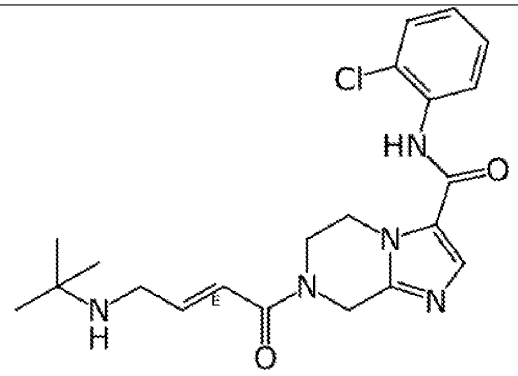
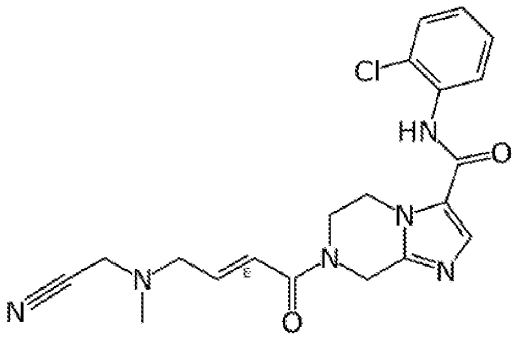
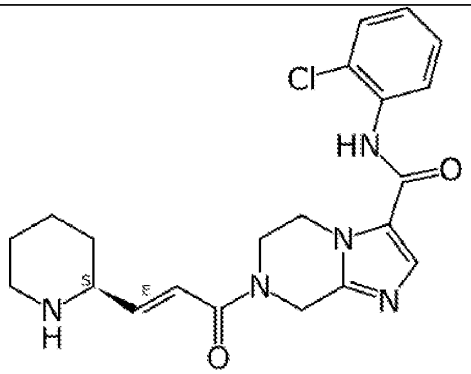
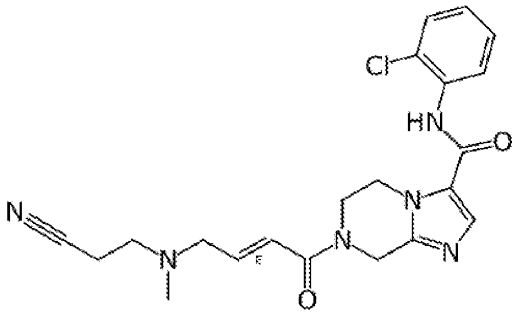
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
566		+++++	+
567		+++++	+
568		++++	+
569		+++	+

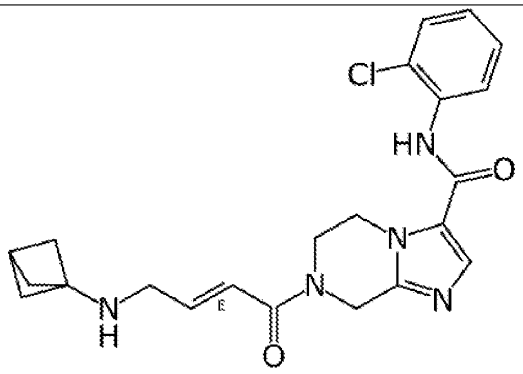
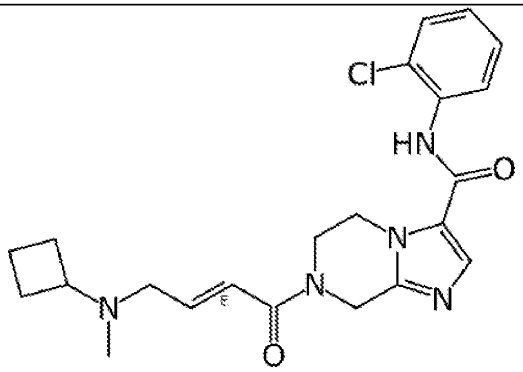
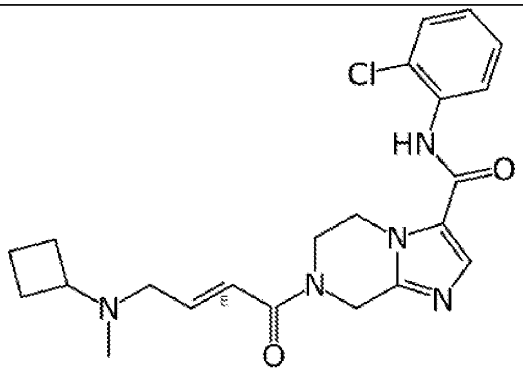
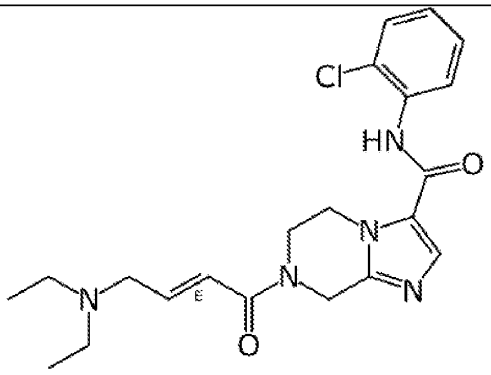
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
570		++++	+
571		+++++	+
572		+++++	+
573		++++	+

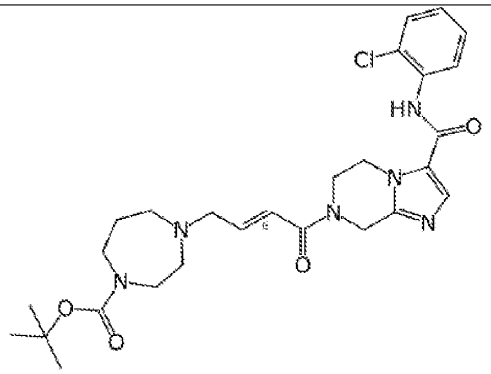
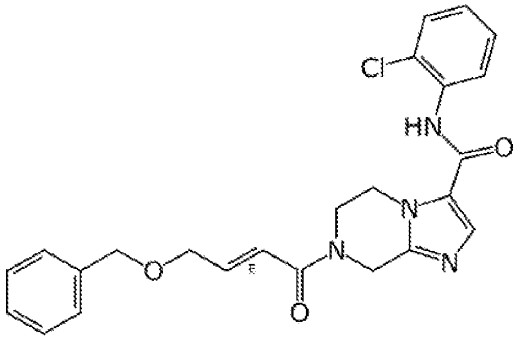
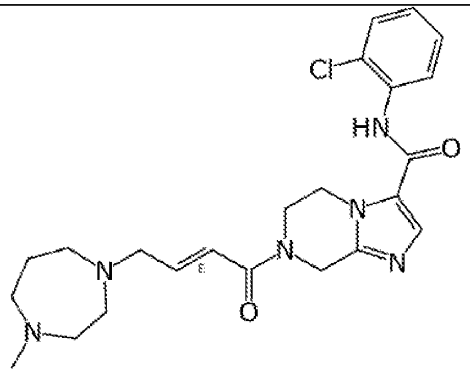
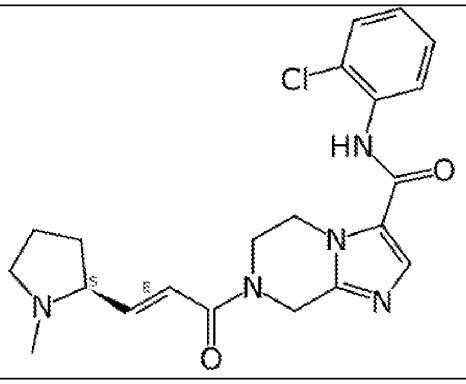
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
574		+++	+
575		++	+
576		++++	+
577		+++	+

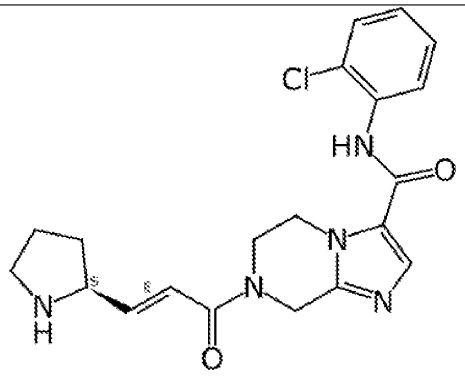
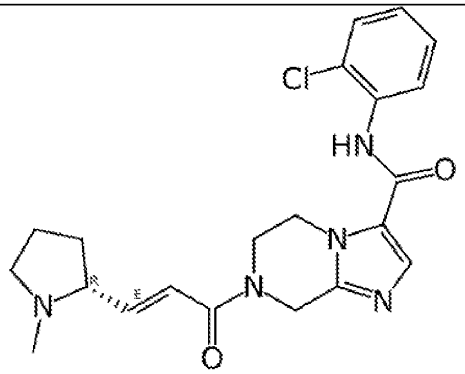
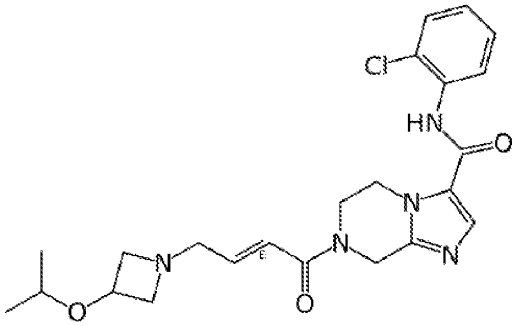
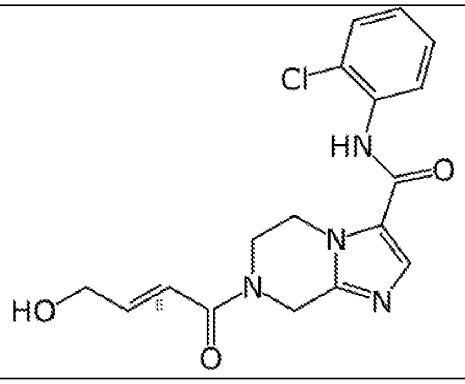
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
578		+++	+
579		++++	+
580		++++	+
581		++	+

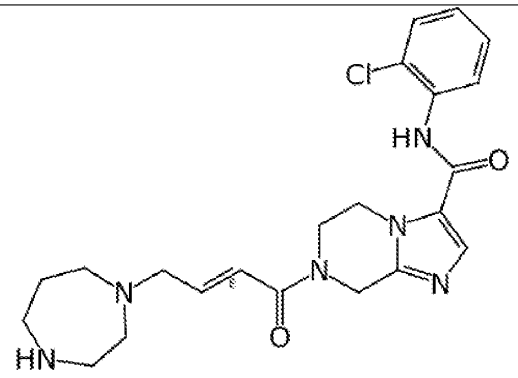
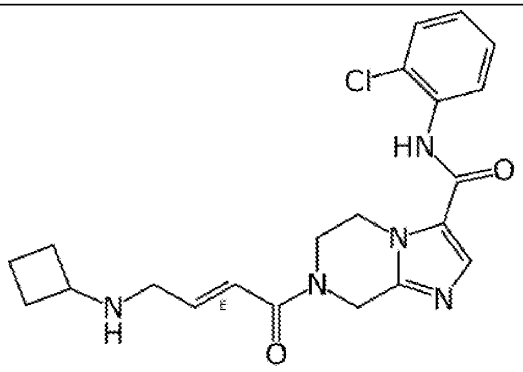
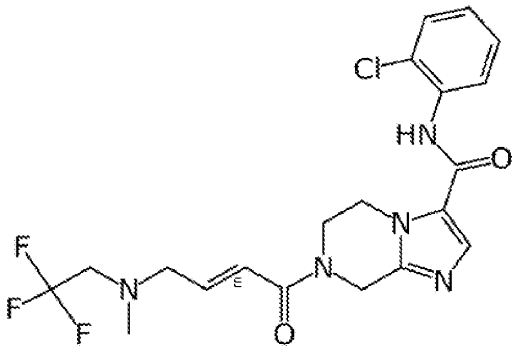
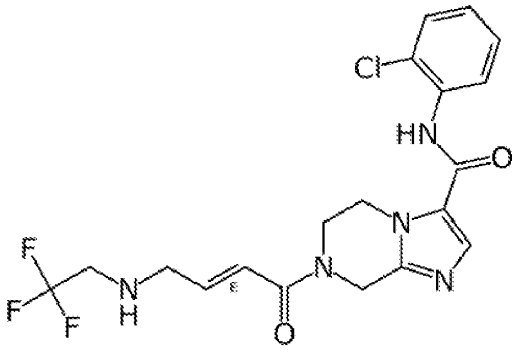
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
582		++	+
583		++	+
584		+++++	+
585		++++	+

