

PYRAZOLE DERIVATIVES AS RET KINASE INHIBITORS**Background**

The Rearranged during transfection (RET) kinase is a single-pass transmembrane
5 receptor belonging to the tyrosine kinase superfamily that is required for normal
development, maturation, and maintenance of several tissues and cell types. The
extracellular portion of the RET kinase contains four calcium-dependent cadherin-like
repeats involved in ligand binding and a juxtamembrane cysteine-rich region necessary for
the correct folding of the RET extracellular domain, while the cytoplasmic portion of the
10 receptor includes two tyrosine kinase subdomains.

RET signaling is mediated by the binding of a group of 35 soluble proteins of the
glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which also
includes neurturin (NTRN), artemin (ARTN), and persephin2 (PSPN). Unlike other receptor
tyrosine kinases, RET does not directly bind to GFLs and requires an additional co-receptor,
15 which can be one of four GDNF family receptor- α (GFR α) family members that are tethered
to the cell surface by a glycosylphosphatidylinositol linkage. GFLs and GFR α family
members form binary complexes that in turn bind to RET and recruit it into cholesterol-rich
membrane subdomains where RET signaling occurs.

Upon binding of the ligand-co-receptor complex, RET dimerization and
20 autophosphorylation on intracellular tyrosine residues recruits adaptor and signaling proteins
to stimulate multiple downstream pathways. Adaptor protein binding to these docking sites
leads to activation of Ras-MAPK and PI3K-Akt/mTOR signaling pathways or to recruitment
of the CBL family of ubiquitin ligases that functions in RET downregulation of the RET-
mediated functions.

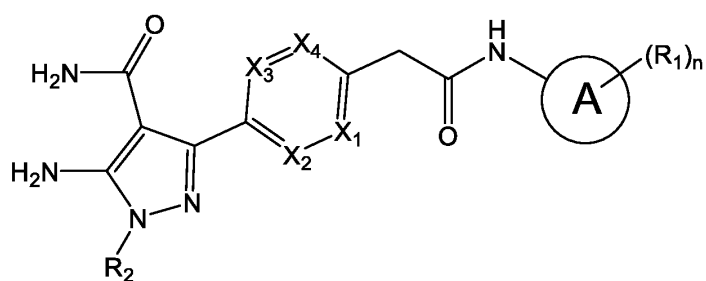
25 Disruptions in normal RET activity due to abnormal RET expression stemming from
genetic alterations in the RET kinase, including protein-gene fusions and activating point
mutations, lead to overactive RET signaling and uncontrolled cell growth, e.g., various
cancer types and certain gastrointestinal disorders such as irritable bowel syndrome (IBS).
The ability to inhibit abnormal RET activity in patients with cancer or other disorders related

-2-

to overactive RET signaling would be of great benefit. Additionally, some RET kinase genetic alterations are altering the conformational structure of a RET kinase to such an extent that a given RET kinase inhibitor may be less effective (or ineffective). In such cases, new RET kinase inhibitors that are effective to the modified RET kinase would greatly benefit patients.

Summary

Disclosed herein are compounds of formula I:



I

10 wherein

A is C₆-C₁₀ aryl or C₅-C₆ heteroaryl;

each R₁ is independently hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, -(C₁-C₄ alkyl)(C₅-C₆ heteroalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicycyl), -(C₀-C₄ alkyl)(C₅-C₆ aryl), -(C₀-C₄ alkyl)(C₅-C₆ heteroaryl), -(C₀-C₄ alkyl)(C₄-C₁₀ heterobicycyl), C₅-C₁₂ spiranyl, C₅-C₁₂ heterospiranyl, dimethylphosphoryl, adamantyl, C₁-C₆ alkoxy, -(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R₁ is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di-, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C₀-C₃ alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, and wherein two R₁ groups can fuse to form a

ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, 3, 4, 5, or 6;

X₁, X₂, X₃, and X₄ are each independently N, CH, C-CH₃, C-CH₂-OH, C-OCH₃, C-CH₂-OCH₃, or C-halogen; and

5 R₂ is C₁-C₆ alkyl, -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₄-C₇ heterocycloalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicyclic) each optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl;
or a pharmaceutically acceptable salt thereof.

10

Further disclosed herein are methods of using the compounds of formula I or pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, to treat cancer, in particular for the treatment of cancer with abnormal RET expression (e.g., a RET-associated cancer like medullary thyroid cancer or RET fusion lung cancer) are also
15 provided. The methods include administering a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof, to a patient in need.

Also provided herein are compounds of formula I or pharmaceutically acceptable salts thereof, for use in therapy. Further provided herein, are the compounds of formula I or pharmaceutically acceptable salts thereof, for use in the treatment of cancer, in particular for
20 use in the treatment of cancer with abnormal RET expression (e.g., a RET-associated cancer like medullary thyroid cancer or RET fusion lung cancer). The use of compounds of formula I or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treating cancer, in particular for use in the treatment of cancer with abnormal RET expression (e.g., a RET-associated cancer like medullary thyroid cancer or RET fusion lung cancer), is
25 also provided.

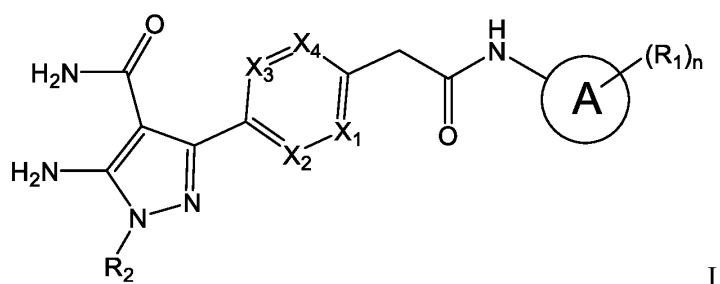
Description

Novel RET kinase inhibitor compounds are described herein. These new compounds could address the need for potent, effective treatment of disorders associated with abnormal

-4-

RET activity, e.g., IBS or cancer, especially cancer stemming from overactive RET signaling (i.e., RET-associated cancers). More specifically, these new compounds could address the need for potent, effective treatment of RET-associated cancers such as lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (e.g., papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid adenoma, endocrine gland neoplasms, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, or cervical cancer.

Provided herein are compounds of formula I:



I

15 wherein

A is C₆-C₁₀ aryl or C₅-C₆ heteroaryl;

each R₁ is independently hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, -(C₁-C₄ alkyl)(C₅-C₆ heteroalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicycyl), -(C₀-C₄ alkyl)(C₅-C₆ aryl), -(C₀-C₄ alkyl)(C₅-C₆ heteroaryl), -(C₀-C₄ alkyl)(C₄-C₁₀ heterobicycyl), C₅-C₁₂ spiranyl, C₅-C₁₂ heterospiranyl, dimethylphosphoryl, adamantyl, C₁-C₆ alkoxy, -(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R₁ is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are

independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C₀-C₃ alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, and wherein two R₁ groups can fuse to form a ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, 3, 4, 5, or 6;

X₁, X₂, X₃, and X₄ are each independently N, CH, C-CH₃, C-CH₂-OH, C-OCH₃, C-CH₂-OCH₃, or C-halogen; and

R₂ is C₁-C₆ alkyl, -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₄-C₇ heterocycloalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicyclic) each optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl; or a pharmaceutically acceptable salt thereof.

In some aspects, in the compounds and pharmaceutically acceptable salts of formula I, at least one of X₁, X₂, X₃, and X₄ is CH. Sometimes, X₁, X₂, X₃, and X₄ are each CH. Alternatively, at least one of X₁, X₂, X₃, and X₄ is N. In an embodiment, X₁ is N and each of X₂, X₃, and X₄ is CH. In another embodiment, X₂ is N and each of X₁, X₃, and X₄ is CH. In some compounds, at least one of X₁ and X₂ is C-Cl or C-F. In other compounds, X₁ and X₂ are independently selected from the group consisting of C-Cl and C-F. In still other compounds, X₁ and X₂ are independently selected from the group consisting of C-Cl and C-F, and X₃ and X₄ are both CH. Alternatively, X₁ and X₃ independently selected from the group consisting of C-Cl and C-F. In some compounds, X₂ is C-OCH₃ or C-CH₂-OH.

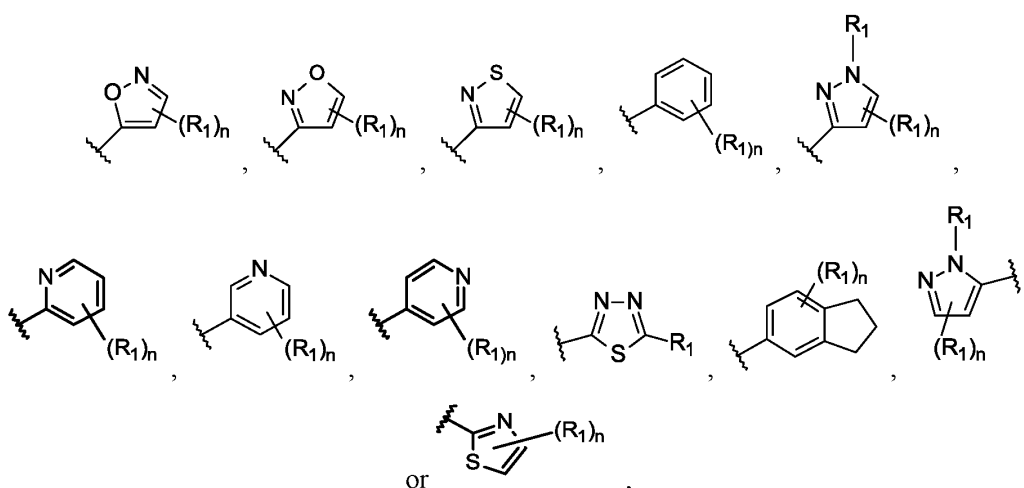
In some compounds and pharmaceutically acceptable salts of formula I, X₂ and X₃ are both N. In other compounds, X₂ and X₃ are both N and X₁ and X₄ are independently selected from CH, C-Cl, C-F, C-OCH₃ and C-CH₂-OH. In still other compounds, X₂ and X₃ are both N and X₁ and X₄ are both CH. In still other compounds, X₂ and X₃ are both N and X₁ and X₄ are independently CH, C-Cl or C-F. In some compounds, X₁ and X₄ are both N. In other

-6-

compounds, X_1 and X_4 are both N and X_2 and X_3 are independently selected from CH, C-Cl, C-F, C-OCH₃ and C-CH₂-OH. In still other compounds, X_1 and X_4 are both N and X_2 and X_3 are both CH. In still other compounds, X_1 and X_4 are both N and X_2 and X_3 are independently CH, C-Cl or C-F.

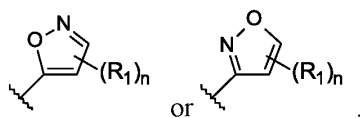
- 5 In some compounds and pharmaceutically acceptable salts of formula I, X_1 and X_3 are both N and X_2 and X_4 are independently selected from CH, C-Cl, C-F, C-OCH₃ and C-CH₂-OH. In other compounds, X_1 and X_3 are both N and X_2 and X_4 are both CH. In other compounds, X_1 and X_3 are both N and X_2 and X_4 are independently CH, C-Cl or C-F.

- 10 In the compounds and pharmaceutically acceptable salts of formula I, or pharmaceutically acceptable salts thereof, A-(R₁)_n is



- 15 wherein a wavy line indicates connection to the backbone and the maximum value of n depends on the number of substitutable positions on the A-ring.

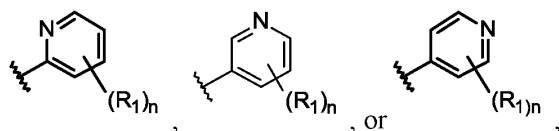
In one aspect, in the compounds and salts of formula I, A-(R₁)_n is



and the maximum value of n depends on the number of substitutable positions on the A-ring.

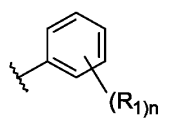
-7-

In an aspect, in the compounds and pharmaceutically acceptable salts of formula I A-(R₁)_n is:



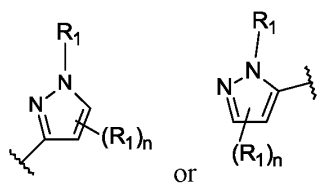
and the maximum value of n depends on the number of substitutable positions on the A-ring.

5 In another aspect, in the compounds and pharmaceutically acceptable salts of formula I A-(R₁)_n is



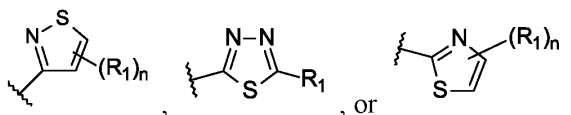
In one embodiment, n is no more than 5. In a further embodiment, n is 1-3 or 1-2. In a further embodiment, when n is three, each R₁ group is independently a halogen, methyl, or a methoxy. In another embodiment, when n is 2, at least one R₁ is a halogen, while the other R₁ is methyl, or a methoxy. In another embodiment, n is 2 and one R₁ is CF₃. In still another embodiment, n is 2, one R₁ is CF₃ and the other R₁ group is -CH₂-piperazinyl, where the piperazinyl is optionally substituted with a C₁-C₄ alkyl group, such as methyl or ethyl.

15 In some aspects, in the compounds and pharmaceutically acceptable salts of formula I A-(R₁)_n is



and the maximum value of n depends on the number of substitutable positions on the A-ring.

In some aspects, in the compounds and pharmaceutically acceptable salts of formula I A-(R₁)_n is

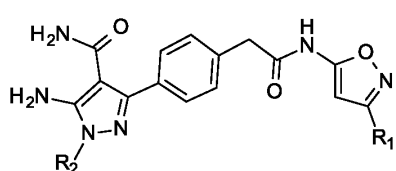


20

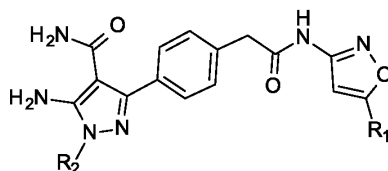
-8-

and the maximum value of n depends on the number of substitutable positions on the A-ring.

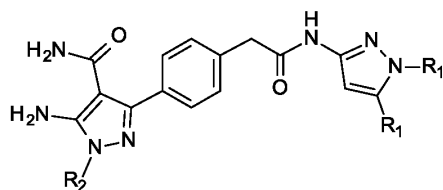
The compounds and pharmaceutically acceptable salts of formula I encompass the compounds and pharmaceutically acceptable salts of formulas Ia, Ib, Ic, and Id:



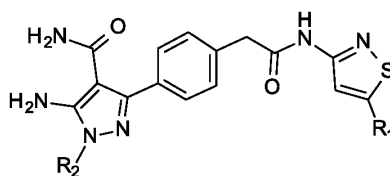
Ia,



Ib,



Ic, and



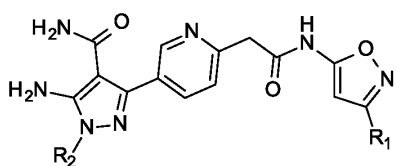
Id.

5

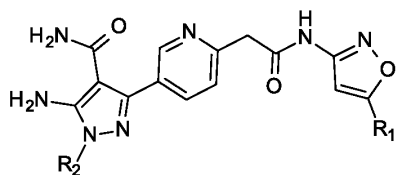
In the compounds and pharmaceutically acceptable salts of formulas Ia, Ib, Ic, and Id, X₁, X₂, X₃, and X₄ of formula I are CH.

The compounds and pharmaceutically acceptable salts of formula I, also encompass the compounds of formula Ie, If, Ig, Ih, Ii, Ij, Ik, Il and pharmaceutically acceptable salts thereof:

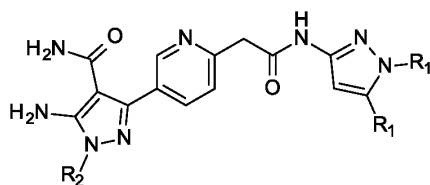
10



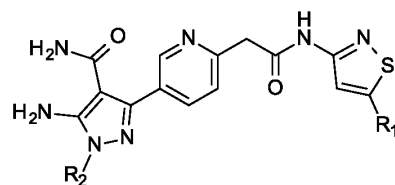
Ie,



If,

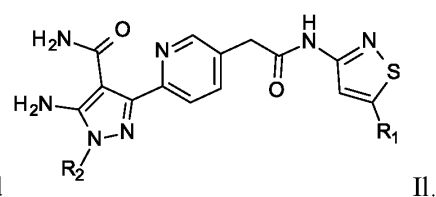
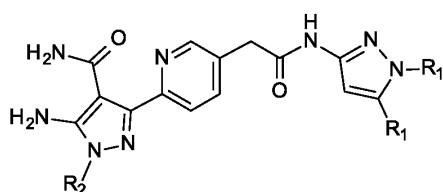
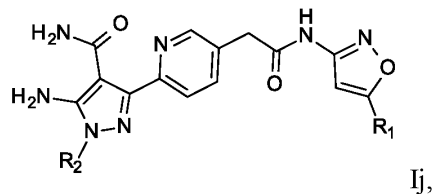
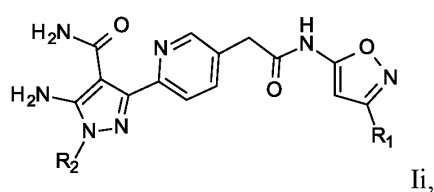


Ig,



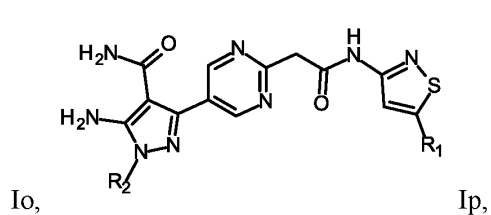
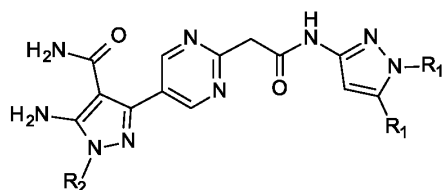
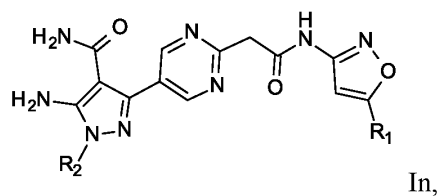
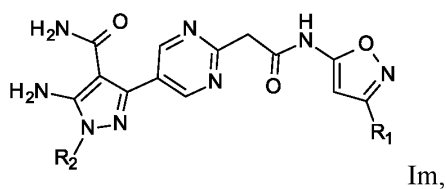
Ih,

-9-

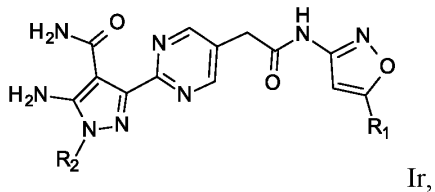
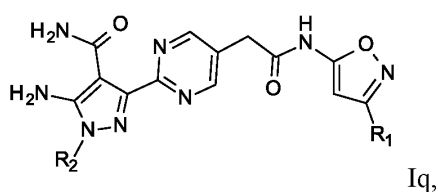


The compounds and pharmaceutically acceptable salts of formulas Ie to II, correspond to formula I, wherein one of X₁, X₂, X₃, and X₄ is N, while the others are CH.

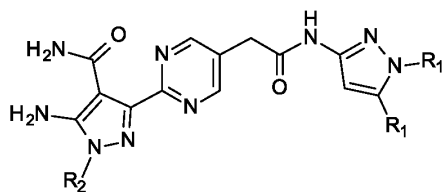
- 5 The compounds and pharmaceutically acceptable salts of formula I, also encompass the compounds of formula Im, In, Io, Ip, Iq, Ir, Is, It, and pharmaceutically acceptable salts thereof:



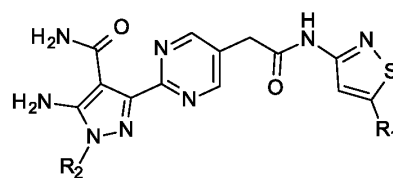
10



-10-



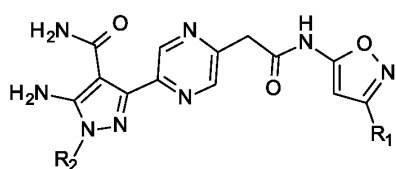
Is, and



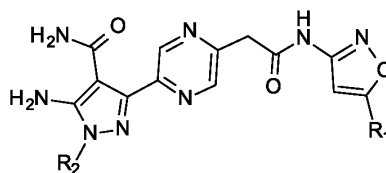
It.

The compounds and pharmaceutically acceptable salts of formulas Im, In, Io, Ip, Iq, Ir, Is, and It correspond to compounds of formula I wherein X₂ and X₃ are both N, while X₁ and X₄ are both CH or X₂ and X₃ are both CH, while X₁ and X₄ are both N.

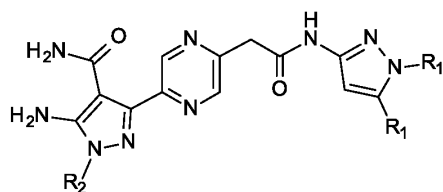
- 5 The compounds of formula I, also encompass the compounds of formula Iu, Iv, Iw, and Ix:



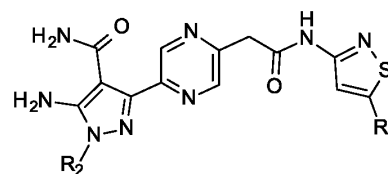
Iu,



Iv,



Iw, and



Ix.

- 10 The compounds and pharmaceutically acceptable salts of formulas Iu, Iv, Iw, and Ix, correspond to compounds of formula I wherein X₁ and X₃ are both N, while X₂ and X₄ are both CH.

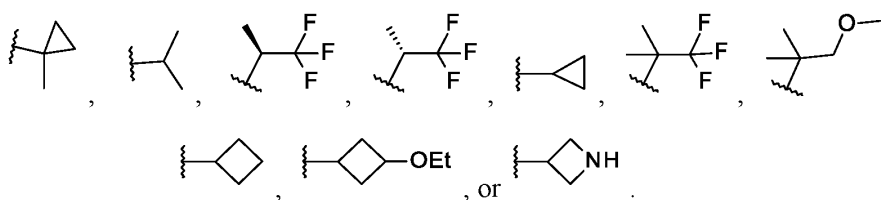
- 15 In the compounds and pharmaceutically acceptable salts of formulas I and Ia to Ix, R₂ is -C₁-C₆ alkyl, -C₁-C₄ alkyl-tetrahydrofuranyl, -C₁-C₆ hydroxyalkyl, -C₁-C₆ haloalkyl, -C₁-C₆ alkyl-O-C₁-C₂ alkyl, -C₃-C₆ cycloalkyl, tetrahydrofuranyl, pyranyl, -C₁-C₄ alkyl-tetrahydropyranyl, -C₁-C₄ alkyl-C₃-C₆ cycloalkyl, and azetidiny, wherein each is unsubstituted or substituted with one or two groups that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl,

-11-

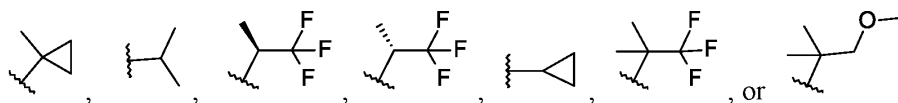
ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl. In an embodiment, the -C₁-C₆ alkyl is an ethyl group.

In an aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to Ix, R₂ is *tert*-butyl, -CH(CH₃)-cyclopropyl, -2-tetrahydrofuranyl, -3-

- 5 tetrahydrofuranyl, -3-pyranyl, -4-pyranyl, -CH(CH₃)CH₂OH, -C(CH₃)₂CH₂OH, -CH₂-(2-tetrahydrofuranyl), -CH₂-(3-tetrahydrofuranyl), -(CH₂)₃OH, -C(CH₃)₂CH₂OCH₃, -CH(CH₃)CF₃, -CH₂CF₃, -C(CH₃)₂CH₂OCH₃, cyclopentyl,



- 10 In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to Ix, R₂ is

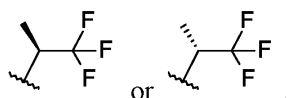


In one aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to Ix, R₂ is



15

In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to Ix, R₂ is



In yet another aspect, in the compounds and pharmaceutically acceptable salts of

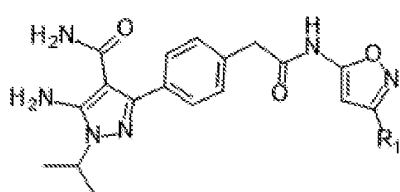
- 20 formulas I and Ia to Ix, R₂ is or .

-12-

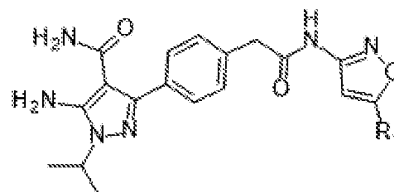
In still another aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to IX, R₂ is .

In still another aspect, in the compounds and pharmaceutically acceptable salts of formulas I and Ia to IX, R₂ is .

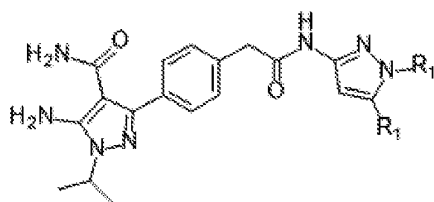
5 In an aspect, the compounds and pharmaceutically acceptable salts of formula I encompass the compounds and pharmaceutically acceptable salts of formulas IIa to IIx, and IIIa to IIIx:



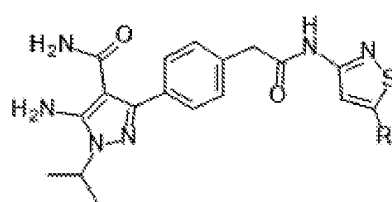
IIa,



IIb,



IIc, and



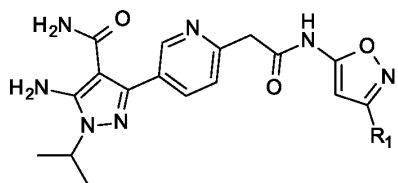
IIId.

10 The compounds and pharmaceutically acceptable salts of formulas IIa, IIb, IIc, and IIId correspond to compounds of formula I wherein X₁, X₂, X₃, and X₄ are CH and R₂ is isopropyl.

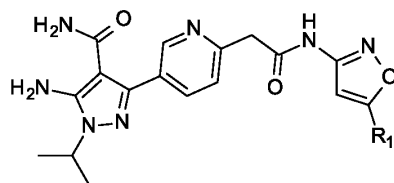
The compounds and pharmaceutically acceptable salts of formula I, also encompass the compounds of formula IIe, IIg, IIh, Ili, IIj, IIk, III and pharmaceutically acceptable salts thereof:

15

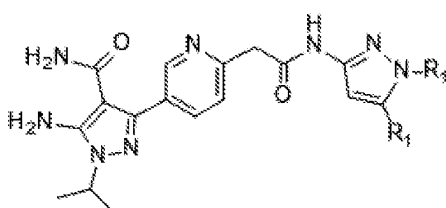
-13-



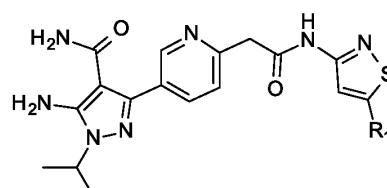
IIe,



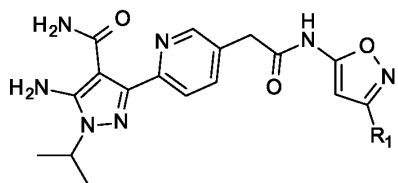
IIIf,



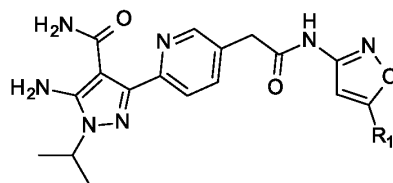
IIg,



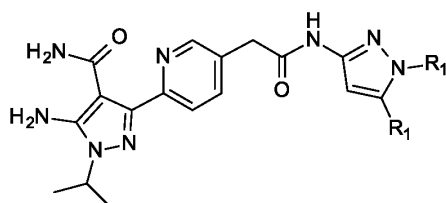
IIh,



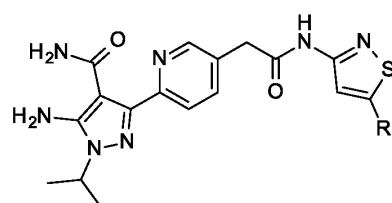
IIi,



IIj,



IIk, and



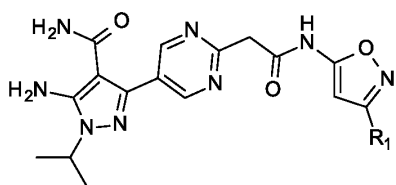
IIl.

- 5 The compounds and pharmaceutically acceptable salts of formulas IIe to IIl, correspond to compounds of formula I, wherein one of X₁, X₂, X₃, and X₄ is N, while the others are CH and R₂ is isopropyl.

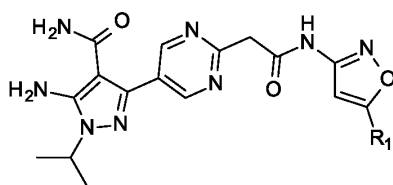
The compounds and pharmaceutically acceptable salts of formula I, also encompass the compounds of formulas IIm, IIn, IIo, IIp, IIq, IIr, IIs, IIu, and pharmaceutically acceptable

10 salts thereof:

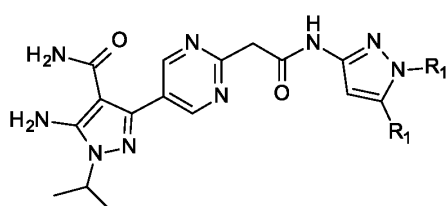
-14-



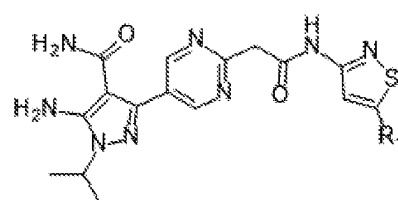
IIIm,



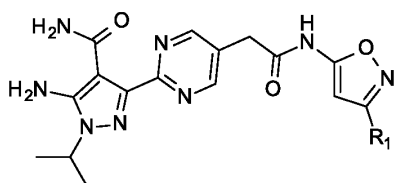
IIIn,



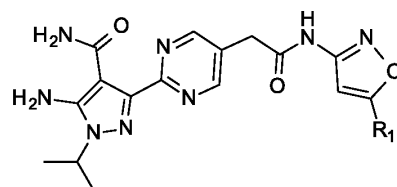
IIo,



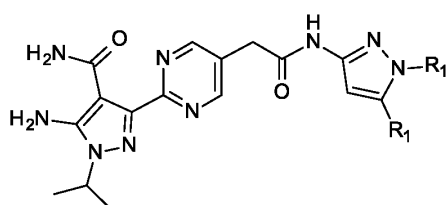
IIp,



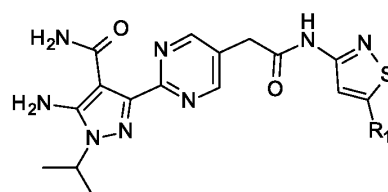
IIq,



IIr,



IIIs, and

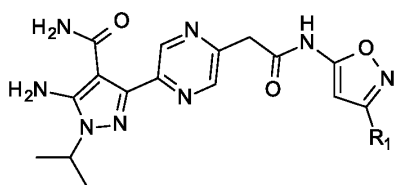


IIIt.

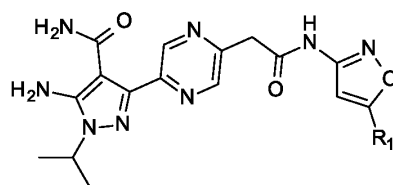
- 5 The compounds and pharmaceutically acceptable salts of formulas IIIm, IIIn, IIo, IIp, IIq, IIr, IIIs, and IIIt correspond to compounds of formula I wherein X₂ and X₃ are both N, while X₁ and X₄ are both CH or X₂ and X₃ are both CH, while X₁ and X₄ are both N and R₂ is isopropyl.

- 10 The compounds of formula I, also encompass the compounds of formula IIu, IIv, IIw, and IIx:

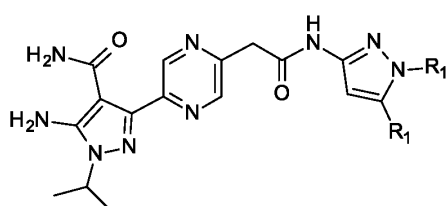
-15-



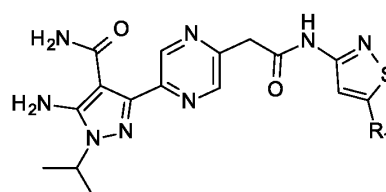
IIu,



IIv,

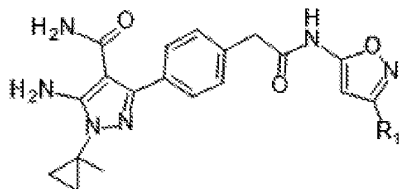


IIw, and

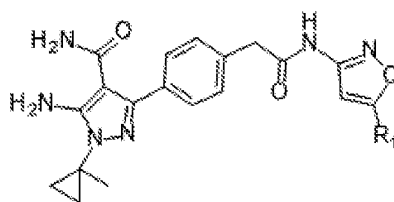


IIx.

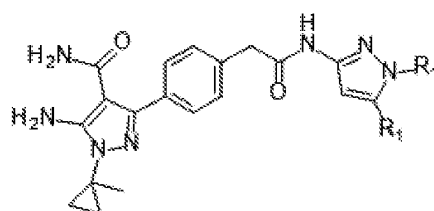
The compounds and pharmaceutically acceptable salts of formulas IIu, IIv, IIw, and IIx, correspond to compounds of formula I wherein X₁ and X₃ are both N, while X₂ and X₄ are both CH, and R₂ is isopropyl. The compounds and pharmaceutically acceptable salts of formula I encompass the compounds of formula IIIa, IIIb, IIIc, and IIId, and pharmaceutically acceptable salts thereof:



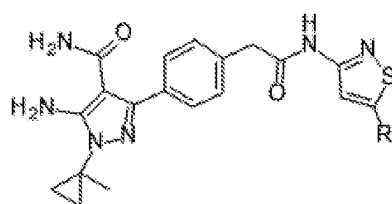
IIIa,



IIIb,



IIIc, and



IIId.