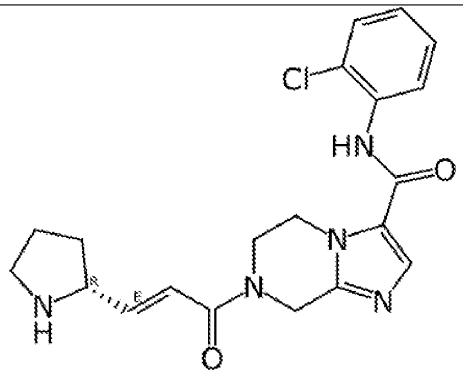
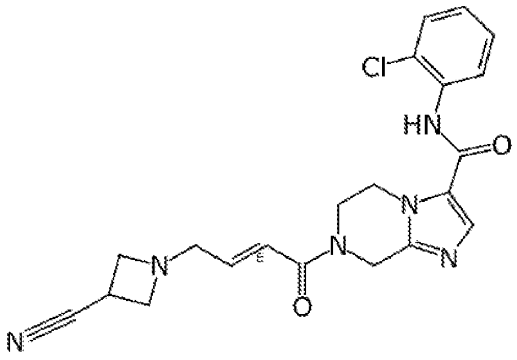
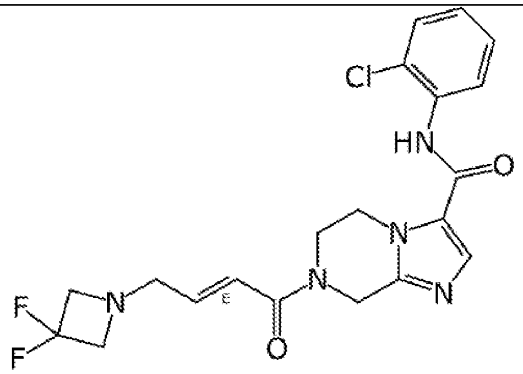
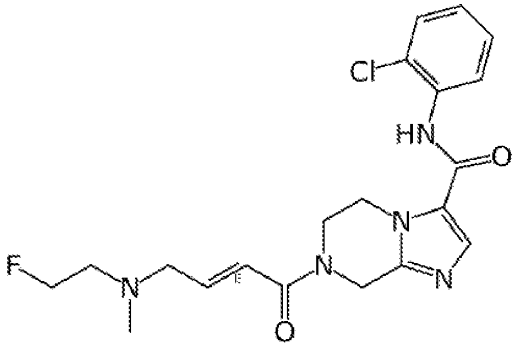
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
586		++++	+
587		+++	+
588		++++	+
589		++	+

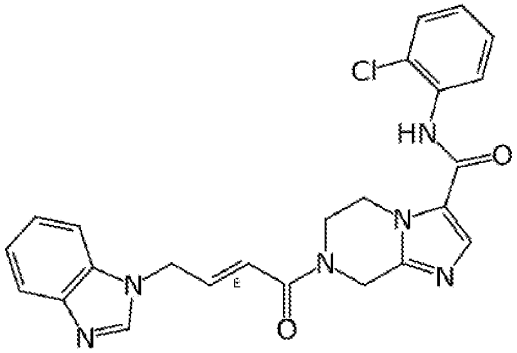
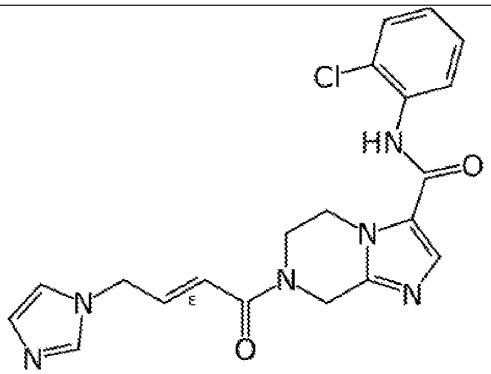
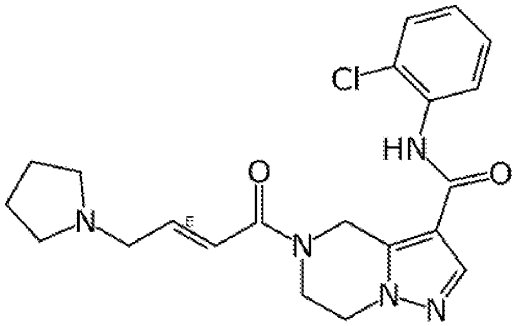
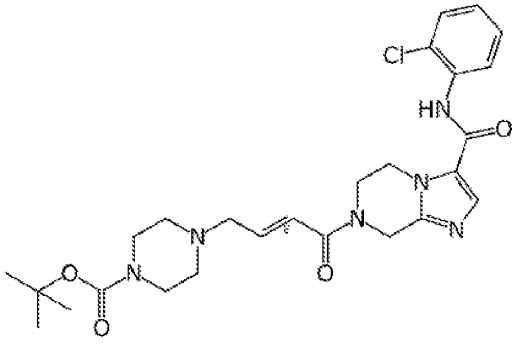
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
590		++++	+
591		++++	+
592			+
593		++++	+

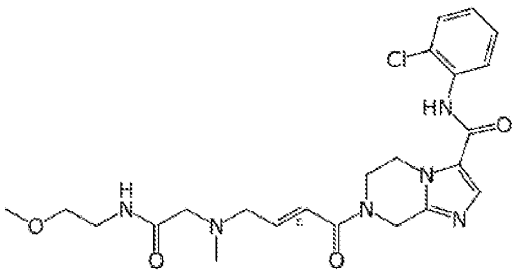
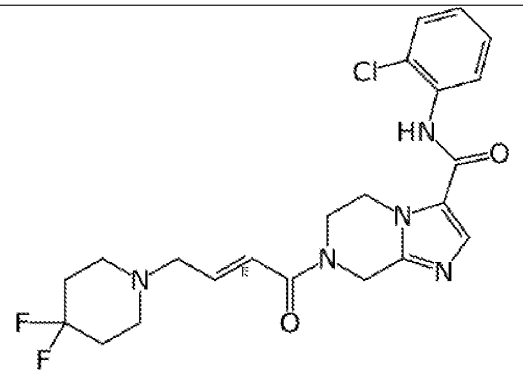
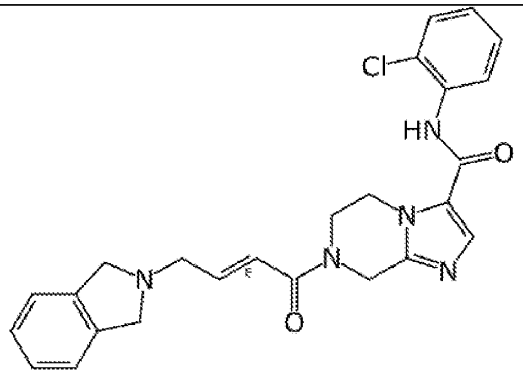
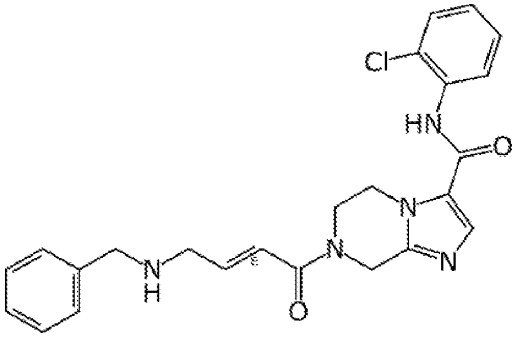
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
594		++++	+
595		++	+
596		++	+
597		+++++	+

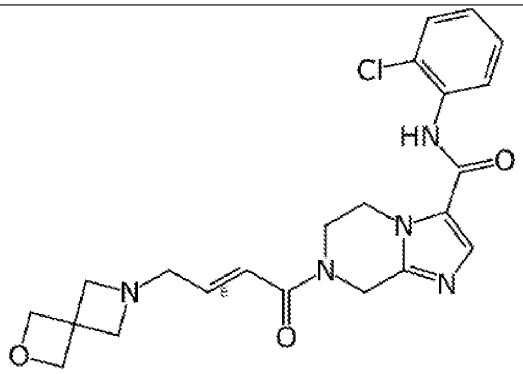
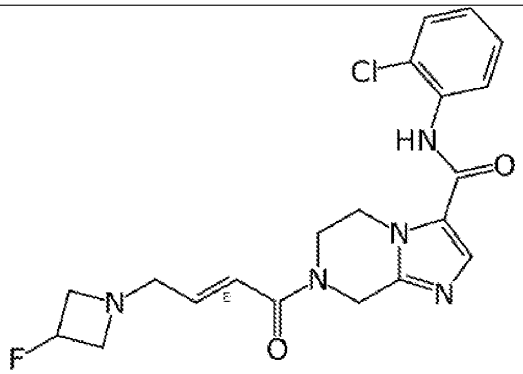
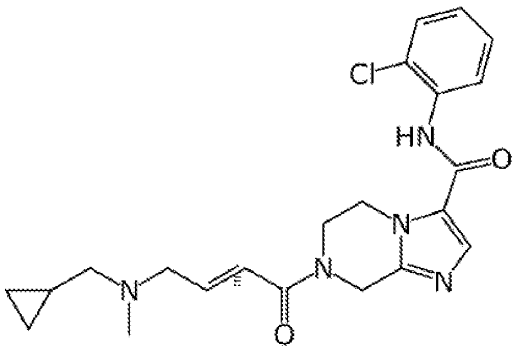
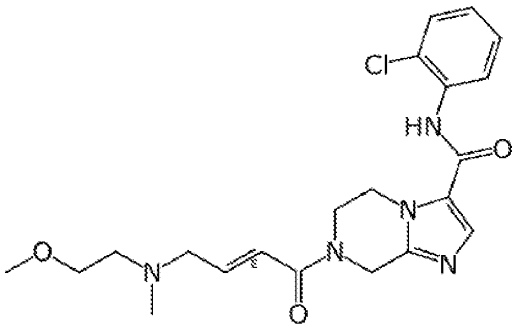
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
598		+++++	+
599		+++++	+
600		+++++	+
601		++++	
602		+++	+

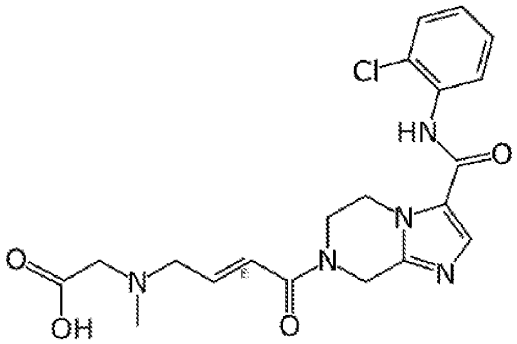
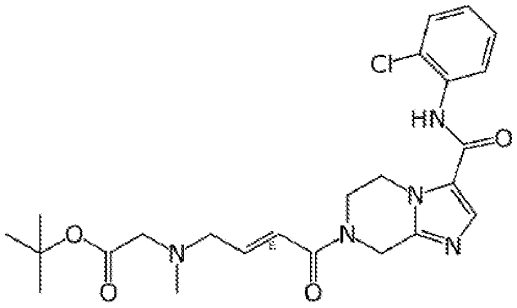
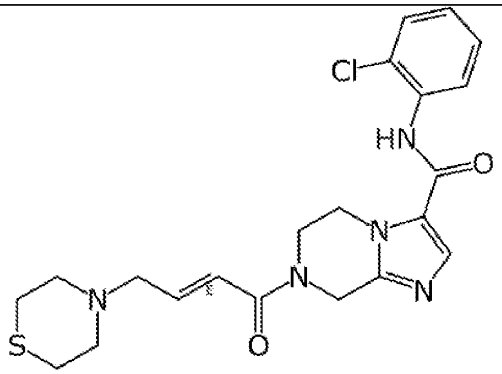
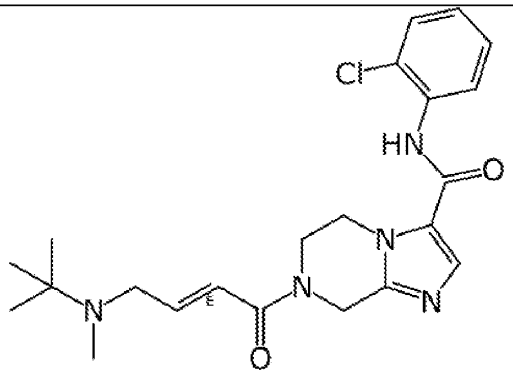
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
603		++++	+
604		+++++	+
605		+	+
606		+++	+