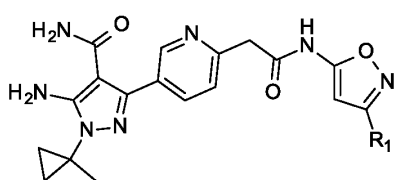
-16-

The compounds and pharmaceutically acceptable salts of formulas IIIa, IIIb, IIIc, and IIId,

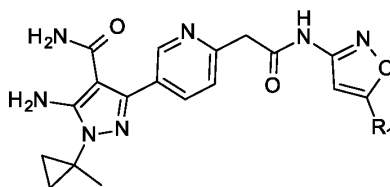
correspond to compounds of formula I wherein X_1 , X_2 , X_3 , and X_4 are CH_3 , and R_2 is



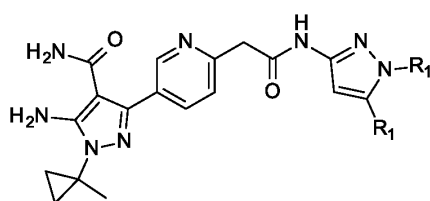
The compounds and pharmaceutically acceptable salts of formula I, also encompass
 5 the compounds of formula IIIe, IIIf, IIIg, IIIh, IIIi, IIIj, IIIk, IIIl and pharmaceutically
 acceptable salts thereof:



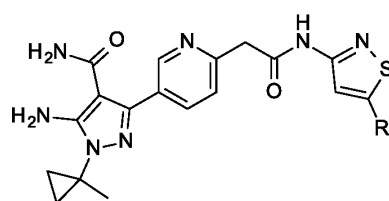
IIIe,



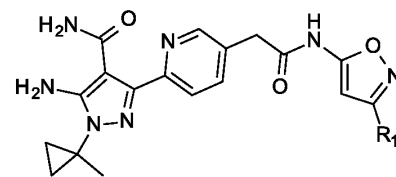
IIIf,



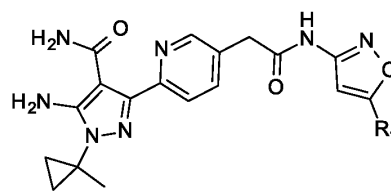
IIIg,



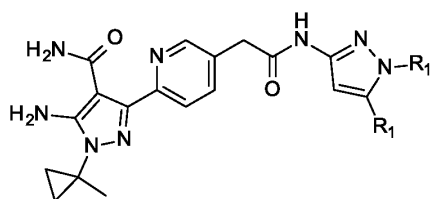
IIIh,



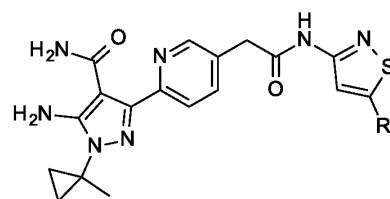
IIIi,



IIIj,

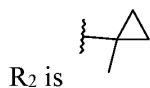


IIIk, and

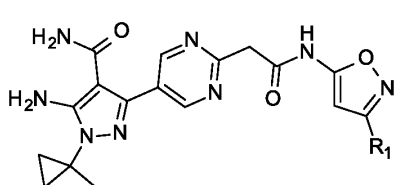
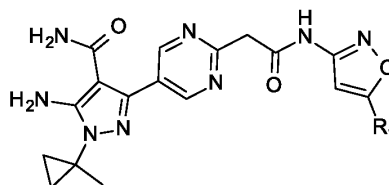


IIIl.

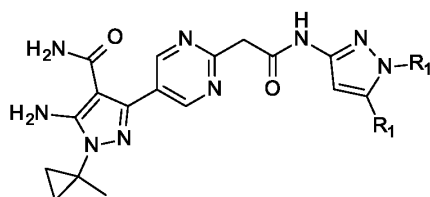
The compounds and pharmaceutically acceptable salts of formulas IIIe to IIIl correspond to compounds of formula I wherein one of X₁, X₂, X₃, and X₄ is N, while the others are CH, and



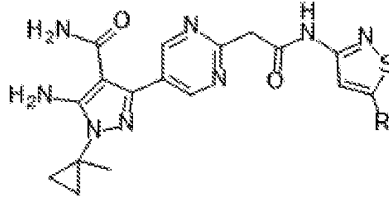
The compounds and pharmaceutically acceptable salts of formula I, also encompass
5 the compounds of formula III_m, III_n, III_o, III_p, III_q, III_r, III_s, III_t, and pharmaceutically
acceptable salts thereof:

III_m,

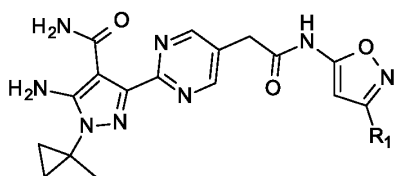
III n,



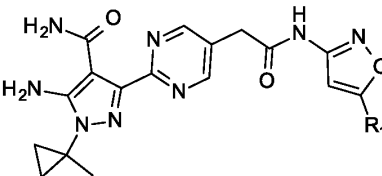
IIIo,



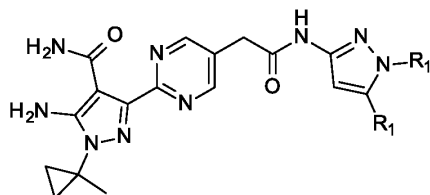
IIIp,



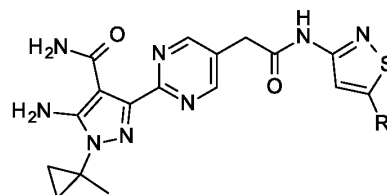
IIIq,



IIIr,



IIIs, and



III t.

The compounds and pharmaceutically acceptable salts of formulas IIIm, IIIn, IIIo, IIIp, IIIq, IIIr, IIIs, and IIIt correspond to compounds of formula I wherein X₂ and X₃ are both N, while

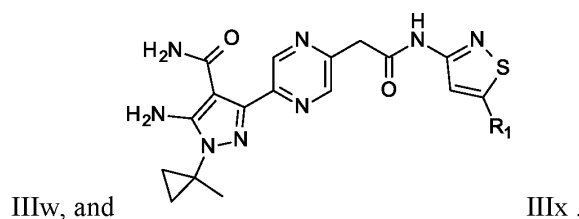
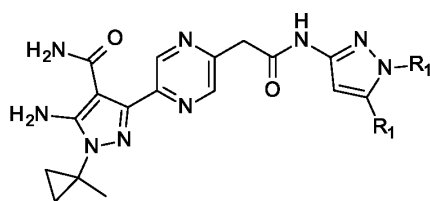
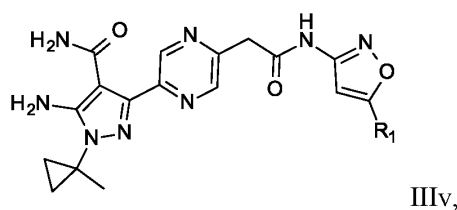
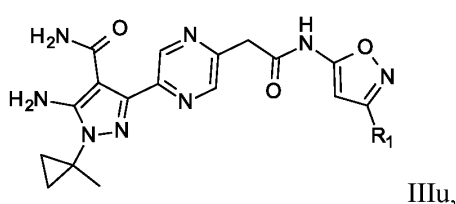
-18-

X₁ and X₄ are both CH or X₂ and X₃ are both CH, while X₁ and X₄ are both N and R₂ is



The compounds of formula I, also encompass the compounds of formula IIIu, IIIv, IIIw, and IIIx:

5



The compounds and pharmaceutically acceptable salts of formulas IIIu, IIIv, IIIw, and IIIx, correspond to compounds of formula I wherein X₁ and X₃ are both N, while X₂ and

10 X₄ are both CH or X₂ and X₄ are both N, while X₁ and X₃ are both CH, and R₂ is



In an aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to Ix, IIa to IIx and IIIa to IIIx, each R₁ is independently hydrogen, C₁-C₆ alkyl, C₄-C₈ bridged bicycloalkyl, C₅-C₁₂ spirane, wherein each R₁ is optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, or mono-, di-, or tri-halomethyl.

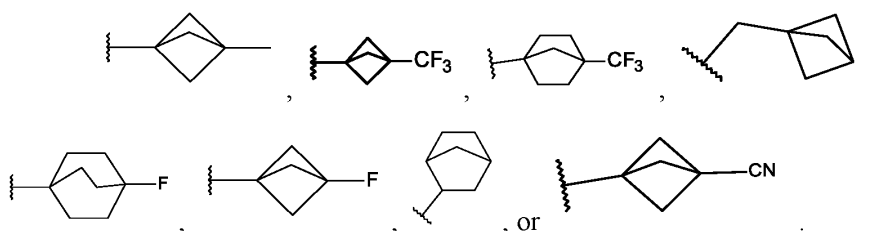
15 In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to Ix, IIa to IIx and IIIa to IIIx, each R₁ is independently 2-chloro-4-methyl-phenyl, 2,4-dichloro-3-fluoro-phenyl, 2-methoxy-4-chloro-phenyl, 2-chloro-4-methoxy-phenyl, 2-chloro-4-trifluoromethyl-phenyl, 2-methoxy-4-chloro-phenyl, 2,2-dimethylpropyl; 2-

chloro-4-fluoro-phenyl; 2,4-dichlorophenyl; 1,1-dimethyl-2,2,2-trifluoroethyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; trifluoromethyl; 1,1-dimethyl-2,2-difluoropropyl; 1,1-dimethyl-3,3,3-trifluoropropyl; 1-methylcyclopropyl; (1-methylcyclopropyl)methyl; 3-methylbicyclo[1.1.1]pentan-1-yl; 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl; or (3,3-dimethylcyclobutyl)methyl.

In a further aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently a C₄-C₈ bridged bicycloalkyl that is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of C₁-C₄ alkyl, CF₃, halo, and CN.

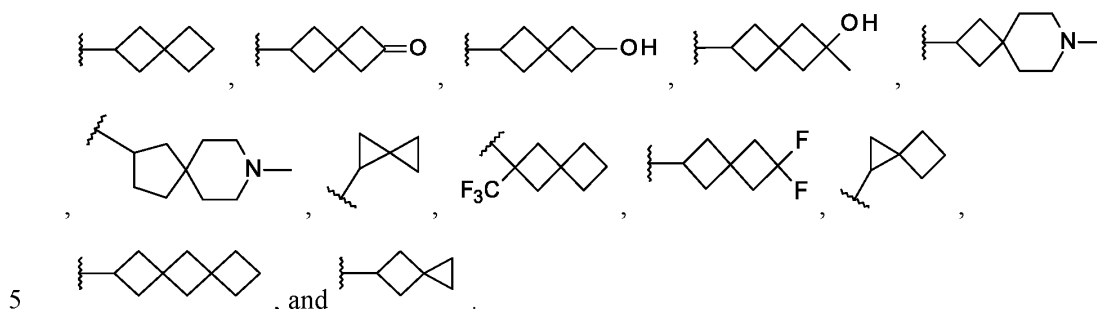
In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently a C₄-C₈ bridged bicycloalkyl that is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of methyl, ethyl, CF₃, halo, and CN.

In some aspects, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently a bridged C₄-C₈ bicycloalkyl that is



In other aspects, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently a C₅-C₁₂ spirane that is unsubstituted or substituted with 1 or 2 groups that are independently selected from the group consisting of =O, -OH, C₁-C₄ alkyl, -CF₃, and halo each R₁ is independently a C₅-C₁₂ heterospirane that is unsubstituted or substituted with 1 or 2 groups that are independently

selected from the group consisting of =O, -OH, C₁-C₄ alkyl, -CF₃, and halo. Examples of C₅-C₁₂ spiranes or C₅-C₁₂ heterospiranes include



In an aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, n is 1 and R₁ is a C₅-C₁₂ spirane that is unsubstituted or substituted with 1 or 2 groups that are independently selected from the group consisting of =O, -OH, methyl, ethyl, CF₃, and halo.

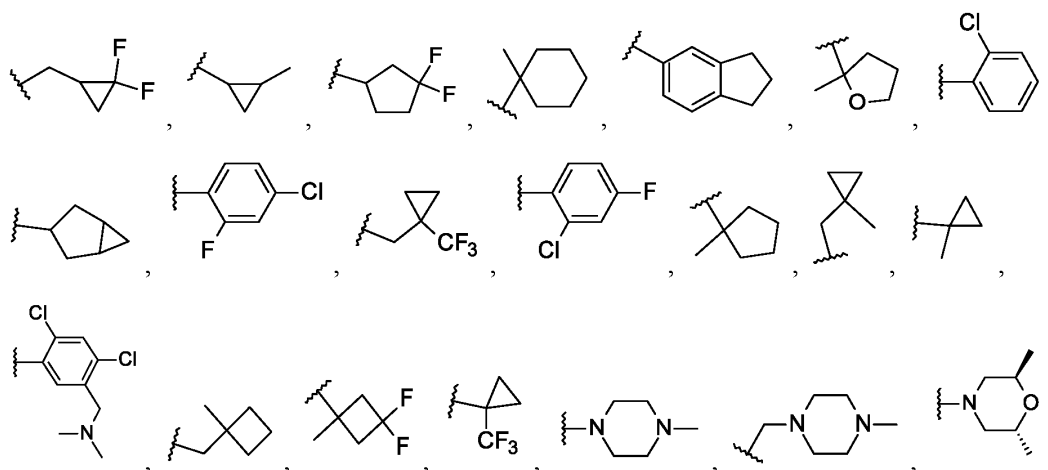
In yet another aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently halogen, C₁-C₆ alkyl, -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(phenyl), -(C₁-C₄ alkyl)(C₅-C₆ heteroalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloheteroalkyl), or -(C₀-C₄ alkyl)(C₅-C₆ heteroaryl), wherein each R₁ is optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, and mono-, di-, or trihalomethyl.

In an aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is unsubstituted. In an alternate aspect, each R₁ is substituted with no more than four groups, or no more than three groups or no more than two groups or only with one group.

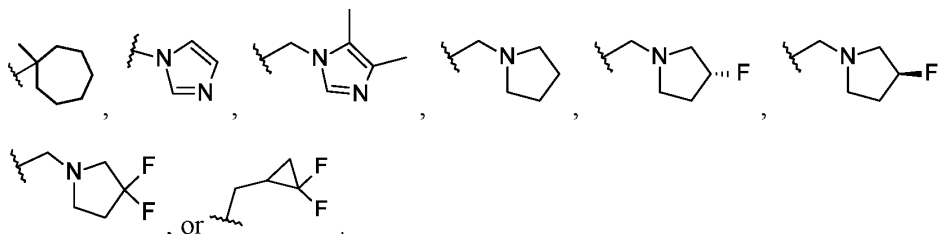
In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently -CH₂C(CH₃)₃, -CH(CH₂CH₃)₂, -CF₂CH₃, -CH₂CH₂CF₃, -C(CH₃)₂F, -C(CH₃)₂CF₃, -CH₂-cyclopentyl, -CH₂-cyclohexyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-morpholinyl, -CH₂-pyrrolidinyl, phenyl, naphthyl, pyran-4-yl, 4-methylphenyl, 4-

-21-

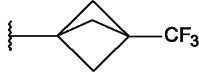
- methoxyphenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, 3-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2,4-dimethylphenyl, 4-chlorophenyl, 2-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 2-methoxyphenyl, 4-difluoromethoxyphenyl, $-\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3-chlorophenyl, methyl, ethyl, *tert*-butyl, isopropyl, trifluoromethyl, 3-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 2,4,6-trifluoromethylphenyl, 3-tetrahydrofuranyl, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{CH}_3)_2\text{OH}$, 3,3-dimethylcyclobut-1-yl, 2,3-dichlorobenzyl, 3,3-difluoromethylcyclobutyl, 2,2-dimethylcycloprop-1-yl, 2,2-difluorocyclopropyl, N-methylimidazolyl, 2-methyl-4-chlorophenyl, 2,4-dichloro-3-fluorophenyl, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, $-\text{CF}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}(\text{CH}_3)\text{cyclopropyl}$, 2,6-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-chloropyrid-2-yl, 2-methylpyrid-3-yl, 4-methylpyrid-3-yl, 3,5-dichloropyrid-2-yl, 3,3-difluorocyclopentyl, fluoro, chloro, bromo, 2-methoxy-4-chloro-phenyl, 2-fluoro-4-chlorophenyl, 3-fluoro-4-chlorophenyl, benzyl, piperidinyl, 4-methyl-piperidinyl, 4-methoxy-piperidinyl, N-methylpyrazol-3-yl, $-\text{C}(\text{O})\text{-piperidinyl}$, $-\text{OCHF}_2$,



-22-



In an aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia

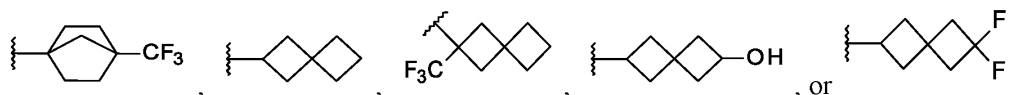
5 to IX, IIa to IIx and IIIa to IIIx, R₁ is 2,2-dimethylpropyl or .

In a further aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, R₁ is 2,2-dimethylpropyl.

In a still further aspect, in the compounds and pharmaceutically acceptable salts of

formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, R₁ is .

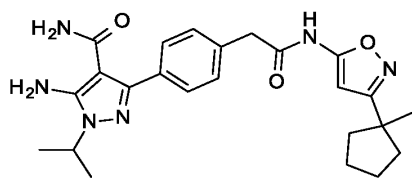
10 In another aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, each R₁ is independently



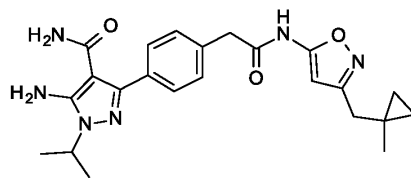
15 In a different aspect, in the compounds and pharmaceutically acceptable salts of formulas I, Ia to IX, IIa to IIx and IIIa to IIIx, R₁ is C₁-C₆ alkyl, which is unsubstituted or substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, and mono-, di-, and tri-halomethyl.

In yet another aspect, the compounds and pharmaceutically acceptable salts of formula I are:

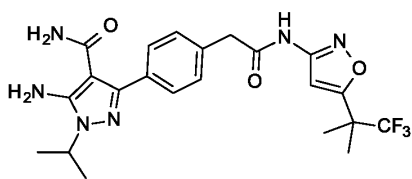
-23-



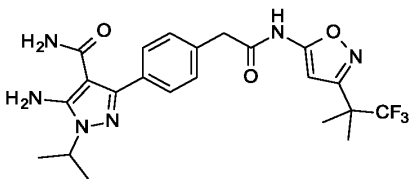
,



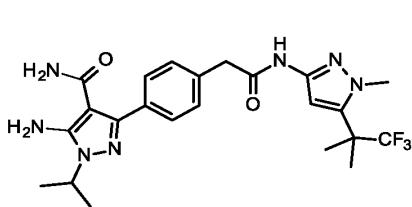
,



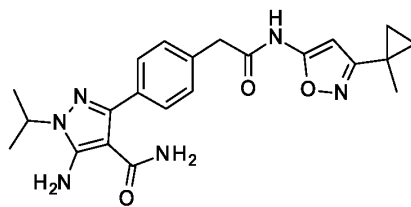
,



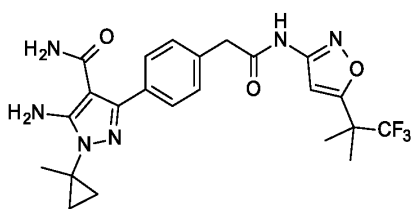
,



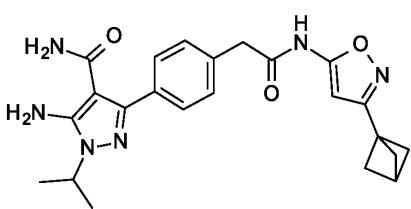
,



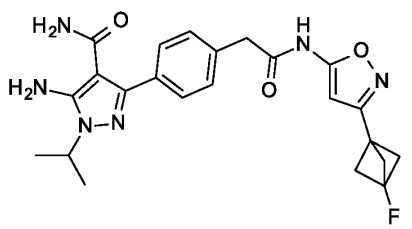
,



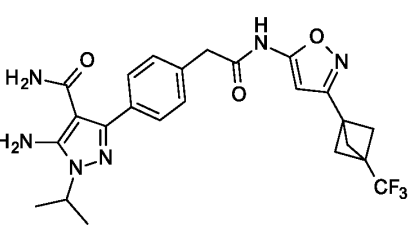
,



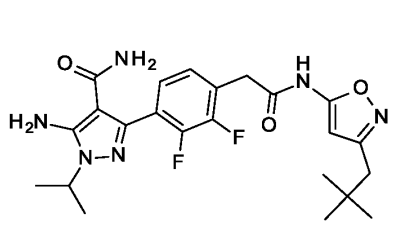
,



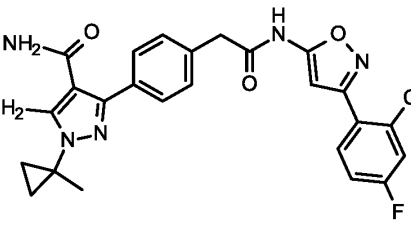
,



,

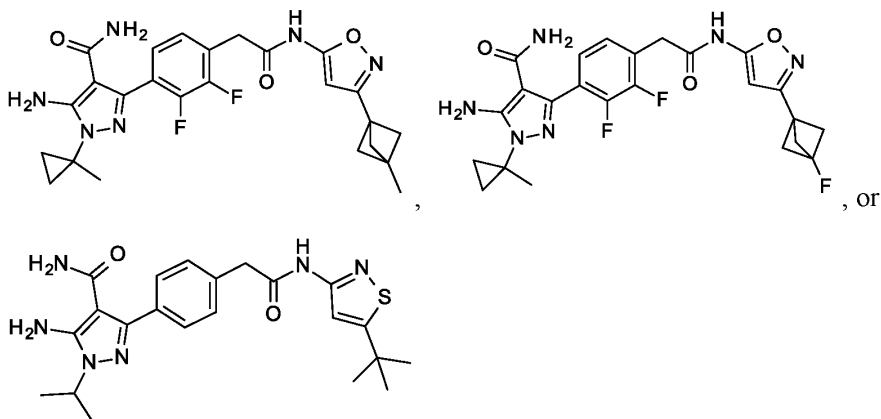


,

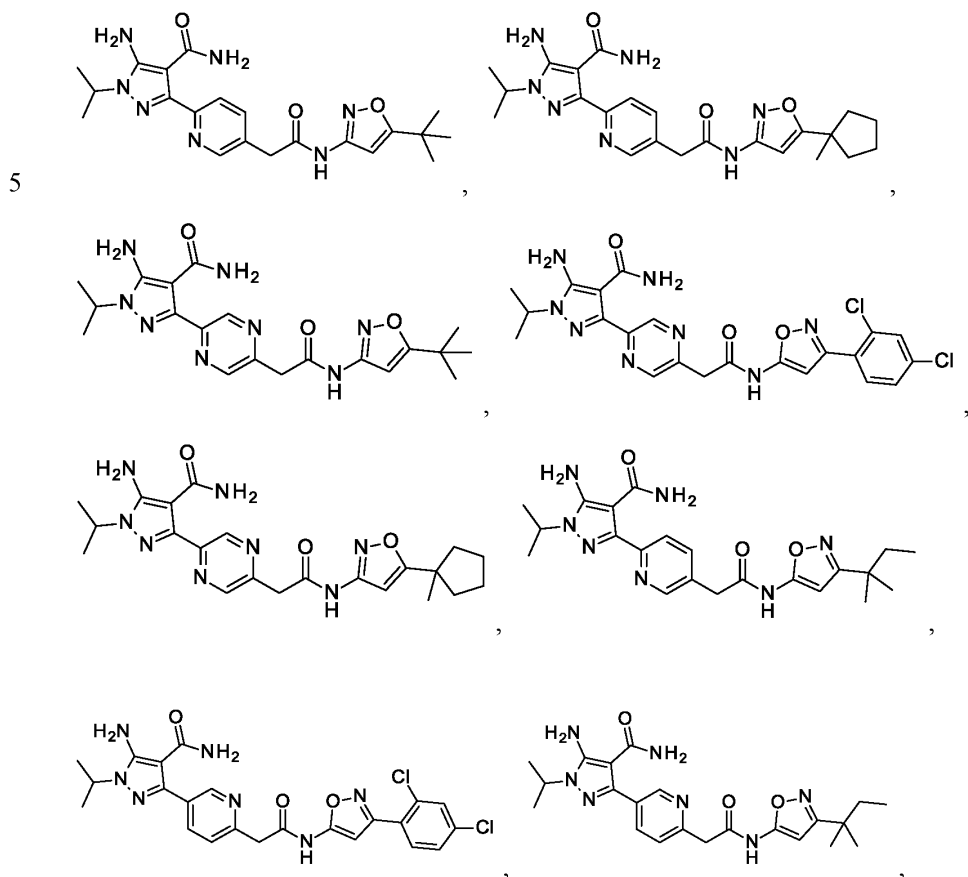


,

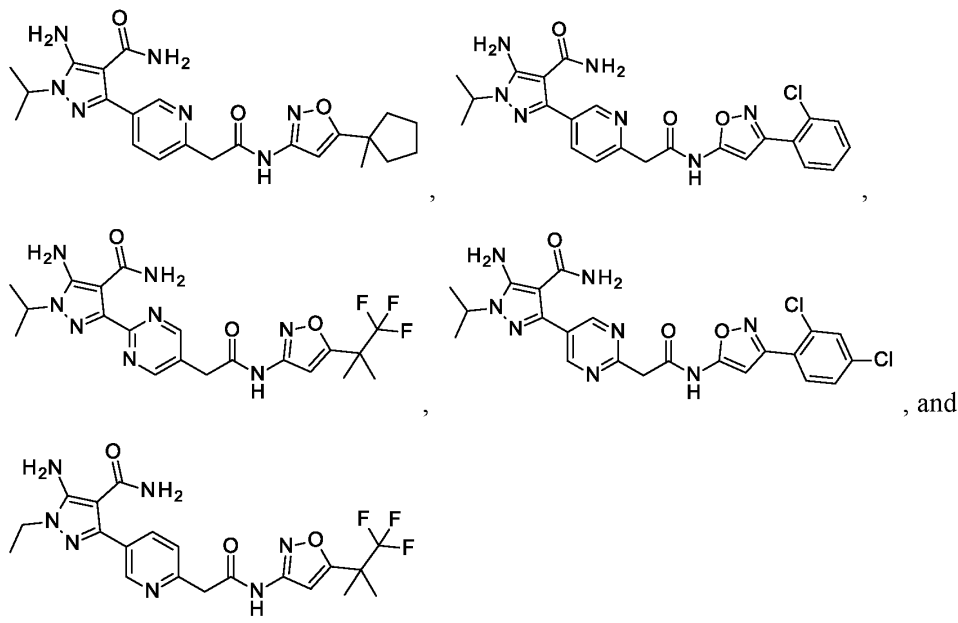
-24-



In still yet another aspect, the compounds and pharmaceutically acceptable salts of formula I:



-25-



5 Definitions

The specific chemical naming conventions used herein are intended to be familiar to one of skill in the chemical arts. Some terms are defined specifically for additional clarity.

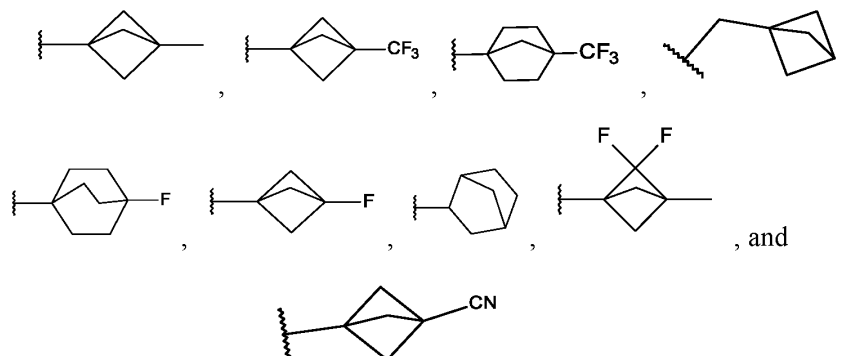
- As used herein, the term alkyl means saturated linear or branched-chain monovalent hydrocarbon radicals of one to six atoms, e.g., "C₁-C₆ alkyl." In cases where a zero is indicated, e.g., C₀-C₄ alkyl or C₀-C₃ alkyl, this component of the substituent group can be absent, thus, if a C₅ heterocycloalkyl substituent is at the R₂ position in formula (I), the C₅ heterocycloalkyl substituent could be described by the -(C₀-C₄ alkyl)(C₃-C₇ heterocycloalkyl) substituent as described for R₂ (i.e., the substituent group would be -(C₀)(C₅ heterocycloalkyl)). Examples include, but are not limited to, methyl, ethyl, propyl, 1-propyl, isopropyl, and butyl. Similarly, as used herein, the term heteroalkyl means saturated linear or branched-chain monovalent alkyl molecules as defined herein containing one or more heteroatoms that have replaced carbon(s) in the alkyl chain. Typically, there are no more than four heteroatoms or no more than three heteroatoms in the heteroalkyl group.

As used herein, the term aryl refers to a functional group or substituent derived from an aromatic ring containing six to ten carbon atoms, e.g., C₆-C₁₀ aryl, or five to six carbon atoms, e.g., C₅-C₆ aryl, and no heteroatoms. Examples of aryl groups include phenyl and naphthyl. As used herein, the term heteroaryl refers to a functional group or substituent
5 derived from an aromatic ring containing carbon atoms and one or more heteroatoms (e.g., nitrogen, oxygen, or sulfur) as part of the aromatic ring. Examples include rings having five or six atoms, at least one of which is a heteroatom. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, and thiazolyl.

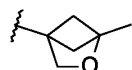
10 As used herein, the term C₃-C₇ cycloalkyl means a cyclic alkyl molecule containing three to seven carbon atoms. Examples of C₃-C₇ cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, and cyclopentyl. Similarly, as used herein, the terms heterocycloalkyl and cycloheteroalkyl mean a cycloalkyl molecule as defined herein, containing three to seven total atoms at least one of which is a heteroatom. Heterocycloalkyl
15 or cycloheteroalkyl groups can be fused to other groups, such as phenyl groups. For example, a piperidine fused to a phenyl can form a tetrahydroisoquinoline or a tetrahydroquinoline.

As used herein, the terms bicyclic, bicycyl, and bicycloalkyl refer to a group having two or more fused or bridged rings. C₄-C₁₀ bicyclic, C₄-C₁₀ bicycyl, and C₄-C₁₀ bicycloalkyl
20 contain from four to ten carbon atoms. When the bicyclic group is fused, the two rings share two adjacent atoms. When the bicyclic group is bridged (also referred to as a bridged bicycloalkyl), the two rings share three or more atoms. Bridged bicycloalkyl groups may have four to ten carbon atoms or four to eight carbon atoms. Such groups may be referred to as “C₄-C₁₀ bridged bicycloalkyl” or “C₄-C₈ bridged bicycloalkyl,” respectively. Bicyclic
25 molecules can be all aliphatic, all aromatic, or mixed aromatic and aliphatic. The term C₄-C₁₀ heterobicyclic refers to C₄-C₁₀ bicyclic groups as defined that also include one or more hetero atoms. Examples of bridged bicycloalkyl groups useful with the compounds of formula (I) include, but are not limited to:

-27-



Examples of C₄-C₁₀ heterobicyclic include, but are not limited to:



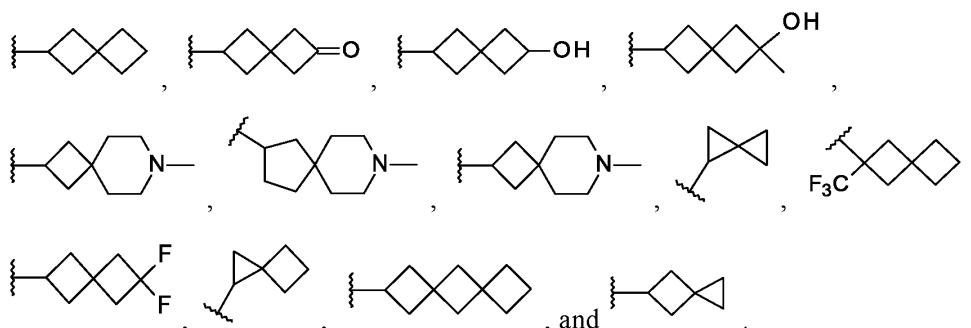
5

As used herein, the terms C₅-C₁₂ spiranyl or spirane or spiranes refers to a spirocyclic ring system. C₅-C₁₂ spiranyl, C₅-C₁₂ spirane and C₅-C₁₂ spiranes refer to spirocyclic rings systems having 5 to 12 ring carbons. The spirocyclic ring system contains at least two and up to four rings, at least two of which must be connected via a spiro attachment. C₅-C₁₂ spiranes may be unsubstituted or substituted as described herein.

10

C₅-C₁₂ heterospiranyl refers to a spirocyclic ring system having 5 to 12 ring atoms, at least one of which is a heteroatom, i.e., not a carbon. The heterospiranyl ring system contains two to four rings, at least two of which must be connected via a spiro attachment. C₅-C₁₂ heterospiranes may be unsubstituted or substituted as described herein. Examples of substituted and unsubstituted C₅-C₁₂ spiranes and C₅-C₁₂ heterospiranes include, but are not limited to:

15



As used herein, the term halogen or halo means fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

As used herein, the term oxo means an oxygen that is double-bonded to a carbon atom, which can be represented as =O.

Compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx can be deuterated or trituted at one or more positions and such deuterated or trituted forms are part of the invention. Deuterium modification involves replacing one or more hydrogen atoms of a drug with deuterium atoms in an attempt to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites. Tritium modification makes the molecule radioactive and allows researchers to determine where the drug is deposited in the body and how it is metabolized.

The compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx described herein may form pharmaceutically acceptable salts. Such pharmaceutically acceptable salts of the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx are intended to be included. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art (*see, e.g., P. Stahl, et al. Handbook of Pharmaceutical Salts: Properties, Selection and Use*, 2nd Revised Edition (Wiley-VCH, 2011); S.M. Berge, *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, Vol. 66, No. 1, January 1977).

The compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein are generally effective over a wide dosage range. For example, dosages per day fall within the range of about 0.01 mg/kg to about 200 mg/kg. Further, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein can be administered, for example, in an amount of about 0.05 mg/kg to about 150, about 0.1 mg/kg to about 150, about 0.5 mg/kg to about 150 mg/kg, about 1 mg/kg to about 150 mg/kg, about 5 mg/kg to about 150 mg/kg, about 5 mg/kg to about 100 mg/kg, about 20 mg/kg to about 40 mg/kg, about 25 mg/kg to about 35 mg/kg, about 50 mg/kg to about 70 mg/kg, about 55 mg/kg to about 65 mg/kg, about 90 mg/kg to about 110 mg/kg, about 95 mg/kg to about 105 mg/kg, or about 50 mg/kg to about 150 mg/kg.