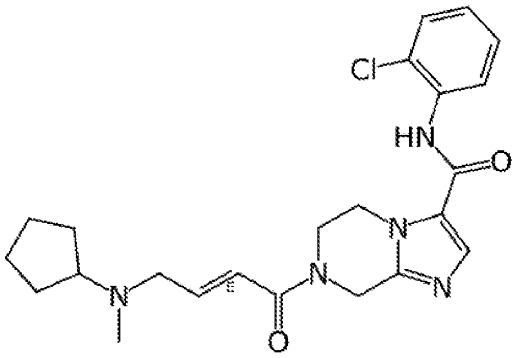
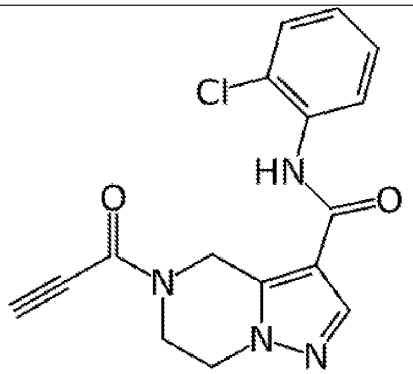
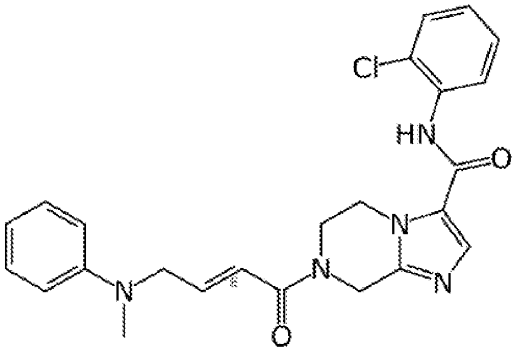
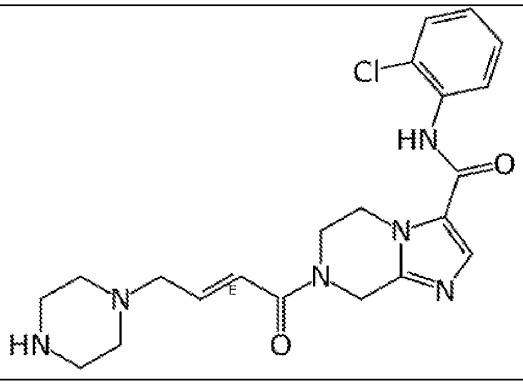
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
607		++++	+
608		+++	+
609		++	+
610		++++	+

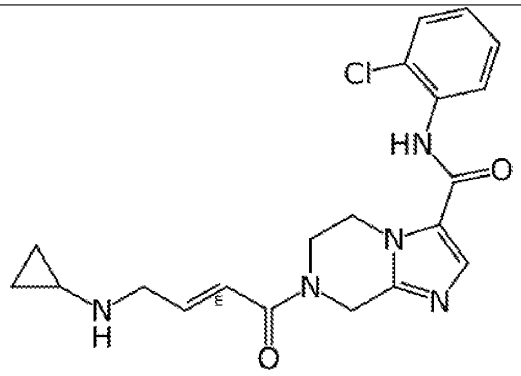
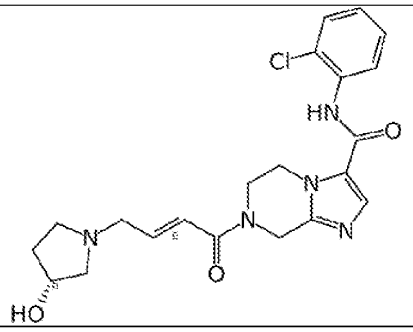
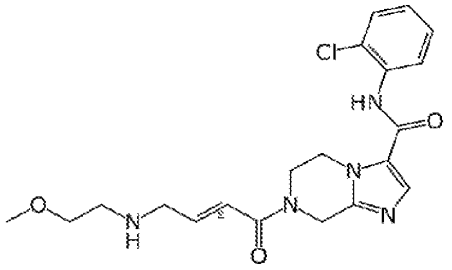
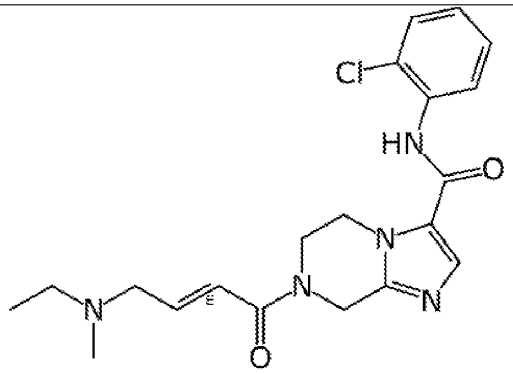
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
611		++	+
612		+++	+
613		++	+
614		++	+

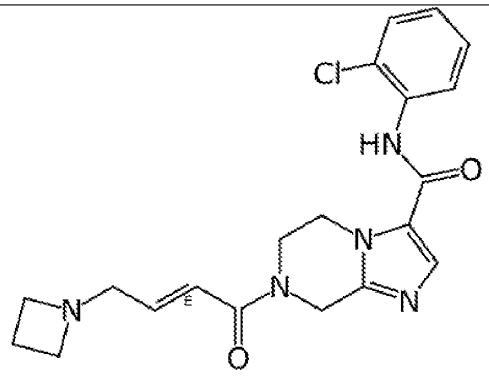
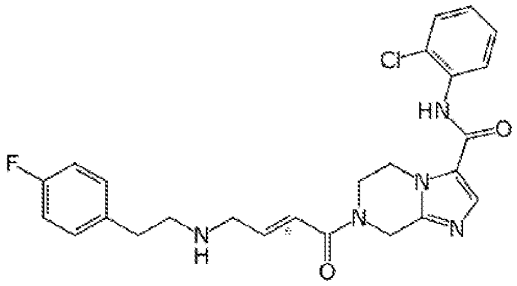
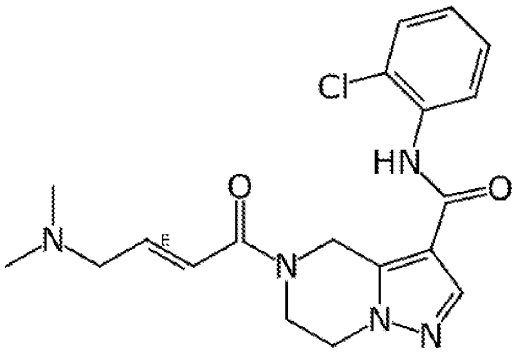
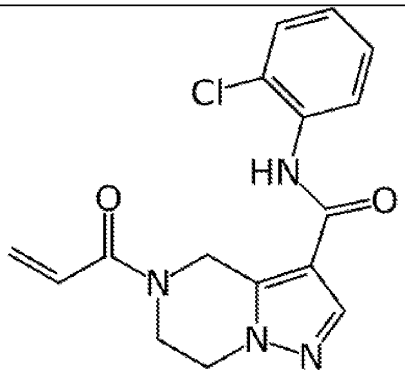
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
615		++	+
616		++	+
617		+++++	+
618		+++++	+

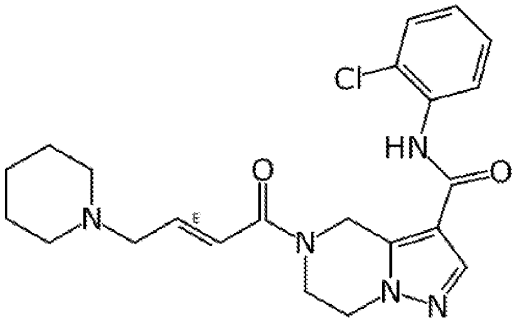
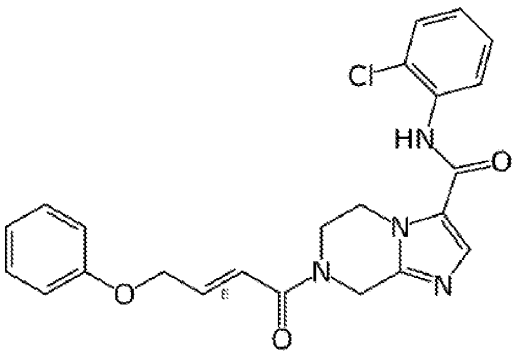
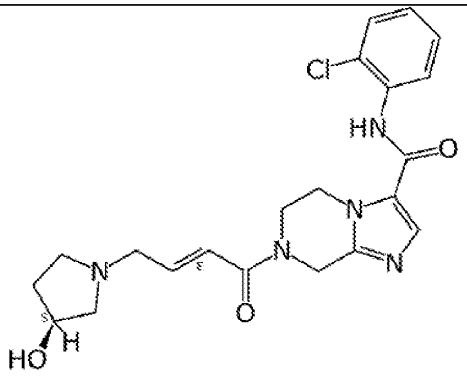
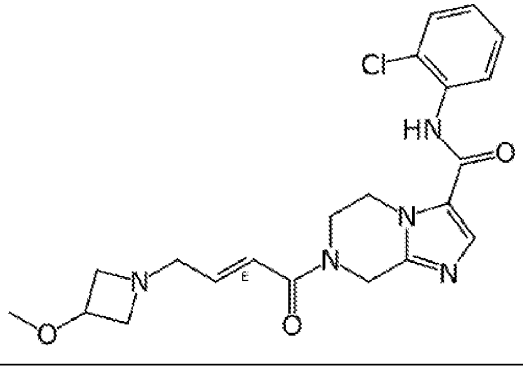
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
619		+++++	+
620		++++	+
621		+++++	+
622		++++	+

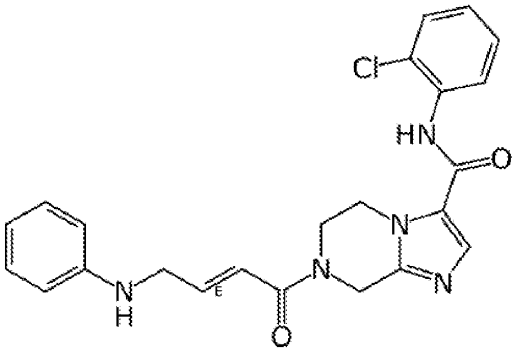
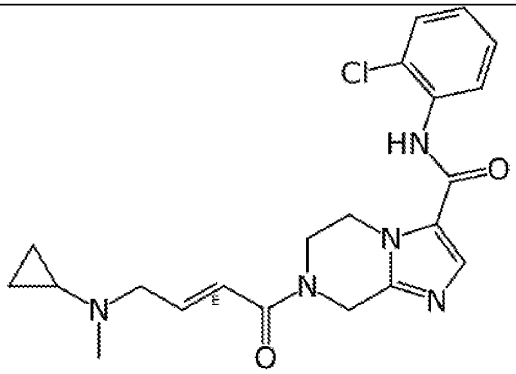
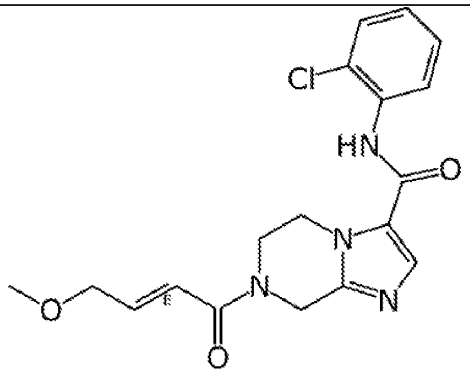
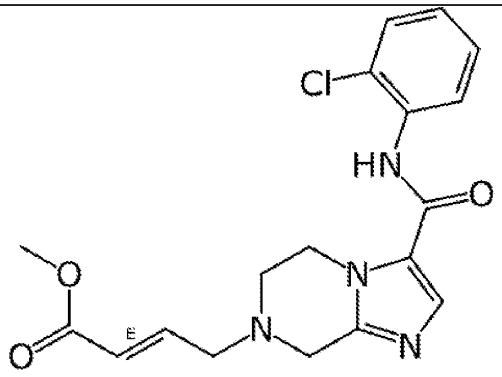
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
623		+ ++	+
624		++++	+
625		+++	+
626		++++	+