Alternatively, compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein can be administered, for example, in an amount of about 0.1 mg/kg to about 15 mg/kg, or about 0.5 mg/kg to about 10 mg/kg, or 1 mg/kg to about 9 mg/kg, or about 2 mg/kg to about 8 mg/kg or about 3 mg/kg to 7 mg/kg. Additionally, the compounds of

5 formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein can be administered, for example, in an amount of about 1 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3 mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, 3.5 mg/kg, 3.6 mg/kg, 3.7 mg/kg, 3.8 mg/kg, 3.9 mg/kg, 4, mg/kg, 4.1 mg/kg, 4.2 mg/kg, 4.3 mg/kg, 4.4 mg/kg, 4.5 mg/kg, 4.6 mg/kg, 4.7 mg/kg, 4.8 mg/kg, 4.9 mg/kg, 5 mg/kg, 5.1 mg/kg, 5.2 mg/kg, 5.3 mg/kg, 5.4 mg/kg, 5.5 mg/kg, 5.6 mg/kg, 5.7 mg/kg, 5.8 mg/kg, 5.9 mg/kg, 6 mg/kg, 6.1 mg/kg, 6.2 mg/kg, 6.3 mg/kg, 6.4 mg/kg, 6.5 mg/kg, 6.6 mg/kg, 6.7 mg/kg, 6.8 mg/kg, 6.9 mg/kg, 7 mg/kg, 7.1 mg/kg, 7.2 mg/kg, 7.3 mg/kg, 7.4 mg/kg, 7.5 mg/kg, 7.6 mg/kg, 7.7 mg/kg, 7.8 mg/kg, 7.9 mg/kg, 8 mg/kg, 8.1 mg/kg, 8.2 mg/kg, 8.3 mg/kg, 8.4 mg/kg, 8.5 mg/kg, 8.6 mg/kg, 8.7 mg/kg, 8.8 mg/kg, 8.9 mg/kg, 9 mg/kg, 9.1 mg/kg, 9.2 mg/kg, 9.3 mg/kg, 9.4 mg/kg, 9.5 mg/kg, 9.6 mg/kg, 9.7 mg/kg, 9.8 mg/kg, 9.9 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, about 100 mg/kg, about 105 mg/kg, about 110 mg/kg, about 115 mg/kg, about 120 mg/kg, about 125 mg/kg, about 130 mg/kg, about 135 mg/kg, about 140 mg/kg, about 145 mg/kg, about 150 mg/kg, about 155 mg/kg, about 160 mg/kg, about 165 mg/kg, about 170 mg/kg, about 175 mg/kg, about 180 mg/kg, about 185 mg/kg, about 190 mg/kg, about 195 mg/kg, or about

15 200 mg/kg. Daily administration can be once-daily or in multiple doses, e.g., twice-daily (BID) administration. Dosing can be 160 mg orally twice daily for patients weighing >50kg or 120 mg for patients weighing <50kg. It will be understood that the amount of a compound actually administered will be determined by a physician, in light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the

20

actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. Possibly CNS involvement/ need for increased CNS exposure is also typically considered.

The compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described
5 herein can be formulated as pharmaceutical compositions that can be administered by a variety of routes. Such pharmaceutical compositions and processes for preparing the same are well known in the art (*see, e.g., Remington: The Science and Practice of Pharmacy* (A. Gennaro, *et al.*, eds., 21st ed., Mack Publishing Co., 2005)). Specifically, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically
10 acceptable salts thereof, can be combined with one or more pharmaceutically acceptable carriers, diluents, or excipients. More particularly, the compounds described herein by formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx can be formulated as pharmaceutical compositions. Further, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof, can be combined with one or
15 more other therapeutic agents. For example, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof, can be a component in a pharmaceutical composition for the treatment of cancer in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally with one or more additional therapeutic agents. In concomitant therapies, when patients have
20 multiple driver mutations/ alterations detected – such as when an EGFR mutation and a clinically significant RET alteration are detected, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx can be administered in combination with a second therapeutic agent. Examples of combinations include, but are not limited to compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and osimertinib. Other examples of combinations include
25 compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx combined with one or more of platinum based chemotherapeutic acids, and/or non-platinum based chemotherapeutic agents. Pharmaceutical compositions containing the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof, can be used in the methods described herein.

The term “treating” (or “treat” or “treatment”) as used herein refers to restraining, slowing, stopping, or reversing the progression or severity of an existing symptom, condition or disorder.

As used herein, the term “irritable bowel syndrome” or “IBS” means gastrointestinal disorders including, but not limited to, diarrhea-predominant, constipation-predominant or alternating stool pattern, functional bloating, functional constipation, functional diarrhea, unspecified functional bowel disorder, functional abdominal pain syndrome, chronic idiopathic constipation, functional esophageal disorders, functional gastroduodenal disorders, functional anorectal pain, and inflammatory bowel disease.

As used herein, the terms “cancer” and “cancerous” refer to or describe the physiological condition in patients that is typically characterized by unregulated cell proliferation. Included in this definition are benign and malignant cancers. By “early stage cancer” or “early stage tumor” is meant a cancer that is not advanced or metastatic or is classified as a Stage 0, I, or II cancer. Examples of cancer include, but are not limited to, lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (e.g., papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid adenoma, endocrine gland neoplasms, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, and cervical cancer.

The term “RET-associated disease or disorder” as used herein refers to diseases or disorders associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a RET gene, a RET kinase, a RET kinase domain, or the expression or activity or level of any of the same described herein).

The term “RET-associated cancer” as used herein refers to cancers associated with or having a dysregulation of a RET gene, a RET kinase (also called herein RET kinase protein), or expression or activity, or level of any of the same. Non-limiting examples of a RET-associated cancer are described herein.

5 The phrase “dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same” refers to a genetic mutation or alteration. Examples of such genetic mutations causing dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same include, but are not limited to, a RET gene translocation that results in the expression of a fusion protein, a deletion in a RET gene that results in the
10 expression of a RET protein that includes a deletion of at least one amino acid as compared to the wild-type RET protein, a mutation in a RET gene that results in the expression of a RET protein with one or more point mutations, or an alternative spliced version of a RET mRNA that results in a RET protein having a deletion of at least one amino acid in the RET protein as compared to the wild-type RET protein or a RET gene amplification that results in
15 overexpression of a RET protein or an autocrine activity resulting from the overexpression of a RET gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a RET protein (e.g., a constitutively active kinase domain of a RET protein) in a cell. A dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be a mutation in a RET gene that encodes a RET protein that is constitutively
20 active or has increased activity as compared to a protein encoded by a RET gene that does not include the mutation. For example, a dysregulation of a RET gene, a RET protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains the 2nd half/portion of RET, and the 1st half of some other gene that is not RET. In some examples,
25 dysregulation of a RET gene, a RET protein, or expression or activity or level of any of the same can be a result of a gene translocation of one RET gene with another non-RET gene.

Methods for the treatment of RET-associated diseases or disorders, in particular for the treatment of IBS or cancer with abnormal RET expression, using the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein are provided. Examples

of cancers with abnormal RET expression include cancers caused by dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same. One such method of treating RET-associated diseases or disorders such as IBS or cancer includes administering a therapeutically effective amount of a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx or pharmaceutically acceptable salts thereof to a patient in need thereof. Another method of treating RET-associated diseases or disorders such as IBS or cancer includes a) detecting a dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx or a pharmaceutically acceptable salt.

The dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same can be the result of one or more chromosome translocations or inversions resulting in a RET gene fusion (i.e., the genetic translocations result in an expressed protein that is a fusion protein containing residues from a non-RET partner protein, and including a minimum of a functional RET kinase domain). Non-limiting examples of RET fusion partners and their associated cancers include ACBD5 (papillary thyroid cancer); AFAP1 (NSCLC); AFAP1L2 (papillary thyroid cancer); AKAP13 (papillary thyroid cancer); BCR (chronic myelomonocytic leukemia); C10orf118 (papillary thyroid cancer); CCDC6 (also called PTC1, D10S170, or H4) (NSCLC, colon cancer, papillary thyroid cancer, adenocarcinomas, lung adenocarcinoma, metastatic colorectal cancer, adenosquamous carcinomas, breast cancer); CCDC88C (NSCLC); CCDC186-RET, CEP55 (diffuse gastric cancer); CGNL1 (pancreatic cancer); CLIP1 (adenocarcinoma); CUX1 (lung adenocarcinoma); DLG5 (non-anaplastic thyroid cancer); DOCK1 (NSCLC); EML4 (papillary thyroid cancer); ERC1 (also called ELKS) (papillary thyroid cancer, breast cancer); ETV6 (salivary cancer); FGFR1OP (CMML, primary myelofibrosis with secondary acute myeloid leukemia); FKBP15 (papillary thyroid cancer); FOXP4 (lung adenocarcinoma); FRMD4A (NSCLC); GOLGA5 (also called PTC5) (papillary thyroid cancer, spitzoid neoplasms); H4L (various); HOOK3 (papillary thyroid cancer); HRH4-RET (thyroid cancer and/or papillary thyroid cancer); HTIF1 (various); KIAA1217 (also called

SKT) (papillary thyroid cancer, lung adenocarcinoma, NSCLC); KIAA1468 (also called PTC9 and RFG9) (papillary thyroid cancer, lung adenocarcinoma); KIF13A (NSCLC); KIF5B (NSCLC, ovarian cancer, spitzoid neoplasms, lung adenocarcinoma, adenosquamous carcinomas); KTN1 (also called PTC8) (papillary thyroid cancer); MBD1 (also known as

5 PCM1) (papillary thyroid cancer); MPRIP (NSCLC); MYH10 (infantile myofibromatosis); MYH13 (medullary thyroid cancer); NCOA4 (also called PTC3, ELE1, and RFG) (papillary thyroid cancer, NSCLC, colon cancer, salivary gland cancer, metastatic colorectal cancer, lung adenocarcinoma, adenosquamous carcinomas diffuse sclerosing variant of papillary thyroid cancer, breast cancer, acinic cell cancer, mammary analog secretory cancer); OLFM4

10 (Small-bowel cancer); PARD3 (NSCLC); PCM1 (papillary thyroid cancer); PIBF1 (bronchiolus lung cell cancer); PICALM (NSCLC); PPFIBP2 (papillary thyroid cancer); PRKAR1A (also called PTC2) (papillary thyroid cancer); PTC1ex9 (a novel CCDC6 rearrangement) (metastatic papillary thyroid cancer); PTC4 (a novel NCO4/ELE1 rearrangement) (papillary thyroid cancer); RAB61P2 (papillary thyroid cancer); RASAL2

15 (Sarcoma); RASGEF1A (breast cancer); RBPMS (NSCLC); RFG8 (papillary thyroid cancer); RRBP1 (colon cancer); RUFY1 (colorectal cancer); RUFY2 (NSCLC; papillary thyroid cancer); RUFY3 (papillary thyroid cancer); SLC12A2 (NSCLC); SORBS2 (papillary thyroid cancer); SPECC1L (papillary thyroid cancer; thyroid gland cancer); SQSTM1 (papillary thyroid cancer); TAF3 (pancreatic cancer); TBL1XR1 (papillary thyroid cancer,

20 thyroid gland cancer); TFG (pancreatic cancer); TIF1G (various); TRIM24 (also called PTC6) (papillary thyroid cancer); TRIM27 (also called RFP) (papillary thyroid cancer); AKAP13 (papillary thyroid cancer); TRIM33 (also called PTC7 and RFG7) (NSCLC, papillary thyroid cancer); and UEVLD (papillary thyroid cancer). The fusion protein can be, for example, KIF5B-RET. Fusions that were identified in single tumors included *CCDC186-RET*, *ERCI-RET*, *KTN1-RET*, and *RUFY3-RET*. Still other RET fusion proteins may not be

25 included in the listing herein or are not yet known; however, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and methods for their use as described herein are expected to be effective inhibitors.

The dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, can be caused by one or more point mutations, insertions, or deletions in a RET gene (compared to wildtype RET). For reference, the sequence of mature human RET protein (SEQ ID NO: 1) is provided here:

```

5   MAKATSGAAG LRLLLLLLLP LLGKVALGLY FSRDAYWEKL YVDQAAGTPL
   LYVHALRDAP EEVPSFRLGQ HLYGTYRTRL HENNWICIQE DTGLLYLNRS
   LDHSSWEKLS VRNRGFPLLT VYLKVFLSPT SLREGECQWP GCARVYFSFF
   NTSFPACSSL KPRELCFPET RPSFRIREN RPPGTFHQFRL LPVQFLCPNI
   SVAYRLLEGE GLPFRCAPDS LEVSTRWALD REQREKYELV AVCTVHAGAR
10  EEVVMVPFPV TVYDEDDSDAP TFPAGVDTAS AVVEFKRKED TVVATLRVFD
   ADVVPASGEL VRRYTSTLLP GDTWAQQTFR VEHWPNETSV QANGSFVRAT
   VHDYRLVLNR NLSISENRTM QLAVLVNDSF FQGPAGVLL LHFNVSVLPV
   SLHLPSTYSL SVSRRARRFA QIGKVCVENC QAFSGINVQY KLGSSGANCS
   TLGVVTS AED TSGILFVN D T KALRRPKCAE LHYMVVATDQ QTSRQAQAQL
15  LVTVEGSYVA EEAGCPLSCA VSKRRLECEE CGGLGSPTGR CEWRQGDGKG
   ITRNFSTCSP STKTCPDGHC DVVETQDINI CPQDCLRGS VGGHEPGEPR
   GIKAGYGTCN CFPEEEKCFC EPEDIQDPLC DELCRTVIAA AVLFSEFIVSV
   LLSAFCIH CY HKFAHKPPIS SAEMTFRRPA QAFPVSYS SSS GARRPSLDSM
   ENQVSVD AFK ILEDPKW EFP RKNLVLGKTL GEGEFGKVVK ATAFHLKGRA
20  GYTTVAVKML KENASPS ELR DLLSEFNVLK QVNHPHVIKL YGACSQDGPL
   LLIVEYAKYG SLRGFLRESR KVGPGYLGSG GSRNSSSLDH PDERALTMGD
   LISFAWQISQ GMQYLAEMKL VHRDLAARNI LVAEGRKM KI SDFGLSRDVY
   EEDSYVKRSQ GRIPVKWMAI ESLFDHIYTT QSDVWSFGVL LWEIVTLGGN
   PYPGIPPERL FNLLKTGHRM ERPDNCSEEM YRLMLQCWKQ EPDKRPVFAD
25  ISKDLEKMMV KRRDYLDLAA STPSDSL IYD DGLSEEETPL VDCNNAPLPR
   ALPSTWIENK LYGMSDPNWP GESPVPLTRA DGTNTGFPRY PNDSVYANWM
   LSPSAAKLMD TFDS

```

Non-limiting examples of potentially activating RET kinase protein point mutations, insertions, or deletions as compared to wild-type RET kinase can occur at the following

amino acid positions: 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 20, 32 (e.g., S32L), 34 (e.g., D34S), 40 (e.g., L40P), 56 (e.g., L56M), 64 (e.g., P64L), 67 (e.g., R67H), 114 (e.g., R114H), 136 (e.g., glutamic acid to stop codon), 145 (e.g., V145G), 180 (e.g., arginine to stop codon), 200, 292 (e.g., V292M), 294, 321 (e.g., G321R), 330 (e.g., R330Q), 338 (e.g., T338I), 360 (e.g.,
5 R360W), 373 (e.g., alanine to valine (p.A373V) frameshift), D378-G385delinsE, 393 (e.g., F393L), 423 (e.g., G423R), 432, 446 (e.g., G446R), 505-506 (6-Base Pair In-Frame Germline Deletion in Exon 7), 510 (e.g., A510V), 511 (e.g., E511K), 513 (e.g., G513D), 515 (e.g., C515R, C515S, C515W), 525 (e.g., R525W), 531 (e.g., C531R, or 9 base pair duplication), 532 (e.g., duplication), 533 (e.g., G533C, G533S), 550 (e.g., G550E), 591 (e.g.,
10 V591I), 593 (e.g., G593E), 595 (e.g., E595D and E595A), 600 (e.g., R600Q), 602 (e.g., I602V), 603 (e.g., K603Q, K603E), 606 (e.g., Y606C), 609 (e.g., C609Y, C609S, C609G, C609R, C609F, C609W, C609C), 611 (e.g., C611R, C611S, C611G, C611Y, C611F, C611W), 616 (e.g., E616Q), 618 (e.g., C618S, C618Y, C618R, C618T, C618G, C618F, C618W), 620 (e.g., C620S, C620W, C620R, C620G, C620L, C620Y, C620F), 623 (e.g.,
15 E623K), 624 (e.g., D624N), 630 (e.g., C630A, C630R, C630S, C630Y, C630F, C630W, C630G), 631 (e.g., D631N, D631Y, D631A, D631G, D631V, D631E), 632 (e.g., E632K, E632G), 632-633 (6-Base Pair In-Frame Germline Deletion in Exon 11), 633 (e.g., 9 base pair duplication), 634 (e.g., C634W, C634Y, C634S, C634R, C634F, C634G, C634L, C634A, or C634T, or an insertion ELCR, or a 12 base pair duplication, or in combination
20 with A640G, A641A, or A641T) (e.g., causing MTC), 634/852 (e.g., C634R/I852M), 635 (e.g., R635G), 636 (e.g., T636P, T636M), 648 (e.g., V648I), 649 (e.g., S649L), 664 (e.g., A664D), 665 (e.g., H665Q), 666 (e.g., K666E, K666M, K666N, K666R), 675 (T675T, silent nucleotide change), 686 (e.g., S686N), 689 (e.g., S689T), 691 (e.g., G691S), 694 (e.g., R694Q), 700 (e.g., M700L), 706 (e.g., V706M, V706A), 713 splice variant (e.g., E713K),
25 732 (e.g., E732K), 736 (e.g., G736R), 748 (e.g., G748C), 765 (e.g., S765P), 766 (e.g., P766S, P766M), 768 (e.g., E768Q, E768D), 769 (e.g., L769L), 770 (e.g., R770Q), 771 (e.g., D771N), 777 (e.g., N777S), 778 (e.g., V778I), 781 (e.g., Q781R), 788 (e.g., I788I), 790 (e.g., L790F, L790T), 791 (e.g., Y791F, Y791N), 791/852 (e.g., Y791F /I852M), 802, 804 (e.g., V804L, V804M, V804E, V804G, V804S) (e.g., causing MTC), 804/918 (e.g.,

V804M/M918T, V804L/M918T), 805 (e.g., E805K), 804/805 (e.g., V804M/E805K), 806 (e.g., Y806F, Y806C, Y806H, Y806Y), 810 (e.g., G810R, G810S, G810A, G810C, G810V), 818 (e.g., E818K), 819 (e.g., S819I), 823 (e.g., G823E), 826 (e.g., Y826M, Y826S), 833 (e.g., R833C), 841 (e.g., P841L, P841P), 843 (e.g., E843D), 844 (e.g., R844W, R844Q, 5 R844L), 848 (e.g., M848T), 852 (e.g., I852M), 865 (e.g., L865V), 870 (e.g., L870F), 873 (e.g., R873W), 876 (e.g., A876V), 881 (e.g., L881V), 882, 883 (e.g., A883F, A883P, A883S, A883T, A883Y), 884 (e.g., E884K), 886 (e.g., R886W), 891 (e.g., S891A), 897 (e.g., R897Q), 898 (e.g., D898V), 900 (e.g., Y900F), 901 (e.g., E901K), 904 (e.g., S904F, S904C), 905 (e.g., Y905F), 907 (e.g., K907E, K907M), 908 (e.g., R908K), 911 (e.g., G911D), 912 10 (e.g., R912P, R912Q), 918 (e.g., M918T, M918V, M918L, M918R) (e.g., causing MTC), 919 (e.g., A919V), 921 (e.g., E921K), 922 (e.g., S922P, S922Y), 930 (e.g., T930M), 961 (e.g., F961L), 972 (e.g., R972G), 981 (e.g., Y981F), 982 (e.g., R982C), 1009 (e.g., M1009V), 1015 (e.g., Y1015F), 1017 (e.g., D1017N), 1041 (e.g., V1041G), 1064 (e.g., M1064T), 1096 (e.g., Y1096F), In-Frame Deletion in Exons 6 and 11, 3bp In-Frame 15 Deletion in Exon 15, Nucleotide position 2136+2 (e.g., 2136+2T>G), del632-636 ins6, and RET-extracellular cysteine mutation (which is defined as a mutation that included at least one of the following cysteine residues: 609, 611, 618, 620, 630, or 634). Other mutations included D631-liter633delinsE, E632-liter633del, A883F, D631-liter633delinsV, L790F, D898-E901del, D898_E901del + D903_S904delinsEP, K666 N, T636-V637insCRT, and 20 D378-G385delinsE. Still other mutations include D631-liter633delinsE, E632-liter633del, A883F, D631-liter633delinsV, L790F, D898-E901del, D898_E901del + D903 _S904delinsEP, K666 N, T636-V637insCRT, and D378-G385delinsE. The RET kinase protein point mutations/insertions/deletions can be, for example, M918T, M918V, C634W, V804L, or V804M. Other RET kinase protein point mutations/insertions/deletions may not 25 be included in the listing herein or are not yet known; however, the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and methods for their use as described herein are expected to be effective inhibitors.

A dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, can also include a splice variation in a RET mRNA which results in an

expressed protein that is an alternatively spliced variant of RET having at least one residue deleted (as compared to the wild-type RET kinase) resulting in a constitutive activity of a RET kinase domain.

A “RET kinase inhibitor” as defined herein refers to compounds that inhibit RET
5 activity using a measurement such as the Biological Assays described below in the examples.

In some cases, a RET kinase containing a mutation, insertion, or deletion is more resistant to inhibition of its phosphotransferase activity by one or more first RET kinase inhibitor(s), as compared to a wildtype RET kinase or a RET kinase not including the same mutation. Such mutations may not decrease the sensitivity of the cancer cell or tumor having
10 the RET kinase to treatment a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein (e.g., as compared to a cancer cell or a tumor that does not include the particular RET inhibitor resistance mutation). In these cases, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased $V_{\max}$, a decreased K_m for ATP, and an increased K_D for a first RET kinase inhibitor, when in the presence of a
15 first RET kinase inhibitor, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same first RET kinase inhibitor.

In other cases, a RET kinase containing a mutation, insertion, or deletion, has increased resistance to a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, as compared to a wildtype RET kinase or a RET kinase not including the
20 same mutation. In such cases, a RET inhibitor resistance mutation can result in a RET kinase that has one or more of an increased $V_{\max}$, a decreased K_m , and a decreased K_D in the presence of a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, as compared to a wildtype RET kinase or a RET kinase not having the same mutation in the presence of the same compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as
25 described herein.

Examples of RET inhibitor resistance mutations can include point mutations, insertions, or deletions in and near the ATP binding site in the tertiary structure of RET kinase, including, but not limited to, the gatekeeper residue, P-loop residues, residues in or near the DFG motif, and ATP cleft solvent front amino acid residues. Additional examples

of these types of mutations include changes in residues that may affect enzyme activity and/or drug binding including but are not limited to residues in the activation loop, residues near or interacting with the activation loop, residues contributing to active or inactive enzyme conformations, changes including mutations, deletions, and insertions in the loop proceeding the C-helix and in the C-helix. Specific residues or residue regions that at which mutations are known to create RET inhibitor resistance include but are not limited to the following amino acids (based on the human wildtype RET protein sequence (SEQ ID NO: 1)): 732 (e.g., E732K); 788 (e.g., I788N); 804 (e.g., V804M, V804L, V804E); 804/805 (e.g., V804M/E805K); 806 (e.g., Y806C, Y806E, Y806S, Y806H, Y806N); 810 (e.g., G810A, G810C, G810R, G810S, G810V); and 865 (e.g., L865V). Further examples of RET inhibitor resistance mutation positions include, but are not limited to, the following amino acids (based on the human wildtype RET protein sequence (SEQ ID NO: 1)): L730P, G731V, E732K, G733V, E734K, L760M, K761E, E762K, N763D, A764V, S765N, P766A, S767C, E768K, L779M, I788M, M868R, K869E, L870Q, V871M, H872R, R873P, D874Y, L881R, L895M, S896N, R897C, D898Y, V899G, Y900D, E901K, E902K, D903Y, S904C, Y905D, V906M, K907E, R908P, S909C, Q910R, G911C, and R912P. These mutations (which may also include single or multiple amino acid changes, insertions within or flanking the sequences, and deletions within or flanking the sequences) are thought to induce a steric hindrance and/or an active conformational effect that changes inhibitor binding characteristics.

Compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein may be useful in treating patients that develop cancers with certain RET inhibitor resistance mutations. For example, resistance mutations that result in an increased resistance to a RET inhibitor like a substitution at amino acid position 804 (e.g., V804M, V804L, or V804E), and/or one or more other RET inhibitor resistance mutations like those discussed above may be treated by either dosing in combination or as a follow-up therapy to existing drug treatments. For example, if a patient is treated with a first RET kinase inhibitor and the patient develops a RET inhibitor resistance mutation, the patient could then be subsequently treated with a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof (assuming that the compound of formulas

I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein is a suitable inhibitor of the particular RET kinase inhibitor mutation present). As another example, if a patient is known to have a particular RET kinase inhibitor mutation (or multiple mutations), the patient could simultaneously be treated with multiple RET kinase inhibitors including a compound (or
5 compounds) of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof that are effective against the RET kinase inhibitor mutation(s) present). Examples of currently known RET kinase inhibitors include pazopanib, sitravatinib, regorafenib, motesanib, RXDX-105, alectinib, BLU6864, cabozantinib, dovitinib, foretinib, lenvatinib, ponatinib, pralsetinib, selpercatinib, sorafenib,
10 sunitinib, and vandetanib.

The types of cancers that can be treated using the compounds of formula I, formula Ia, formula Ib, formula Ic, formula Id and pharmaceutically acceptable salts thereof, include hematological cancer or solid tumor cancer. Examples of the types of cancer that can be treated using a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described
15 herein include lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), thyroid cancer (e.g., Anaplastic thyroid cancer, Hurthle cell thyroid cancer, follicular thyroid cancer, poorly differentiated thyroid cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, or refractory differentiated thyroid cancer), thyroid adenoma, endocrine gland neoplasms, lung adenocarcinoma,
20 bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, mammary cancer, mammary carcinoma, mammary neoplasm, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, and cervical cancer.
25 Specifically, the types of cancer can be lung cancer or thyroid cancer. More specifically, the cancer can be non-small cell lung carcinoma or medullary thyroid cancer. Further examples of the types of cancers that can be treated using the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and the methods as described herein include acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in adolescents, adrenocortical

carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic

5 lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, neoplasms by site, neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell

10 tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, thoracic neoplasms, head and neck neoplasms, CNS tumor, primary CNS tumor, heart cancer, hepatocellular cancer,

15 histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline

20 tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, neoplasms by site, neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung

25 cancer, lung neoplasm, pulmonary cancer, pulmonary neoplasms, pulmonary carcinosarcoma, respiratory tract neoplasms, bronchogenic carcinoma, bronchial neoplasms, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary

cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy and breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, colon cancer, colonic neoplasms, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

10 Examples of the types of hematological cancers that can be treated using the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and the methods as described herein include leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In one embodiment, the hematological cancer (e.g., the hematological cancer that is a RET-associated cancer) is AML or CMML.

25 Examples of the types of solid tumor cancers that can be treated using the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx and the methods as described herein include thyroid cancer (e.g., papillary thyroid carcinoma, medullary thyroid carcinoma), lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, xanthogranuloma tumor, breast cancer, colon cancer, colorectal cancer,

rectal neuroendocrine cancer, prostate cancer, renal cell carcinoma, head and neck tumors, neuroblastoma, and melanoma.

Also provided herein is a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof, for use in the treatment of RET-associated diseases or disorders such as IBS or cancer. Cancers that can be treated using a compound of formula I, Ia, Ib, Ic and/or Id, or pharmaceutically acceptable salts thereof, are described herein above. The treatment of RET-associated diseases or disorders can also include a step of performing an *in vitro* assay using a biological sample from a patient, determining the presence of a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, and administering a therapeutically effective amount of the compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, to the patient if a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same is present. In these uses, the biological sample can be a tumor sample and the tumor sample can be analyzed using methods known to those of skill in the art such as genomic/DNA sequencing. Additionally, in these uses the sample can be obtained from the patient prior to the first administration of the compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein. In these uses of the compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein in a therapy can be based upon a patient being selected for treatment by having at least one dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same. Also, in these therapeutic uses a compound of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein, or pharmaceutically acceptable salts thereof, may be administered to the patient at a dose of about 1 mg/kg to 200 mg/kg (effective dosage sub-ranges are noted herein above).

Certain stereochemical centers have been left unspecified and certain substituents have been eliminated in the following schemes for the sake of clarity and are not intended to limit the teaching of the schemes in any way. Furthermore, individual isomers, enantiomers, and diastereomers may be separated or resolved by one of ordinary skill in the art at any convenient point in the synthesis of compounds of the invention, by methods such as selective crystallization techniques or chiral chromatography (See for example, J. Jacques, et

al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen, "Stereochemistry of Organic Compounds", Wiley-Interscience, 1994). The designations "isomer 1" and "isomer 2" refer to the compounds that elute from chiral chromatography first and second, respectively, under the conditions described herein and if

5 chiral chromatography is initiated early in the synthesis, the same designation is applied to subsequent intermediates and examples. Additionally, the intermediates described in the following schemes may contain a number of nitrogen or oxygen protecting groups. The variable protecting group may be the same or different in each occurrence depending on the particular reaction conditions and the particular transformations to be performed. The

10 protection and deprotection conditions are well known to the skilled artisan and are described in the literature (See for example "Greene's Protective Groups in Organic Synthesis", Fourth Edition, by Peter G.M. Wuts and Theodora W. Greene, John Wiley and Sons, Inc. 2007). Certain abbreviations are defined as follows: "ACN" refers to acetonitrile; "ATP" refers to adenosine triphosphate; "bis(pinacolato)diboron" refers to 4,4,4',4',5,5,5',5'-octamethyl-2,2'-

15 bi-1,3,2-dioxaborolane; "Boc" refers to *tert*-butoxycarbonyl; "Boc₂O" refers to di-*tert*-butyl dicarbonate; "BSA" refers to Bovine Serum Albumin; "BTFFH" refers to Fluoro-*N,N,N',N'*-bis(tetramethylene)formamidinium hexafluorophosphate; "Bu" refers to butyl; "COMU[®]" refers to (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate; "DCM" refers to dichloromethane or methylene chloride; "DIPEA"

20 refers to *N,N*-diisopropylethylamine or *N*-ethyl-*N*-isopropyl-propan-2-amine; "DMAP" refers to 4-dimethylaminopyridine; "DMF" refers to *N,N*-dimethylformamide; "DMSO" refers to dimethyl sulfoxide; "DTT" refers to dithiothreitol; "EtOAc" refers to ethyl acetate; "ee" refers to enantiomeric excess; "Et₂O" refers to diethyl ether; "EtOH" refers to ethanol or ethyl alcohol; "FA" refers to formic acid; "GST" refers to glutathione S-transferase;

25 "HATU" refers to 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate; "HEK" refers to human embryonic kidney; "hr" or "hrs" refers to hour or hours; "HOAc" refers to acetic acid; "HTRF" refers to homogeneous time resolved fluorescence; "IgG" refers to immunoglobulin G; "IPA" refers to isopropyl alcohol or isopropanol; "IPAm" refers to Isopropylamine; "iPr₂O" refers to isopropyl ether;

“ $[\text{Ir}(\text{OMe})(1,5\text{-cod})]_2$ ” refers to di- μ -methanolatodiiiridium(Ir-Ir) - cycloocta-1,5-diene or (1,5-cyclooctadiene)(methoxy)iridium(I) dimer or bis(1,5-cyclooctadiene)di- μ -methoxydiiiridium(I); “KOAc” refers to potassium acetate; “LDA” refers to lithium diisopropylamide; “MeI” refers to methyl iodide or iodomethane; “MeOH” refers to methanol or methyl alcohol; “MeTHF” refers to 2-methyltetrahydrofuran; “min” refers to minute or minutes; “ $\text{Mn}(\text{dpm})_3$ ” refers to manganese(3+) tris[(3Z)-2,2,6,6-tetramethyl-5-oxo-3-hepten-3-olate], $\text{Mn}(\text{TMHD})_3$, Shenvi hydrogenation catalyst, or tris(dipivaloylmethanato)manganese; “NaOAc” refers to sodium acetate; “NaOMe” refers to sodium methoxide; “NMI” refers to 1-methylimidazole or N-methylimidazole; “Parkins catalyst” refers to hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) and is CAS # 173416-05-2; “PBS-T” refers to Phosphate Buffered Saline + Tween®20; “ $\text{Pd}(\text{dppf})\text{Cl}_2$ ” refers to [1,1’ bis(diphenylphosphino)ferrocene]dichloropalladium (II); “ $\text{Pd}(\text{dppf})\text{Cl}_2$) CH_2Cl_2 ” refers to [1,1’ bis(diphenylphosphino)ferrocene]dichloropalladium (II), coupled with DCM; “PE” refers to petroleum ether; “ PhSiH_3 ” refers to phenylsilane; “RT” refers to room temperature; “SFC” refers to supercritical fluid chromatography; “*tert*-BuOH” refers to *tert* butyl alcohol; “TBTU” refers to *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate or *N,N,N',N'*-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate; “TCFH” refers to *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate; “TEA” refers to triethylamine; “TFA” refers to trifluoroacetic acid; “THF” refers to tetrahydrofuran; “T3P®” refers to propanephosphonic acid anhydride, 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide, or PPACA; “ t_{R} ” refers to retention time and “WT” refers to wild-type.