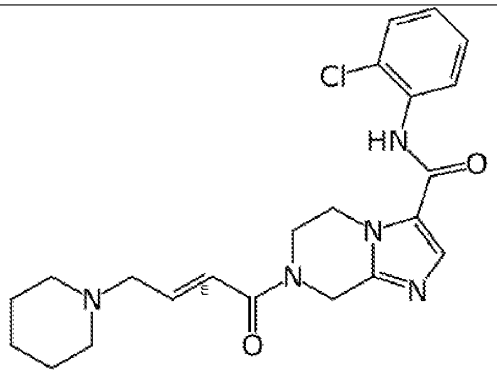
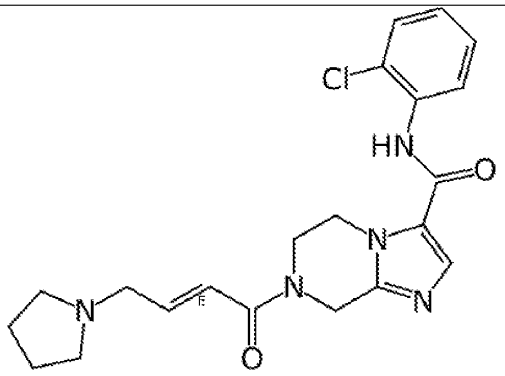
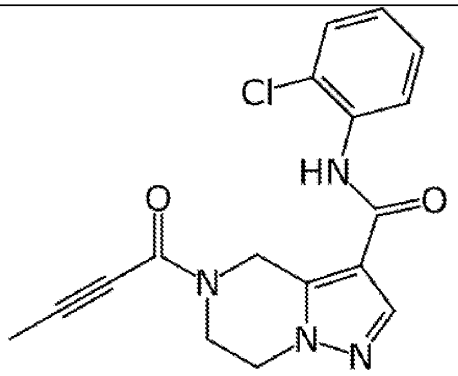
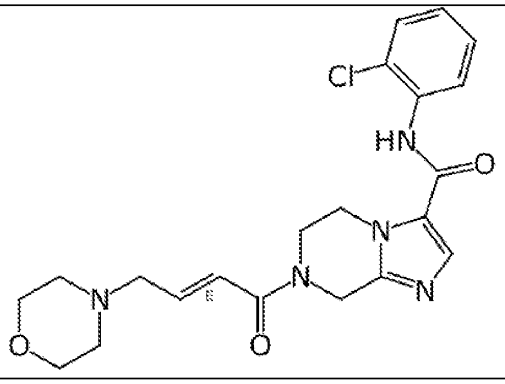
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
627		++++	+
628		+++++	+
629		++	+
630		++	+

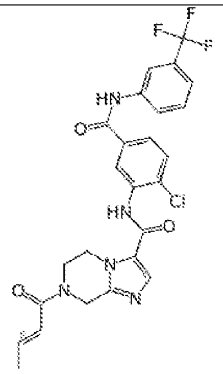
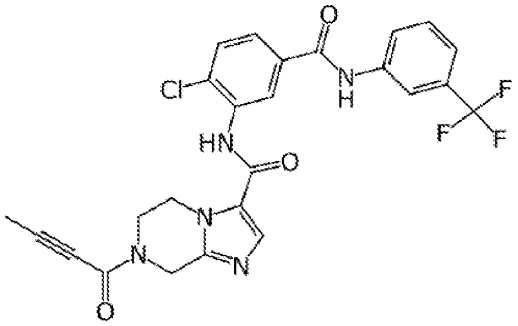
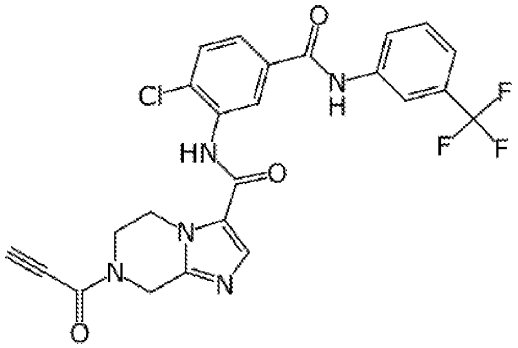
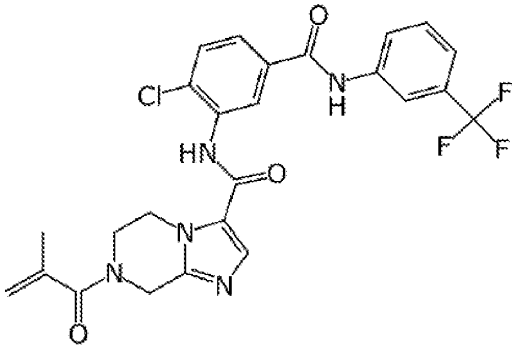
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
631		++++	+
632		+++++	+
633		++++	+
634		+++++	+
635		++++	+
636		+++++	+
637		++	

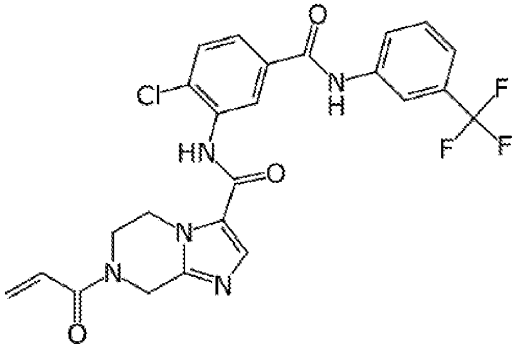
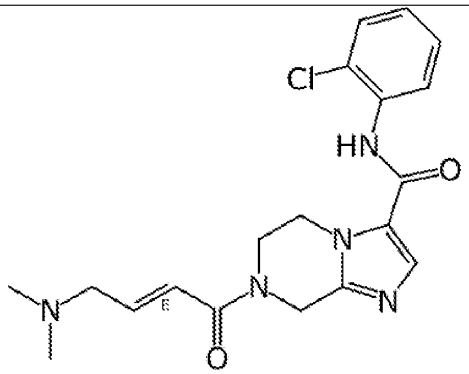
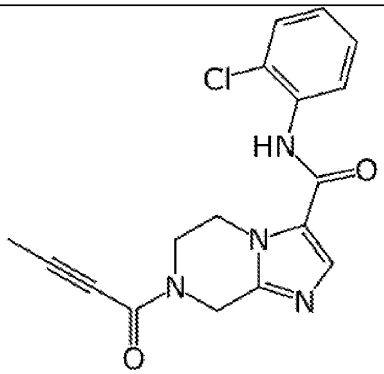
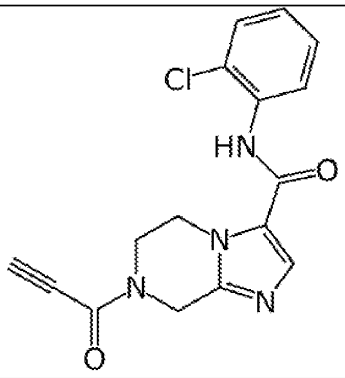
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
638		+++++	++
639		+++++	+
640		++	+
641		++	+

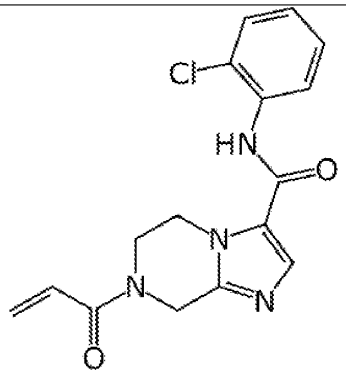
Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
642		+	+
643		+	+
644		+++++	+
645		+++++	+

Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
646		+++	+
647		++++	+
648		+++	
649		+	+
650		++	+

Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
651		+++++	+
652		++++	
653		+++++	+
654		++	+
655		+	
656		++	+
657		+	

Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
658		++++	+++
659		+++++	+++
660		+++++	+++
661		+++	+++

Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
662		+++++	+++
663		+++++	+
664		++++	
665		++	+
666		+++++	++

Entry No.	Structure	EphB3 1mM ATP[A]: Vendor IC_{50} (μM)	EphB2 1mM ATP[B]: Vendor IC_{50} (μM)
667		++++	+

A: +: > 2 uM, ++: 0.5-2 uM, +++: 0.19-0.5 uM, ++++: 0.19-0.05 uM, +++++: <0.05

B: +: >1 uM, ++: 0.3-1 uM, +++: < 0.3 uM

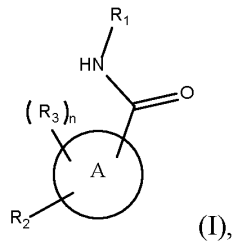
EQUIVALENTS

[01411] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference.

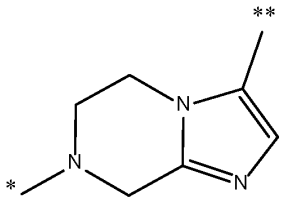
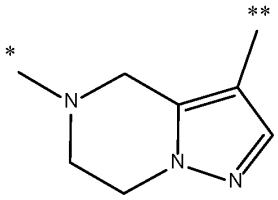
[01412] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

CLAIMS:

1. A compound of Formula (I):



(I),

Ring A is  or , wherein * indicates R_2 attachment and ** indicates amide attachment;

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-

membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, $-NH_2$, $-NH(C_1$-C_6 alkyl), $-N(C_1$-C_6 alkyl)$_2$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, C_1-C_7 alkoxy, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-CO(C_1$-C_6 alkyl), or $-CO_2(C_1$-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, $-NH-CO_2(C_1$-C_6 alkyl), or $-NH_2$;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, $-CO_2(R_{2g})$, $-CON(R_{2g})(R_{2h})$, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $-C(O)-NH(C_1$-C_6 alkyl-C_1-C_6 alkoxy), $–(O(C_2$ alkyl))$_{1\text{-}6}$, or $–(O(C_2$ alkyl))$_{1\text{-}6}$-NH_2;

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

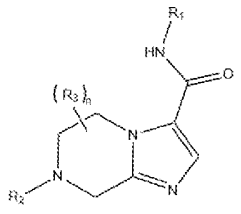
each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl, or

two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle; and

n is 0, 1, 2, 3, or 4..

2. A compound of Formula (II):



(II),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}),

or two R_{1a}, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- or 6-membered heterocycle;

each R_{1b} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{1c} independently is C_6-C_{10} aryl optionally substituted with one or more halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is C_2-C_6 alkenyl or -C(O)R_{2a}, wherein the C_2-C_6 alkenyl is optionally substituted with one or more R_{2b};

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, -N(R_{2c})(R_{2d}), -OR_{2c}, -CO_2(R_{2c}), C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2e};

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R_{2f};

each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

each R_{2e} independently is halo, -CN, -OH, -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, C_1-C_7 alkyl, C_2-C_7 alkenyl, C_2-C_7 alkynyl, C_1-C_7 haloalkyl, C_1-C_7 alkoxy, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -CO(C_1-C_6 alkyl), or -CO_2(C_1-C_6 alkyl), wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, -NH-CO_2(C_1-C_6 alkyl), or -NH_2;

each R_{2f} independently is halo, -CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), -CON(R_{2g})(R_{2h}), C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy), –(O(C_2 alkyl))$_{1\text{-}6}$, or –(O(C_2 alkyl))$_{1\text{-}6}$-NH_2;

each R_{2g} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more halo, C_1-C_6 alkyl, or C_1-C_6 haloalkyl;

each R_{2h} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl, or

two R_3, together with the atoms to which they are attached, form a C_3-C_6 cycloalkyl or 5- to 6-membered heterocycle; and

n is 0, 1, 2, 3, or 4.

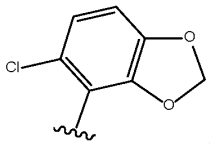
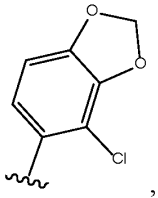
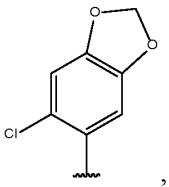
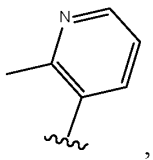
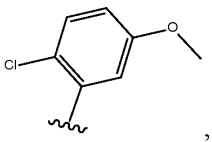
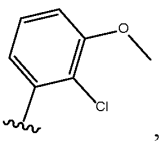
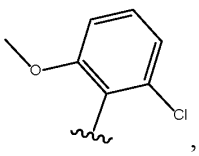
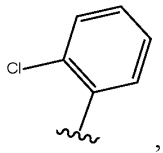
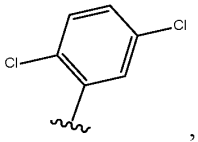
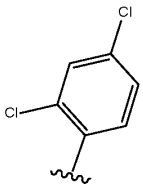
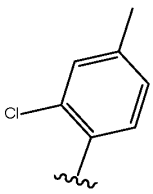
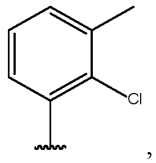
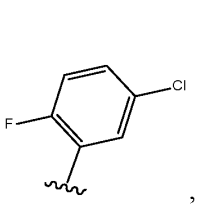
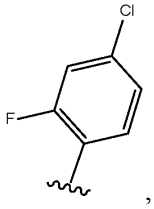
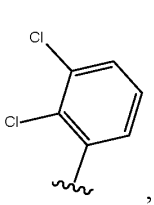
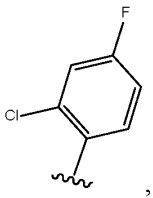
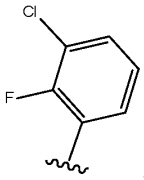
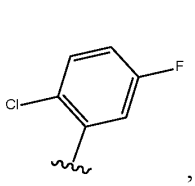
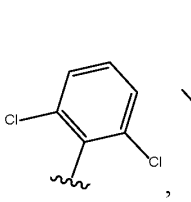
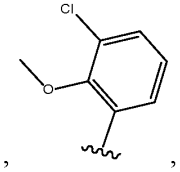
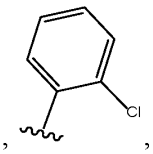
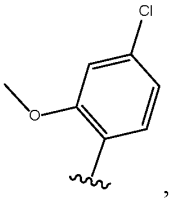
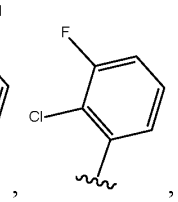
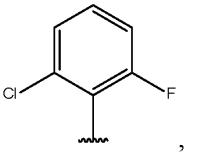
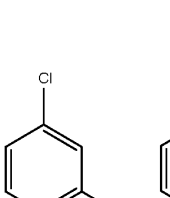
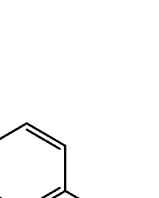
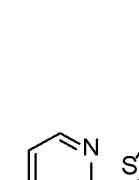
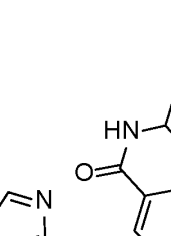
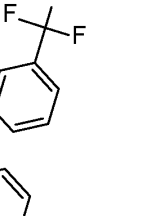
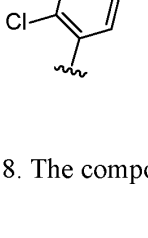
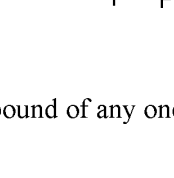
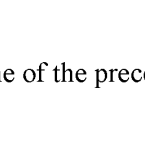
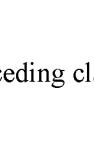
3. The compound of any one of the preceding claims, wherein R_1 is phenyl or 5- or 6-membered heteroaryl, wherein each phenyl or 5- or 6-membered heteroaryl independently is substituted with one or more R_{1a},

wherein each R_{1a} is halo, C_1-C_6 alkyl, C_1-C_6 alkoxyl, or -C(O)N(R_{1b})(R_{1c}), or two R_{1a}, together with the atoms to which they are attached, form a 5- or 6- membered heterocycle, as valency permits.

4. The compound of any one of the preceding claims, wherein R_{1a} is Cl, F, CF_3, methyl, or methoxy.

5. The compound of any one of the preceding claims, wherein R_{1b} is H.

6. The compound of any one of the preceding claims, wherein R_{1c} is C_6-C_{10} aryl optionally substituted with one or more C_1-C_6 haloalkyl.

7. The compound of any one of the preceding claims, wherein R_1 is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , or .

8. The compound of any one of the preceding claims, wherein R_2 is -C(O)R_{2a}.

9. The compound of any one of claims 1-7, wherein:

R_2 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}; and

R_{2b} is halo, 4- to 10- membered heterocyclyl, -N(R_{2c})(R_{2d}), -OR_{2c}, C_6-C_{10} aryl, or -CO_2(R_{2c}), wherein the heterocyclyl or aryl is optionally substituted with one or more R_{2e}.

10. The compound of any one of claims 1-7 or 9, wherein R_{2b} is Cl.

11. The compound of any one of the preceding claims, wherein R_{2c} is H.

12. The compound of any one of claims 1-10, wherein R_{2c} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_6-C_{10} aryl, wherein the alkyl, cycloalkyl, or aryl is optionally substituted with one or more R_{2f}.

13. The compound of any one of the preceding claims, wherein R_{2d} is H, methyl, or ethyl.

14. The compound of any one of the preceding claims, wherein R_{2e} is F, Cl, -OH, -CN, -CO(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, or -CO_2(C_1-C_6 alkyl).

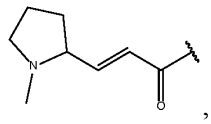
15. The compound of any one of claims 1-13, wherein R_{2e} is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, or 5- to 10-membered heterocyclyl, wherein the alkyl, haloalkyl, alkoxy, cycloalkyl, or heterocyclyl, is optionally substituted with one or more -CN, -OH, C_1-C_6 alkoxy, or -NH-CO_2(C_1-C_6 alkyl).

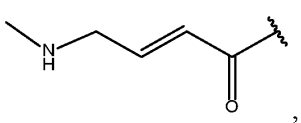
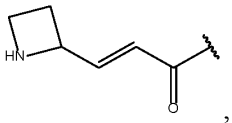
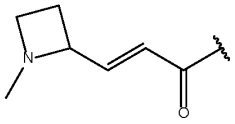
16. The compound of any one of the preceding claims, wherein each R_{2f} is independently halo, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CO_2(R_{2g}), C_3-C_6 cycloalkyl, C_6-C_{10} aryl, C_1-C_6 haloalkyl, or -C(O)-NH(C_1-C_6 alkyl-C_1-C_6 alkoxy).

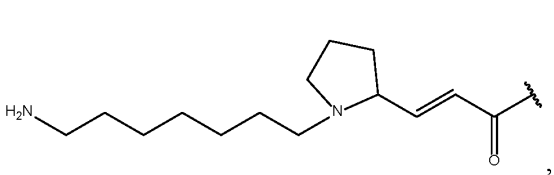
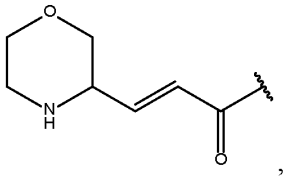
17. The compound of any one of the preceding claims, wherein each R_{2f} is independently F, -CN, methyl, methoxy, phenoxy, -CO_2(R_{2g}), cyclopropyl, phenyl, -CF_3, or -C(O)-NH(ethyl-methoxy).

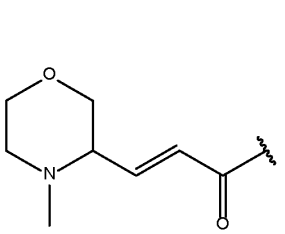
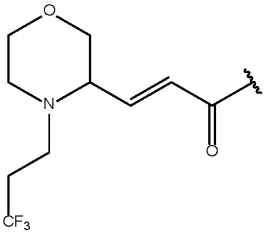
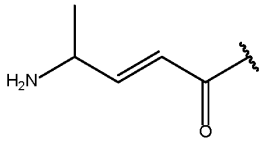
18. The compound of any one of the preceding claims, wherein each R_{2g} is independently H or C_1-C_6 alkyl.

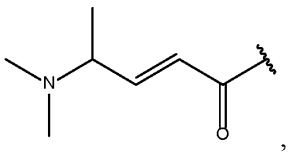
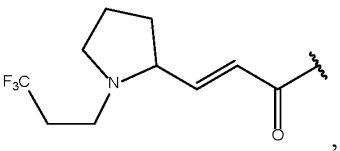
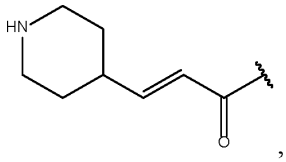
19. The compound of any one of the preceding claims, wherein each R_{2g} is independently H or *tert*-butyl.

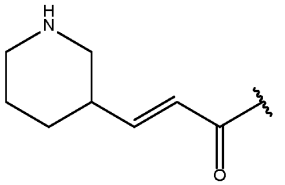
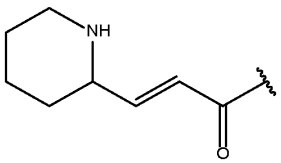
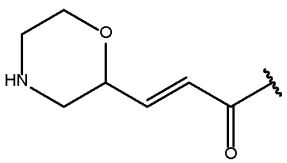
20. The compound of any one of the preceding claims, wherein R_2 is ,

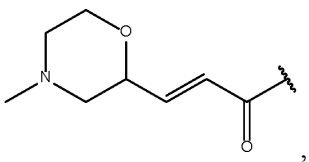
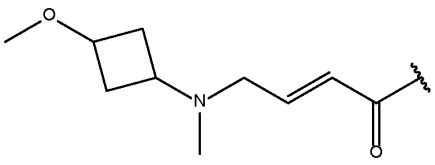
, , ,

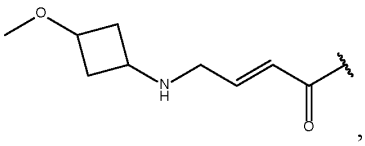
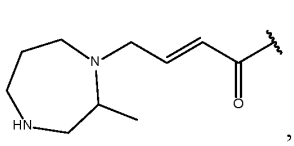
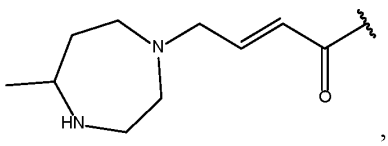
, ,