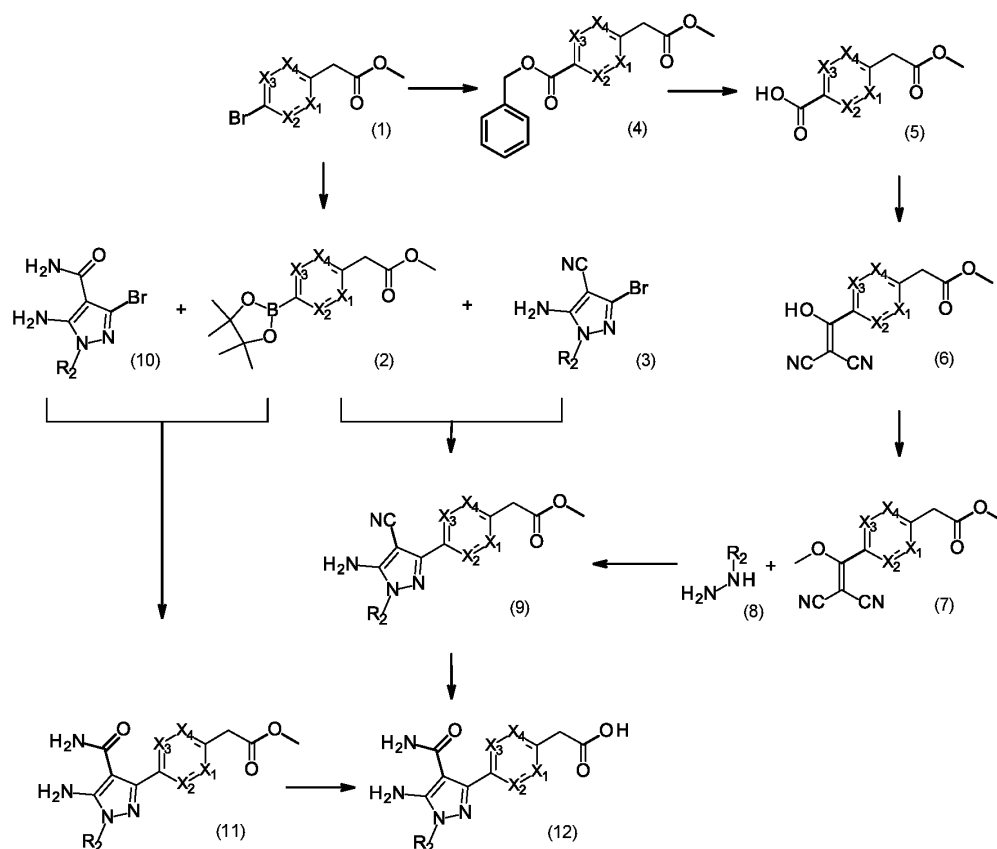
The compounds of the present invention, or pharmaceutically acceptable salts thereof, may be prepared according to the following Preparations and Examples by methods well known and appreciated in the art. Suitable reaction conditions for the steps of these Preparations and Examples are well known in the art and appropriate substitutions of solvents and co-reagents are within the skill of the art. Likewise, it will be appreciated by those skilled in the art that synthetic intermediates may be isolated and/or purified by various

well known techniques as needed or desired, and that frequently, it will be possible to use various intermediates directly in subsequent synthetic steps with little or no purification. As an illustration, compounds of the preparations and examples can be isolated, for example, by silica gel purification, isolated directly by filtration, or crystallization. Furthermore, the skilled artisan will appreciate that in some circumstances, the order in which moieties are introduced is not critical. The particular order of steps required to produce the compounds of the present invention is dependent upon the particular compound being synthesized, the starting compound, and the relative liability of the substituted moieties, as is well appreciated by the skilled chemist. All substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

In the schemes below, all substituents unless otherwise indicated, are as previously defined. The reagents and starting materials are generally readily available to one of ordinary skill in the art. Others may be made by standard techniques of organic and heterocyclic chemistry which are analogous to the syntheses of known structurally similar compounds and the procedures described in the Preparations and Examples which follow including any novel procedures. Intermediates and processes useful for the synthesis of the compounds described by formula (I) are intended to be included in this description.

-47-

Scheme 1



Scheme 1 depicts the preparation of the compounds of (12). A person of ordinary skill in the art will recognize that borylation of aryl bromide (1) under typical Miyaura reaction conditions may provide boronic ester (2). Treatment of boronic ester (2) with the appropriate bromopyrazole (3) and metal catalyst, under Suzuki coupling conditions, may afford amino pyrazole (9).

Alternatively, palladium-catalyzed carbonylation of aryl bromide (1) with carbon monoxide and benzyl alcohol may provide benzyl carboxylate (4). Palladium-catalyzed debenzylation of benzyl carboxylate (4) with hydrogen may provide carboxylic acid (5). Preparation of the acyl chloride of acid (5) and subsequent reaction with malononitrile under

-48-

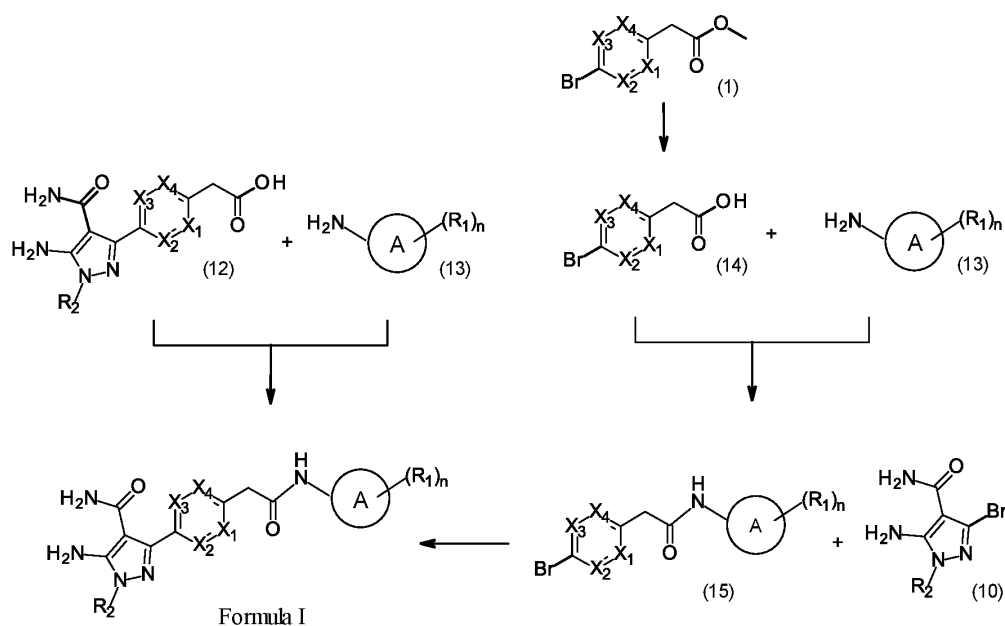
basic conditions may afford malononitrile (6). Methylation of vinyl alcohol (6) may be achieved with dimethyl sulfate to provide methoxy (7). Reacting the appropriately substituted hydrazine (8) with the dinitrile Michael acceptor (7) can also afford amino pyrazole (9).

- 5 Treatment of boronic ester (2) with the appropriate bromopyrazole (10) and metal catalyst, under Suzuki coupling conditions, may afford amino pyrazole (11). Carboxylic acid (12) may be obtained by saponification of ester (11) with the proper nucleophilic base.

Alternatively, carboxylic acid (12) may also be obtained from the ester (9) in a two-step one pot reaction of oxidation and saponification using peroxide and base.

10

Scheme 2



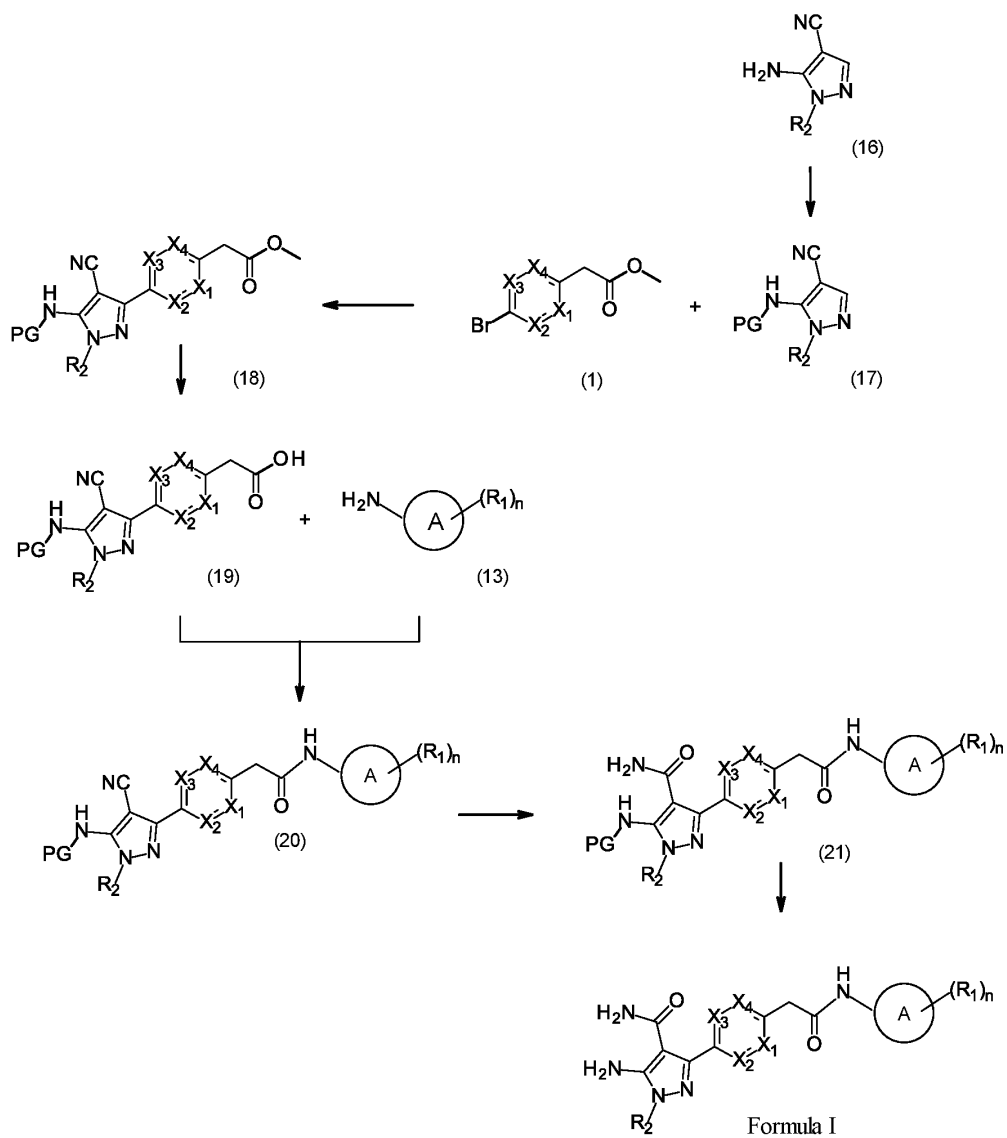
- 15 Scheme 2 depicts the preparation of the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein. Saponification of ester (1) may furnish carboxylic acid (14) in essentially the same manner as described for the carboxylic acid (12) in Scheme 1. The skilled artisan will recognize that carboxylic acid (14) and primary amine (13) may

be joined by utilizing the appropriate amide coupling reagent under conditions suitable for amide bond formation to provide amide (15). Borylation of aryl bromide (15) under typical Miyaura reaction conditions, followed by treatment of the in-situ boronic ester with bromopyrazole (10) and metal catalyst, under Suzuki coupling conditions, may afford
5 compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx.

Alternatively, amide coupling of carboxylic acid (12) and primary amine (13) may provide compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx in essentially the same manner described for amide (15) above.

-50-

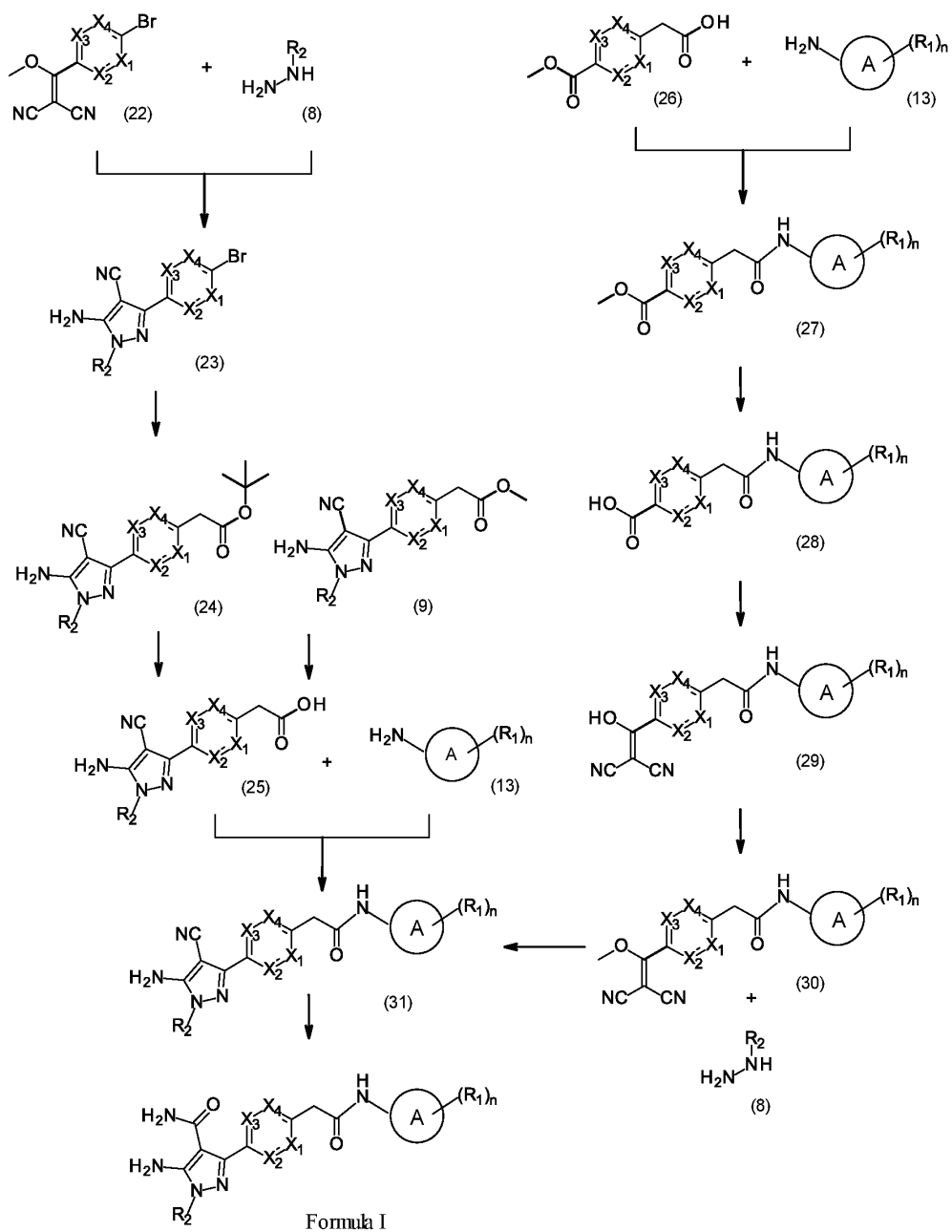
Scheme 3



Scheme 3 depicts additional preparations of the compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx as described herein. Protection of primary amine (16) with an appropriate protecting group may provide the mono- or bis- protected amino pyrazole (17).

Iridium-catalyzed C-H borylation of pyrazole (17), followed by treatment of the in-situ boronic ester with aryl bromide (1) and metal catalyst, under Suzuki coupling conditions, may afford biaryl (18). Saponification of ester (18) may furnish carboxylic acid (19) in essentially the same manner as described for the carboxylic acid (12) in Scheme 1. Amide
5 coupling of carboxylic acid (19) and primary amine (13) may provide amide (20) in essentially the same manner as described for the amide (12) in Scheme 2. The nitrile moiety of amino pyrazole (20) may be converted to carboxamide (21), under a variety of conditions such as metal catalyzed hydration, acidic hydrolysis, and oxidation. Removal of the
10 protecting group from the protected amino pyrazole (21) may provide additional compounds of formulas I, Ia to IX, IIa to IIx, and/or IIIa to IIIx as described herein.

Scheme 4



Scheme 4 depicts alternative preparations of the compounds of formulas I, Ia to Ix, IIa to IIX, and/or IIIa to IIIx as described herein. Reacting the appropriately substituted hydrazine (8) with the dinitrile Michael acceptor (22) can afford amino pyrazole (23) in essentially the same manner as described for the amino pyrazole (9) in Scheme 1. Treatment of aryl bromide (23) with the appropriate alkylzinc halide and metal catalyst, under Negishi coupling conditions may afford *tert*-butyl ester (24). Acidic deprotection of *tert*-butyl ester (24) may provide carboxylic acid (25).

Alternatively, saponification of ester (9) may furnish carboxylic acid (25) in essentially the same manner as described for the carboxylic acid (12) in Scheme 1. Amide coupling of carboxylic acid (25) and primary amine (13) may provide amide (31) in essentially the same manner as described for the amide (12) in Scheme 2.

Alternatively, amide coupling of carboxylic acid (26) and primary amine (13) may provide amide (27) in essentially the same manner as described for the amide (12) in Scheme 2. Saponification of ester (27) may furnish carboxylic acid (28) in essentially the same manner as described for the carboxylic acid (12) in Scheme 1. Preparation of the acyl chloride of acid (28) and subsequent reaction with malononitrile under basic conditions may afford malononitrile (29). Methylation of vinyl alcohol (29) may be achieved with dimethyl sulfate to provide methoxy (30). Reacting the appropriately substituted hydrazine (8) with the dinitrile Michael acceptor (30) can afford amino pyrazole (31) in essentially the same manner as described for the amino pyrazole (9) in Scheme 1.