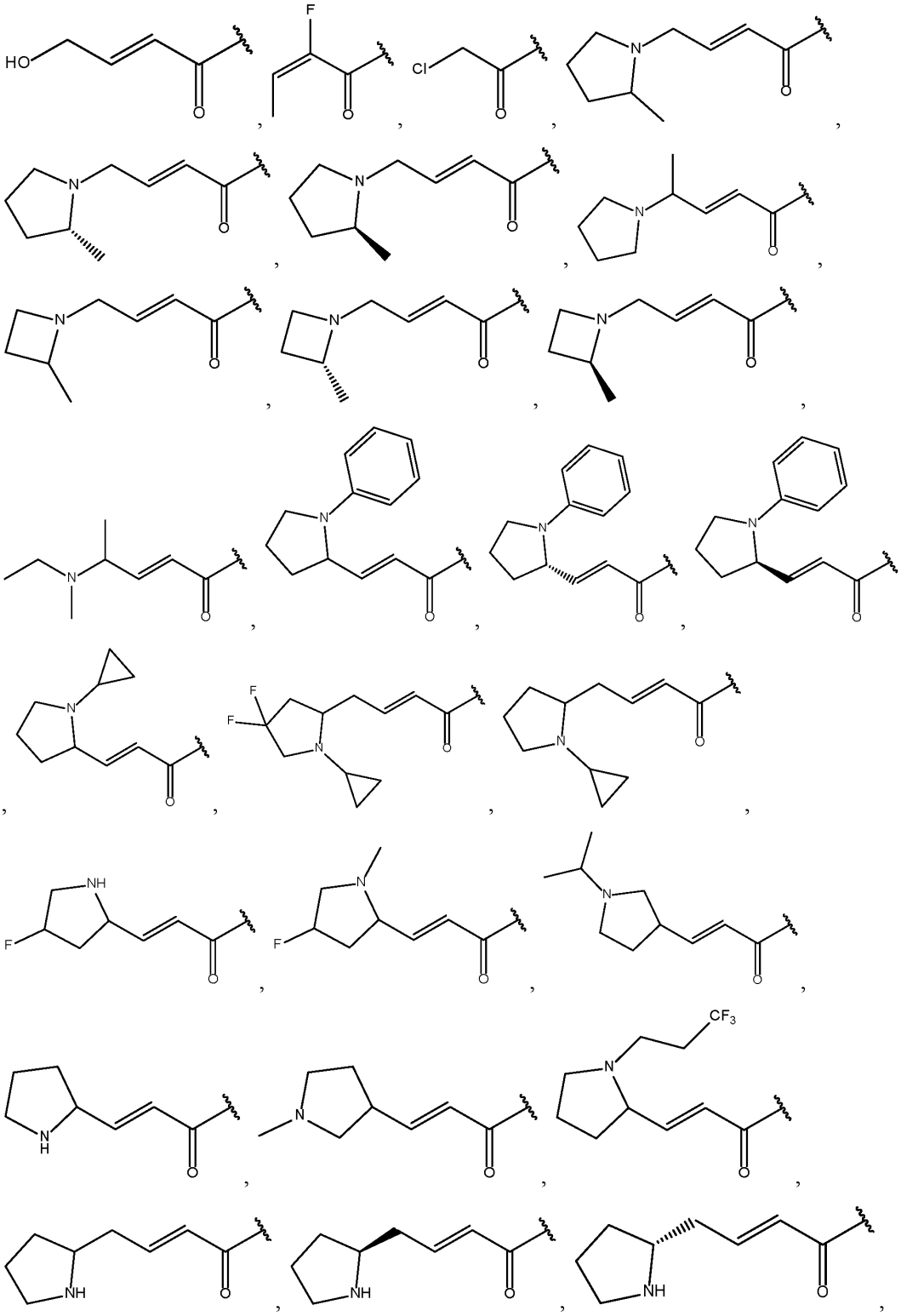
, , ,

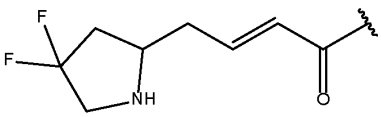
, , ,

, , ,

, ,

, , ,

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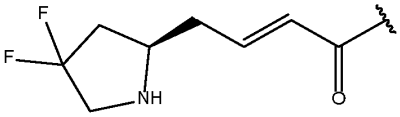
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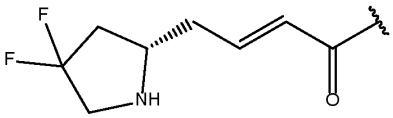
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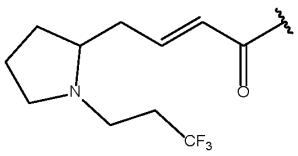
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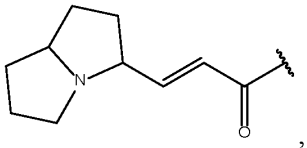
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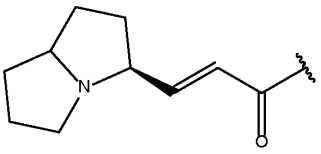
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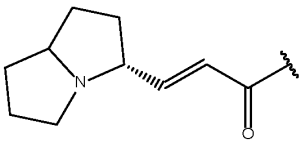
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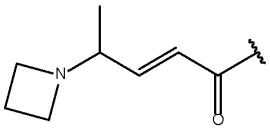
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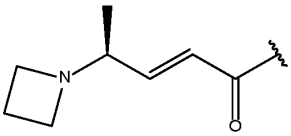
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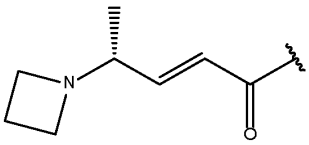
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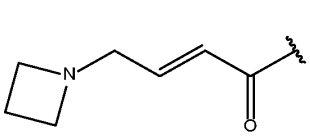
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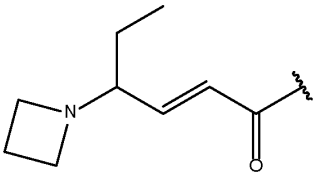
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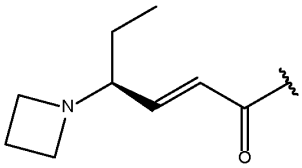
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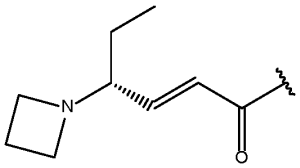
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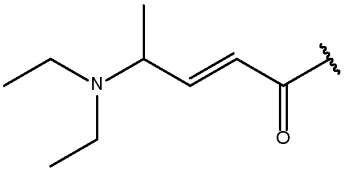
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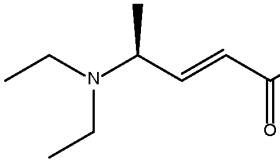
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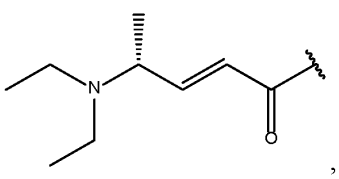
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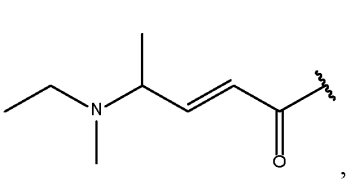
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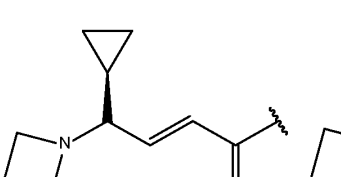
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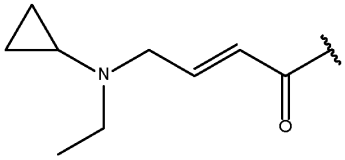
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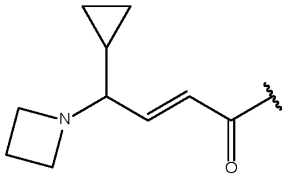
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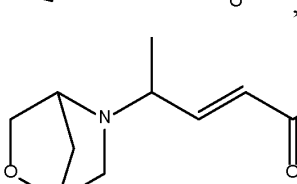
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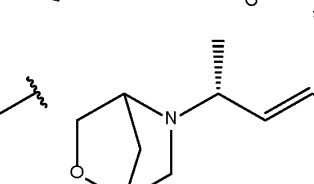
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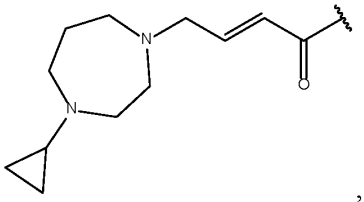
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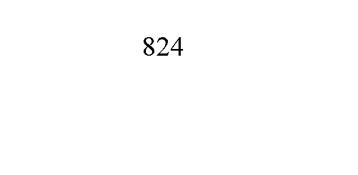
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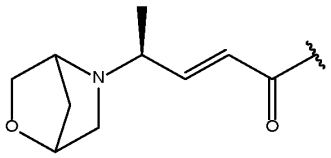
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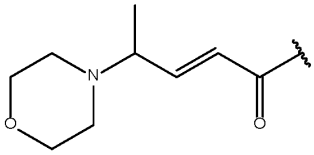
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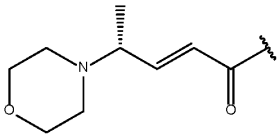
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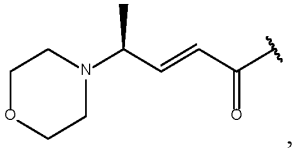
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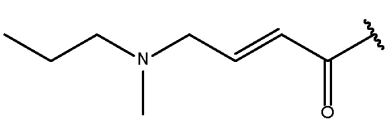
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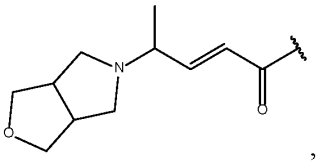
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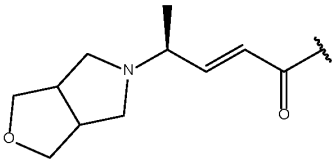
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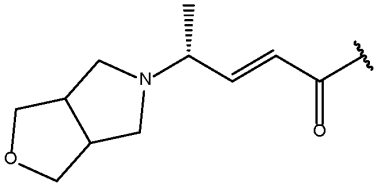
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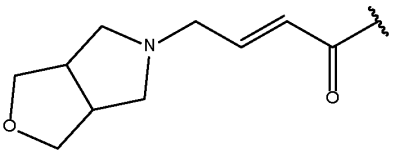
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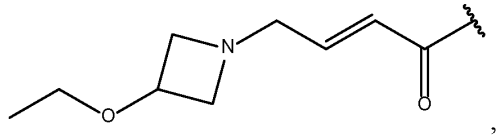
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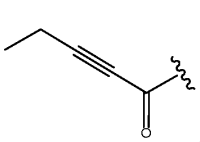
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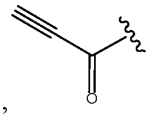
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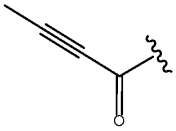
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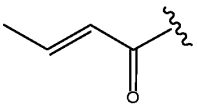
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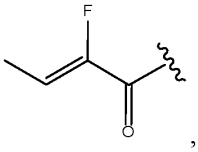
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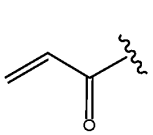
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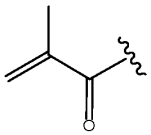
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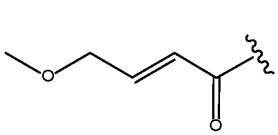
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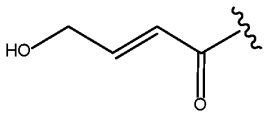
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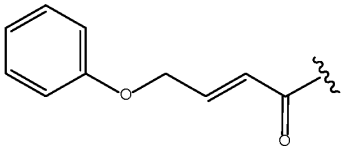
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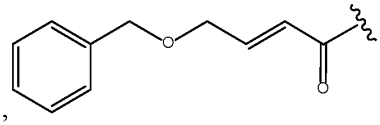
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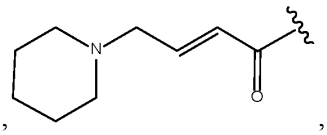
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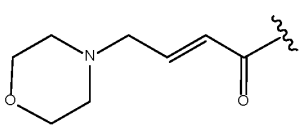
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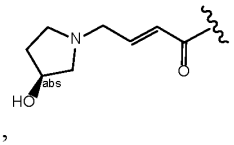
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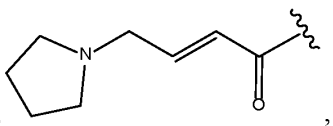
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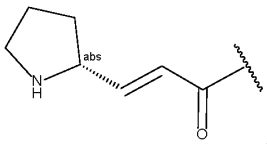
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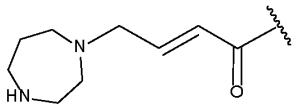
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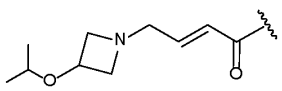
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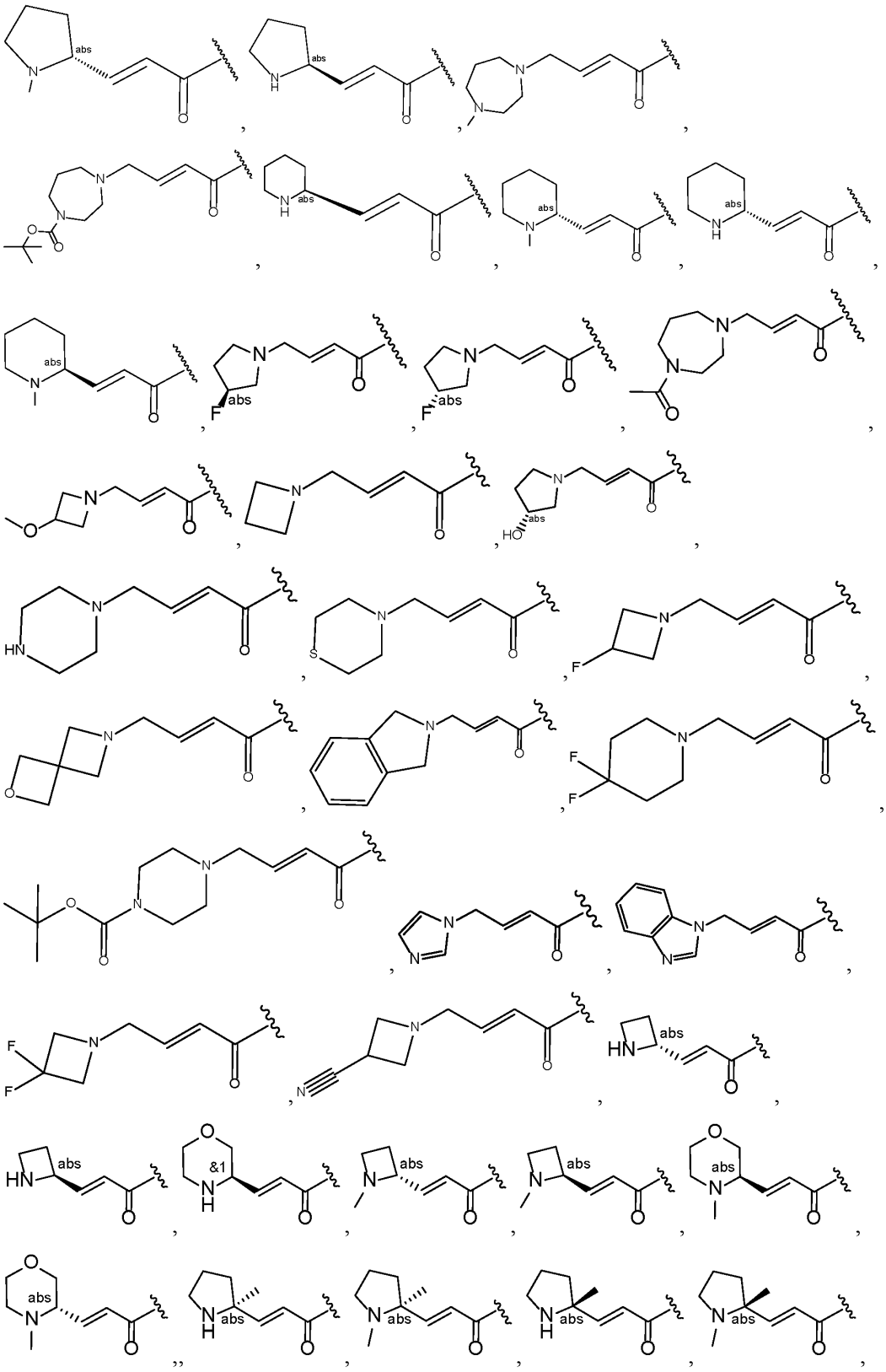
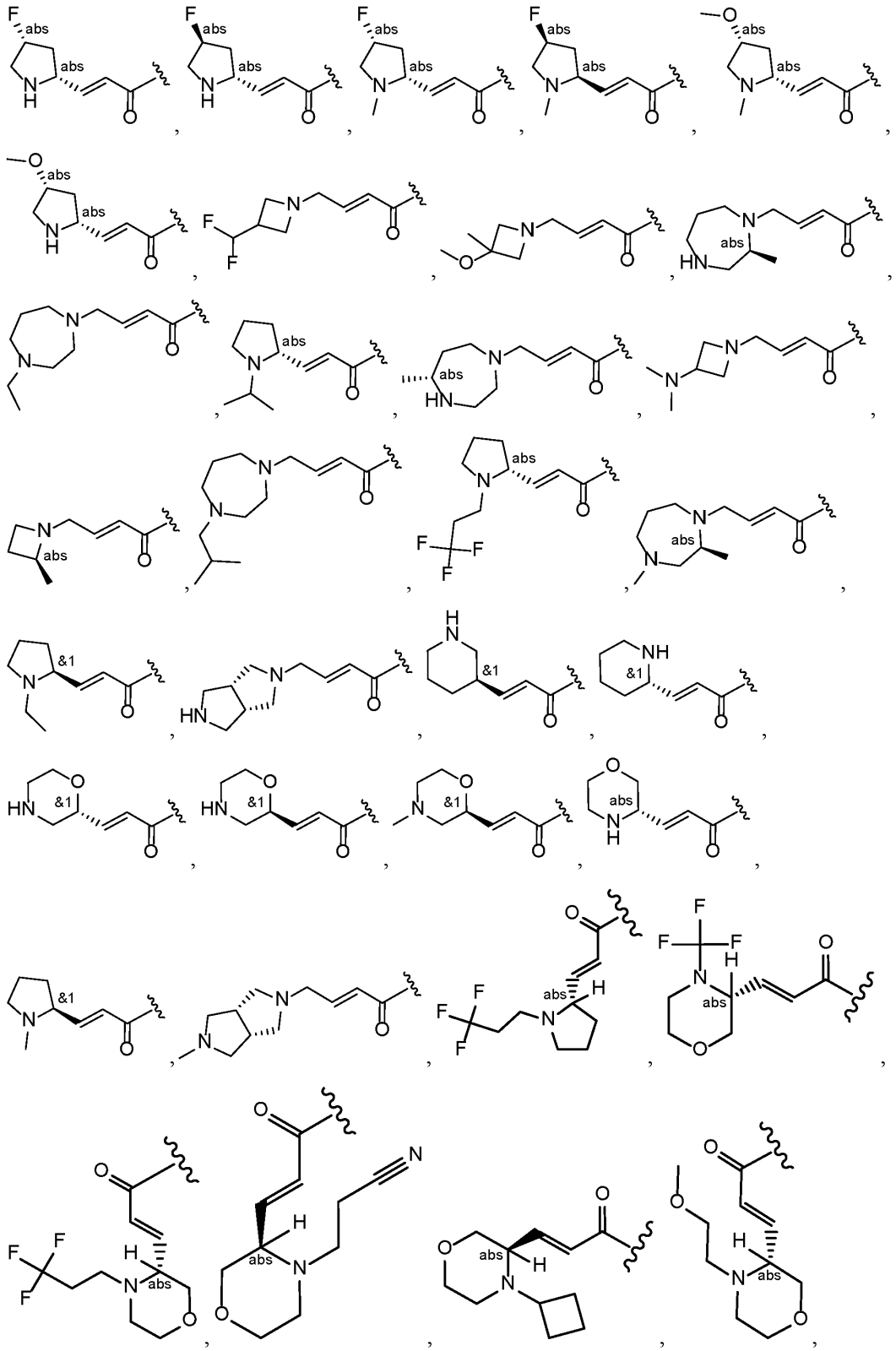
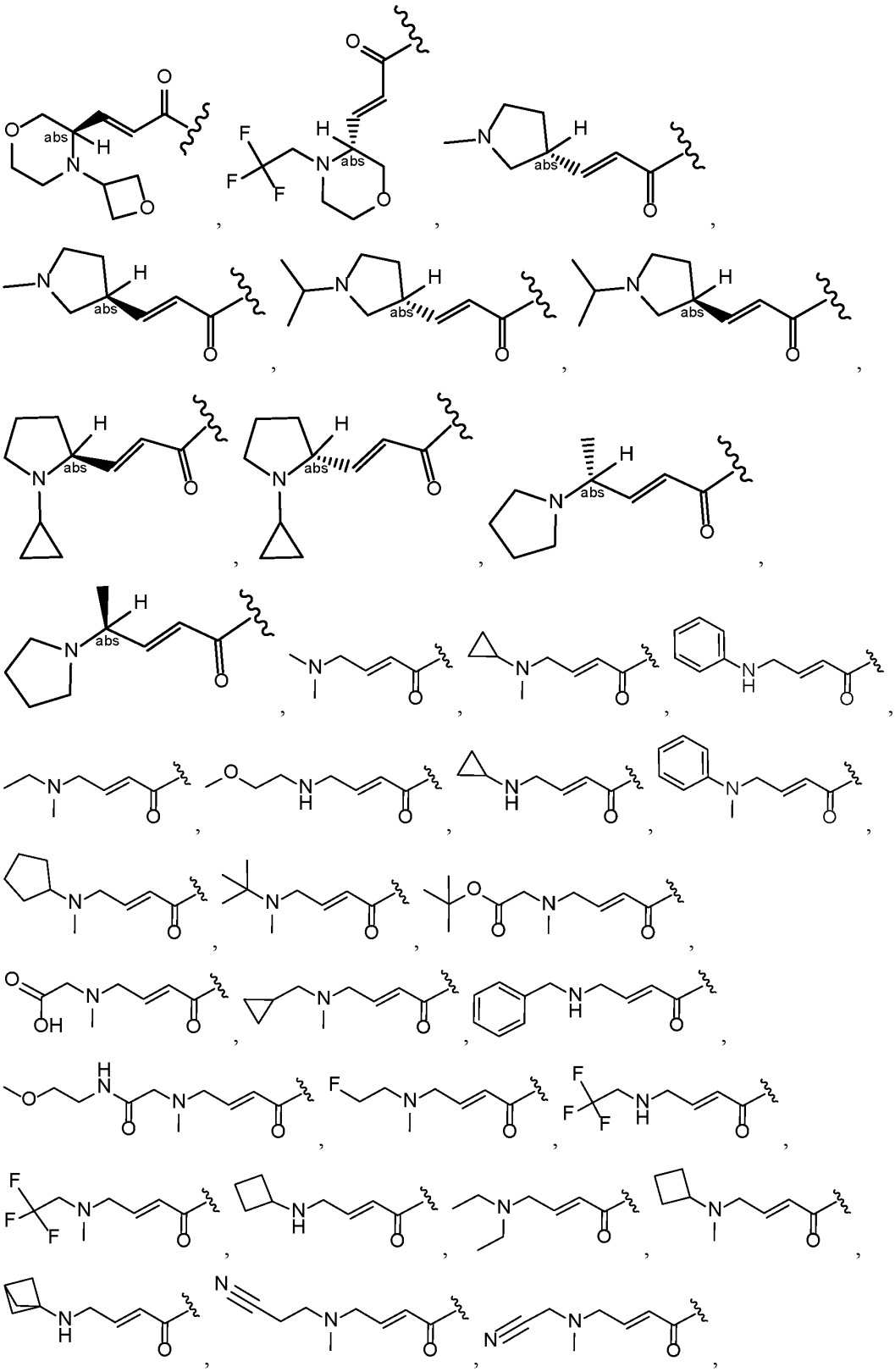
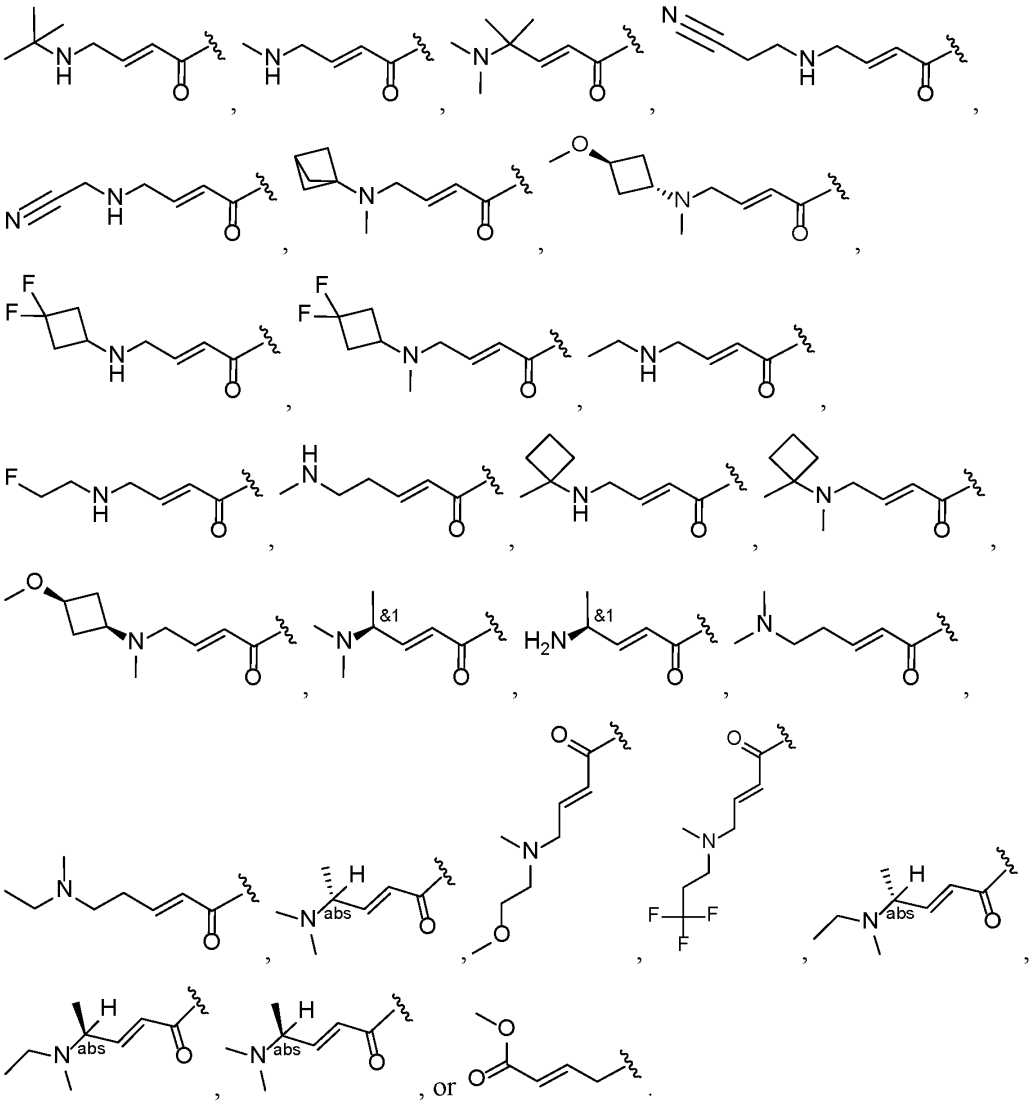




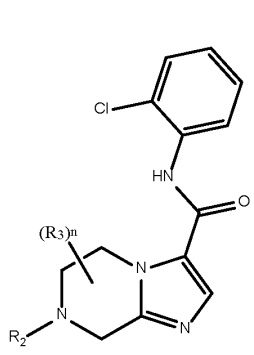




21. The compound of any one of the preceding claims, wherein R_3 is C_1-C_6 alkyl or C_3-C_{10} cycloalkyl.

22. The compound of any one of the preceding claims, wherein R_3 is methyl or cyclopropyl.

23. The compound of any one of the preceding claims, wherein the compound is of Formula (II-a), (II-b), (II-b'), (II-c) (II-c'), (II-d), or (II-d'):



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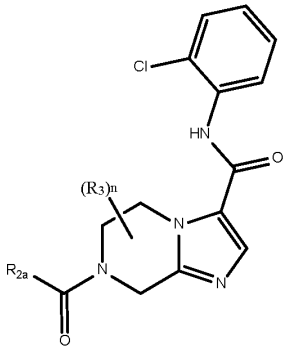
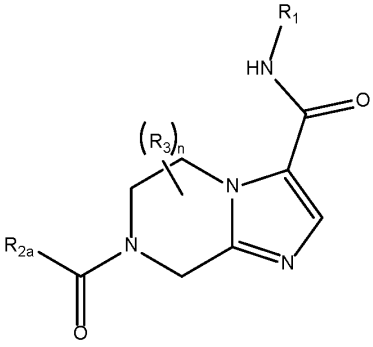
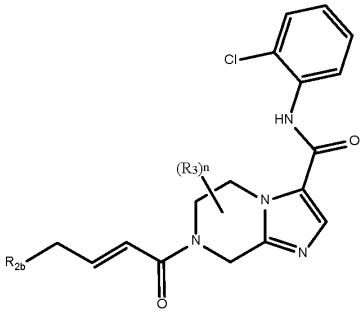


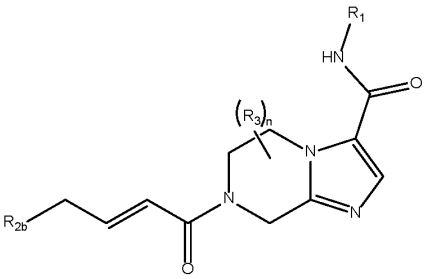
(II-b);



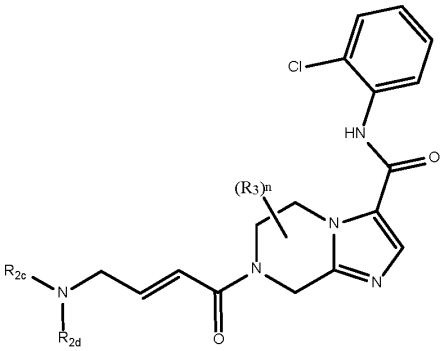
(II-b');



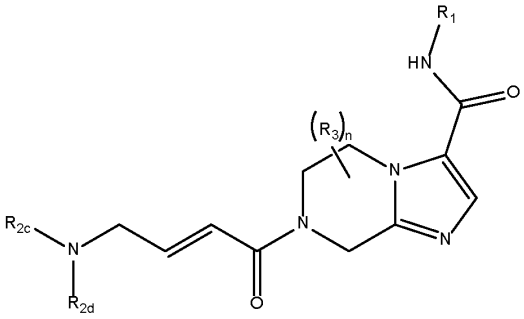
(II-c);



(II-c');



(II-d);

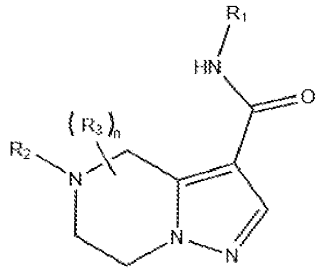


or (II-d'),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

(II-c)

24. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_6-C_{10} aryl optionally substituted with one or more R_{1a};

each R_{1a} independently is halo, -OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, or C_1-C_6 alkoxyl;

R_2 is $-C(O)R_{2a}$;

R_{2a} is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with one or more R_{2b};

each R_{2b} independently is halo, $-N(R_{2c})(R_{2d})$, $-OR_{2c}$, $-CO_2(R_{2c})$, C_3-C_6 cycloalkyl, 4- to 10-membered heterocyclyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each R_{2c} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

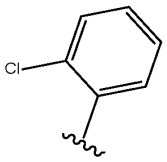
each R_{2d} independently is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 haloalkyl;

R_3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_3-C_{10} cycloalkyl, or 5- to 10-membered heterocyclyl; and

n is 0, 1, 2, 3, or 4.

25. The compound of claim 1 or claim 24, wherein R_1 is phenyl optionally substituted with one or more R_{1a}.

26. The compound of any one of claims 1 or 24-25, wherein R_{1a} is halo.

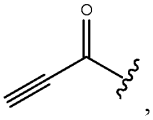
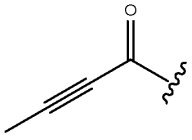
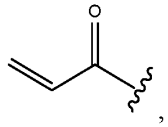
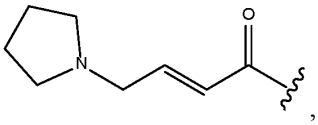
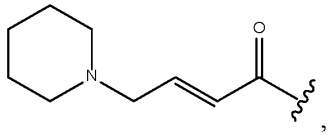
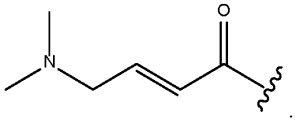
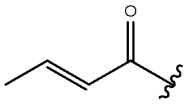
27. The compound of any one of claims 1 or 24-26, wherein R_1 is .

28. The compound of any one of claims 1 or 24-27, wherein R_{2a} is C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the alkenyl or alkynyl is optionally substituted with one or more R_{2b}.

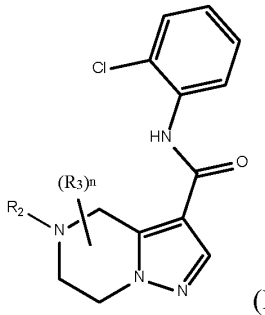
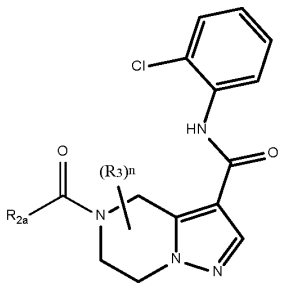
29. The compound of any one of claims 1 or 24-28, wherein R_{2b} is independently -$N(R_{2c})(R_{2d})$ or 4- to 10-membered heterocyclyl.

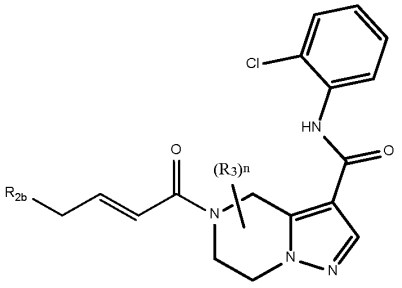
30. The compound of any one of claims 1 or 24-29, wherein R_{2c} is methyl.

31. The compound of any one of claims 1 or 24-30, wherein R_{2d} is methyl.

32. The compound of any one of claims 1 or 24-31, wherein R_2 is , , , , , or  .

33. The compound of any one of claims 1 or 24-32, wherein the compound is of Formula (III-a), (III-b), or (III-c).

 (III-a);  (III-b); or



(III-c),

or a prodrug, solvate, or pharmaceutically acceptable salt thereof.

34. The compound of any one of the preceding claims, wherein the compound is selected from Table 1 or Table 2, or a prodrug, solvate, isotopic derivative, or pharmaceutically acceptable salt thereof.

35. A compound of any one of the preceding claims obtainable by, or obtained by, a method described herein.

36. An intermediate obtained by a method for preparing the compound of any one of the preceding claims.

37. A pharmaceutical composition comprising the compound of any one of the preceding claims and a pharmaceutical acceptable diluent or carrier.

38. A method of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound of any one of the preceding claims, or the pharmaceutical composition of claim 37.

39. The compound or pharmaceutical composition of any one of claims 1-37, for use in treating or preventing a disease or disorder.

40. Use of the compound of any one of claims 1-35 in the manufacture of a medicament for treating or preventing a disease or disorder.

41. Use of the compound of any one of claims 1-35 for treating or preventing a disease or disorder.

42. The method, compound, or use of any one of claims 38-41, wherein the disease or disorder is a neurodegenerative disease or disorder, a psychiatric or neurodevelopmental disease or disorder, a viral or infectious disease or disorder, an autoimmune disease or disorder, or an eye disease or disorder.

43. The method, compound, or use of claim 42,

wherein the neurodegenerative disease or disorder is neuromyelitis optica ("NMO"), transverse myelitis, myelin oligodendrocyte glycoprotein, acute disseminated encephalomyelitis ("ADEM"), optic neuritis, amyloidosis, Parkinson's disease, Alzheimer's disease, cerebral amyloid angiopathy, Pick's disease, frontotemporal dementia, dementia with Lewy bodies, corticobasal degeneration, progressive supranuclear palsy, amyotrophic lateral sclerosis ("ALS"), Huntington's disease, traumatic brain injury, stroke, fatty liver disease, endometriosis, paraneoplastic disorders, inflammatory demyelinating polyneuropathy, amyotrophy, fibromyalgia, multiple system atrophy, Friedrich's ataxia, or cerebellar ataxia.

wherein the psychiatric or neurodevelopmental disease or disorder is schizophrenia, major depressive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, agoraphobia, post-traumatic stress disorder, autism spectrum disorder, cerebral palsy, Nasu Hakola disease, bipolar disorder, or substance abuse.

wherein the viral or infectious disease or disorder is neuro-HIV, viral encephalitis, meningitis, neurocysticercosis, neurosyphilis, neuro-Lyme disease, infectious myelopathies, COVID-19 neuroinflammation, enteroviruses, poliovirus, Epstein-Barr virus (EBV), human herpesvirus, cytomegalovirus, rabies virus, herpes simplex virus, measles, progressive multifocal leukoencephalopathy John Cunningham ("PML JC") virus, bacterial meningitis, prion disease, or Creutzfeldt Jakob disease.

wherein the autoimmune disease or disorder is antibody-mediated encephalitis, neurological complications of connective tissue damage, neurosarcoidosid, demyelinating diseases (non-MS), idiopathic autoimmune CNS and PNS syndromes, paraneoplastic neurological disease, CNS vasculitis, type 1 diabetes, type 2 diabetes, Crohn's disease, systemic lupus erythematous ("SLE"), irritable bowel disorders, asthma, chronic obstructive pulmonary disease ("COPD"), atopic dermatitis, obesity-associated inflammation, heart disease, ulcerative colitis, psoriasis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, Sjögren's syndrome, Reiter's disease, multiple sclerosis, autoimmune encephalitis, myasthenia gravis, idiopathic pulmonary fibrosis, ankylosing spondylitis, antiphospholipid

antibody syndrome, osteomyelitis, gout, Henoch-Schonlein Purpura, dermatomyositis, idiopathic arthritis, scleroderma, Kawasaki disease, mixed connective tissue damage, myositis, spondyloarthritis, undifferentiated connective tissue disease, systemic sclerosis, or autoimmune hepatitis.

wherein the eye disease or disorder is uveitis, keratitis, conjunctivitis, thyroid eye disease, age-related macular degeneration, glaucoma, diabetic retinopathy, diabetes-related macular edema, or scleritis.

44. The method, compound, or use of any one of claims 38-42, wherein the disease or disorder is selected from autoimmune encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, concentric sclerosis, Charcot-Marie-Tooth disease, Guillain-Barre syndrome, HTLV-I associated myelopathy ("HAM"), Schilder's disease, dementia, frontotemporal lobar dementia, accessory nerve disorder, autonomic dysreflexia, peripheral neuropathy, chemotherapy-induced peripheral neuropathies, mononeuropathy, polyneuropathy, radial neuropathy, ulnar neuropathy, Villaret's syndrome, diabetic neuropathy, nerve paralysis, progressive bulbar palsy, pseudobulbar palsy, spinal bulbar muscular atrophy, myotonic dystrophy, inclusion body myositis, seizure disorders, lysosomal storage disorders, transmissible spongiform encephalopathy, spinocerebellar ataxia, spinal muscular atrophy, Horner's syndrome, adrenoleukodystrophy, macular degeneration, and Lewy Body syndrome.

45. The method, compound, or use of claim 43 or 44, wherein the disease or disorder is autoimmune encephalomyelitis or multiple sclerosis.

46. The method, compound, or use of claim 43, wherein the disease or disorder is amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, or Huntington's disease.

47. The method, compound, or use of claim 43 or 46, wherein the Alzheimer's disease is Alzheimer's disease with APOE4.

48. The method, compound, or use of claim 43 or 46-47, wherein the multiple sclerosis is progression independent of relapses.