The nitrile moiety of amino pyrazole (31) may be converted to additional compounds of formulas I, Ia to Ix, IIa to IIX, and/or IIIa to IIIx as described herein, under a variety of conditions such as metal catalyzed hydration, acidic hydrolysis, and oxidation.

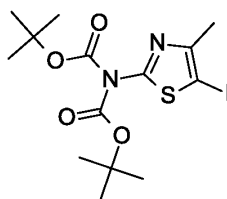
In an optional step, a pharmaceutically acceptable salt of a compound of formulas I, Ia to Ix, IIa to IIX, and/or IIIa to IIIx can be formed by reaction of an appropriate free base of formulas I, Ia to Ix, IIa to IIX, and/or IIIa to IIIx with an appropriate pharmaceutically acceptable acid in a suitable solvent under standard conditions. Additionally, the formation of such salts can occur simultaneously upon deprotection of a nitrogen protecting group. The formation of such salts is well known and appreciated in the art. See, for example, Gould,

P.L., "Salt selection for basic drugs," *International Journal of Pharmaceutics*, **33**: 201-217 (1986); Bastin, R.J., *et al.* "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," *Organic Process Research and Development*, **4**: 427-435 (2000); and Berge, S.M., *et al.*, "Pharmaceutical Salts," *Journal of Pharmaceutical Sciences*, **66**: 1-19, (1977). "Salt selection for basic drugs," *International Journal of Pharmaceutics*, **33**: 201-217 (1986). One of ordinary skill in the art will appreciate that a compound of formulas I, Ia to IX, IIa to IIx, and/or IIIa to IIIx is readily converted to and may be isolated as a pharmaceutically acceptable salt.

Preparations and Examples

Preparation 1

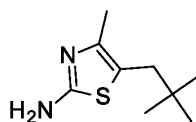
tert-Butyl N-(*tert*-butoxycarbonyl)-N-(5-iodo-4-methyl-1,3-thiazol-2-yl)carbamate



A mixture of 5-iodo-4-methyl-1,3-thiazol-2-amine (16.0 g, 66.7 mmol), Boc₂O (32.0 g, 146 mmol) and DMAP (0.81 g, 6.63 mmol) in THF (200 mL) is stirred for 2 hr at RT under N₂. The mixture is concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 12:1 to 5:1 PE:EtOAc to give the title compound (20.0 g, 68%) as a yellow solid. ES/MS (m/z) 441.0 (M+H).

Preparation 2

5-(2,2-Dimethylpropyl)-4-methyl-1,3-thiazol-2-amine



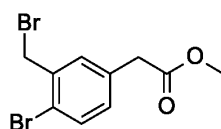
Zinc chloride (5.84 mL, 4.09 mmol, 0.7 M in THF) is added to a solution of bromo(2,2-dimethylpropyl)magnesium (6.50 mL, 3.25 mmol, 0.5 M in THF) at 0 °C and the

-55-

mixture is stirred for 30 min at 0 °C under N₂. To this mixture is added *tert*-butyl N-(*tert*-butoxycarbonyl)-N-(5-iodo-4-methyl-1,3-thiazol-2-yl)carbamate (1.20 g, 2.73 mmol) and Pd(*t*-Bu₃P)₂ (0.28 g, 0.55 mmol) in portions over 1 min at RT. The mixture is stirred for an additional 2 hr at 100 °C under N₂. The reaction is quenched by the addition of saturated aq. NH₄Cl (20 mL) at RT. The mixture is extracted with EtOAc (2x50 mL). The combined organic extracts are washed with brine (2x30 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 45% to 52% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (80 mg, 16%) as a yellow solid. ES/MS (m/z) 185.1 (M+H).

Preparation 3

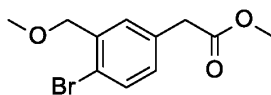
Methyl 2-[4-bromo-3-(bromomethyl)phenyl]acetate



To a stirred solution of methyl 2-(4-bromo-3-methyl-phenyl)acetate (5.50 g, 22.6 mmol) in CCl₄ (200 mL) at RT under N₂ is added successively 1-bromopyrrolidine-2,5-dione (4.23 g, 23.8 mmol) and 2-[(E)-(1-cyano-1-methyl-ethyl)azo]-2-methyl-propanenitrile (1.30 g, 7.92 mmol). The reaction mixture is stirred at 80 °C for 5 hr. The mixture is poured in a solution of NaHCO₃ and the aqueous layer is extracted with DCM (2x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The material is purified by silica gel chromatography, eluting with a gradient of 2% to 10% EtOAc in cyclohexane to give the title compound as a colorless oil (1.69 g, 23%). ES/MS (m/z) 342 (M+Na).

Preparation 4

Methyl 2-[4-bromo-3-(methoxymethyl)phenyl]acetate

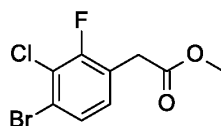


-56-

To a stirred solution of methyl 2-[4-bromo-3-(bromomethyl)phenyl]acetate (0.60 g, 1.86 mmol) in MeOH (10 mL) at 5 °C under N₂ is added NaOMe (0.41 mL, 2.19 mmol, 30 wt% in MeOH). The reaction mixture is stirred at RT overnight. The reaction mixture is concentrated, H₂O is added to the residue, and the mixture is extracted with EtOAc (2x). The combined organic extracts are washed with brine, dried over NaSO₄, filtered, and concentrated under reduced pressure to give the title compound as a pale yellow oil (0.42 g, 83%). ES/MS (m/z) 274 (M+H).

Preparation 5

Methyl 2-(4-bromo-3-chloro-2-fluoro-phenyl)acetate



To 2-(4-bromo-3-chloro-2-fluorophenyl)acetic acid (0.50 g, 1.78 mmol) in MeOH (15 mL) at 0 °C under N₂ is added dropwise thionyl chloride (0.39 mL, 5.33 mmol). The mixture is allowed to warm to RT and stirred for 16 hr. The mixture is concentrated under reduced pressure and dried under vacuum. The material is purified by silica gel chromatography, eluting with a gradient of 25% to 100% DCM in heptane to give the title compound as a colorless oil (0.50 g, 100%).

The following compound in Table 1 is prepared essentially as described for methyl 2-(4-bromo-3-chloro-2-fluoro-phenyl)acetate, using the appropriate acid, adjusting the reaction time to determine completion of the reaction, and purifying chromatography as appropriate, and substituting EtOH for MeOH to prepare the ethyl ester if desired.

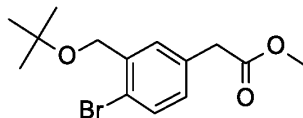
Table 1

Prep No.	Chemical Name	Structure
6	Ethyl 3-methylbicyclo[1.1.1]pentane-1-carboxylate	

Preparation 7

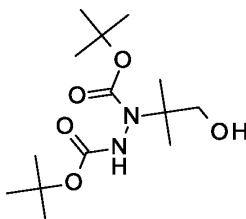
Methyl 2-[4-bromo-3-(*tert*-butoxymethyl)phenyl]acetate

-57-



To a suspension of Ag-trifluoromethanesulfonate (0.44 g, 1.71 mmol) in dry *tert*-BuOH (10 mL) and dry DCM (20 mL), protected from visible light, is added a solution of methyl 2-[4-bromo-3-(bromomethyl)phenyl]acetate (0.50 g, 1.55 mmol) in dry DCM (5 mL)
 5 at RT under N₂. The reaction mixture is stirred at RT for 16 hr, then poured into saturated aq. NaHCO₃. The aqueous layer is extracted with DCM (2x). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound as a colorless oil (0.51 g, 95%). ¹H NMR(d₆-DMSO, 400 MHz) δ (ppm) 7.53 (d, J=8.1 Hz, 1H), 7.39 (d, J=2.2 Hz, 1H), 7.12 (dd, J=8.1, 2.3 Hz, 1H), 4.41 (s, 2H), 3.70 (s,
 10 2H), 3.62 (s, 3H), 1.25 (s, 9H).

Preparation 8

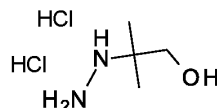
2-[(*tert*-Butoxycarbonyl)][(*tert*-butoxycarbonyl)amino]amino]-2-methylpropan-1-ol

To a stirred solution of Mn(dpm)₃ (0.42 g, 0.69 mmol) in IPA (150 mL) is added
 15 methallyl alcohol (5.00 g, 69.3 mmol), di-*tert*-butyl azodicarboxylate (24.0 g, 103 mmol), and PhSiH₃ (7.50 g, 69.3 mmol) dropwise at 0 °C under N₂. The mixture is stirred for 1 hr at 0 °C under N₂ and for 12 hr at RT under N₂. The solvent is removed under reduced pressure and the residue is purified by silica gel chromatography, eluting with a gradient of 10:1 to 4:1 PE:EtOAc to give the title compound (15.0 g, 71 %) as a white solid. ¹H NMR (CDCl₃, 300
 20 MHz) δ 4.30-4.02 (m, 2H), 3.42-3.19 (m, 1H), 1.59-1.42 (m, 24H).

Preparation 9

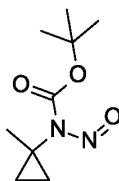
2-Hydrazinyl-2-methylpropan-1-ol 2HCl

-58-



To a solution of 2-[(*tert*-butoxycarbonyl)][(*tert*-butoxycarbonyl)amino]amino]-2-methylpropan-1-ol (15.0 g, 49.3 mmol) in 1,4-dioxane (100 mL), HCl (50 mL, 4 N in 1,4-dioxane) is added and the mixture is stirred for 2 hr at RT. The reaction is concentrated under reduced pressure. The crude product is triturated with Et₂O (30 mL) to give the title compound (4.4 g, 63%) as a white solid. ¹H NMR (d₆-DMSO, 300 MHz) δ 6.41 (s, 5H), 3.40 (s, 2H), 1.14 (s, 6H).

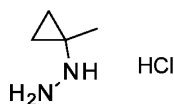
Preparation 10

tert-Butyl N-(1-methylcyclopropyl)-N-nitroso-carbamate

To a stirred solution of *tert*-butyl N-(1-methylcyclopropyl)carbamate (2.00 g, 11.7 mmol) in DCM (20 mL) is added *tert*-butyl nitrite (2.40 g, 23.3 mmol) in portions at RT under N₂ and the mixture is stirred for 2 hr at RT under N₂. The mixture is concentrated under reduced pressure and the residue is purified by silica gel chromatography, eluting with 25:1 to 20:1 PE:EtOAc to give the title compound (1.30 g, 55%) as a brown liquid. ¹H NMR (d₆-DMSO) δ 1.59 (s, 9H), 1.10 (s, 3H), 0.86-0.84 (m, 2H), 0.70-0.65 (m, 2H).

Preparation 11

(1-Methylcyclopropyl)hydrazine hydrochloride



To a stirred solution of *tert*-butyl N-(1-methylcyclopropyl)-N-nitroso-carbamate (1.20 g, 5.99 mmol) in HCl (8 mL, 4 N in 1,4-dioxane) is added Zn (0.78 g, 11.9 mmol) in portions at 0 °C under N₂ and the mixture is stirred for 12 hr at RT under N₂. The mixture is filtered,

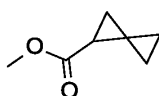
-59-

the filter cake is washed with H₂O (3x10 mL), and the filtrate is concentrated under reduced pressure to give the title compound (2.0 g, crude) as an off-white solid which is used directly without further purification. ¹H NMR (d₆-DMSO) δ 1.30 (s, 3H), 0.77-0.73 (m, 2H), 0.54-0.50 (m, 2H).

5

Preparation 12

Methyl spiro[2.2]pentane-2-carboxylate

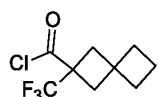


To a stirred solution of spiro[2.2]pentane-1-carboxylic acid (95%, 1.25 g, 10.6 mmol) in Et₂O (37.5 mL) and MeOH (7.5 mL) at 0 °C is added 2 M diazomethyl(trimethyl)silane in hexanes (6.9 mL, 13.8 mmol) dropwise. The reaction mixture is stirred at RT overnight. Et₂O is removed under reduced pressure and the reaction mixture is diluted with pentane (125 mL). The solution is washed with saturated aq. NaHCO₃ (2x), H₂O (3x), and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (1.53 g, crude) as a yellow oil which is used directly without further purification.

15

Preparation 13

2-(Trifluoromethyl)spiro[3.3]heptane-2-carbonyl chloride



2-(Trifluoromethyl)spiro[3.3]heptane-2-carboxylic acid (1.02 g, 4.90 mmol) is suspended in DCM (40 mL) and DMF (0.10 mL). The slurry is cooled to 0 °C and oxalyl chloride (3.0 mL, 6.00 mmol, 2 M in DCM) is added. The reaction is stirred at 0 °C for 5 min then allowed to warm to RT and stirred for 1 hr. The solvent is removed under reduced pressure to give a yellow residue. The residue is used without further purification.

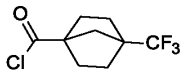
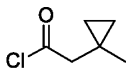
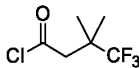
The following compounds in Table 2 are prepared essentially as described for 2-(trifluoromethyl)spiro[3.3]heptane-2-carbonyl chloride using the appropriate acid, oxalyl chloride (1-1.5 eq) and solvents (DCM, DMF) ranging from 0-50 mL and adjusting reaction

25

-60-

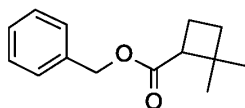
time to determine completion of the reaction. The reaction temperature can range from 0 °C-25 °C.

Table 2

Prep No.	Chemical Name	Structure
14	4-(Trifluoromethyl)bicyclo[2.2.1]heptane-1-carbonyl chloride	
15	2-(1-Methylcyclopropyl)acetyl chloride	
16	4,4,4-Trifluoro-3,3-dimethyl-butanoyl chloride	

Preparation 17

5 Benzyl 2,2-dimethylcyclobutanecarboxylate

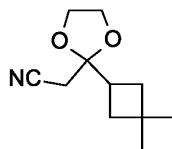


To a stirred solution of 2,2-dimethylcyclobutane-1-carboxylic acid (1.50 g, 11.7 mmol) in DCM (20 mL) at 0 °C under N₂ is added dropwise oxalyl chloride (1.0 mL, 11.7 mmol) followed by DMF (30 µL). The mixture is slowly allowed to warm to RT and stirred for 5 hr. Benzylalcohol (1.4 mL, 13.5 mmol) is added dropwise at 0°C and the reaction mixture is slowly allowed to warm to RT and stirred for 20 hr. The mixture is poured into saturated aq. NaHCO₃. The aqueous layer is extracted with pentane (2x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by silica gel chromatography, eluting with a gradient of 5% to 50% DCM in pentane to give the title compound (2.6 g, 100%) as a colorless oil. ES/MS (m/z) 219 (M+H).

Preparation 18

2-[2-(3,3-Dimethylcyclobutyl)-1,3-dioxolan-2-yl]acetonitrile

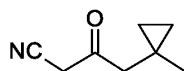
-61-



To a stirred solution of 3-(3,3-dimethylcyclobutyl)-3-oxo-propanenitrile (0.60 g, 4.00 mmol) in DCM (8 mL) at 25 °C under N₂ is added ethane-1,2-diol (0.67 mL, 12.0 mmol) and chloro(trimethyl)silane (1.5 mL, 12.0 mmol). The reaction mixture is stirred at reflux for 12 hr and cooled to RT. NaHCO₃ (aq) is added. The aqueous layer is extracted with DCM. The combined organic extract is washed with brine, dried over Na₂SO₄, filtered, and dried under vacuum. The residue is purified by silica gel chromatography, eluting with a gradient of 10% to 30% EtOAc in cyclohexane to give the title compound (0.56 g, 72%) as a colorless oil. ¹H NMR (d₆-DMSO, 400 MHz) δ (ppm) 4.09-3.98 (m, 2H), 4.01-3.90 (m, 2H), 2.79 (s, 2H), 2.61 (s, 2H), 1.79-1.57 (m, 6H), 1.41 (s, 2H), 1.12 (s, 3H), 1.01 (s, 3H).

Preparation 19

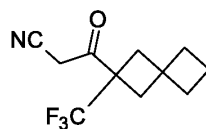
4-(1-Methylcyclopropyl)-3-oxo-butanenitrile



ACN (0.36 mL, 6.89 mmol) and benzyl 2-(1-methylcyclopropyl)acetate (1.27 g, 6.22 mmol) are combined in THF (15 mL) under N₂ and cooled to -78 °C. LDA (11.0 mL, 22.0 mmol, 2 M in THF) is added dropwise and the reaction is stirred for 10 min at -78 °C. The reaction is allowed to warm to 21 °C over 1 hr. The reaction is acidified to pH 1 with conc. HCl and the mixture is extracted with EtOAc (3x100 mL). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated to give the title compound (1.4 g, crude) as an orange oil. The material is used without further purification.

Preparation 20

3-Oxo-3-[2-(trifluoromethyl)spiro[3.3]heptan-2-yl]propanenitrile



-62-

ACN (0.28 mL, 5.36 mmol) and benzyl 2-(trifluoromethyl)spiro[3.3]heptane-2-carboxylate (1.40 g, 4.69 mmol) are combined in THF (15 mL) under N₂ and cooled to -78 °C. LDA (2.82 mL, 5.64 mmol, 2 M in THF) is added dropwise and the reaction is stirred for 10 mins at -78 °C. The reaction is allowed to warm to 21 °C over 1 hr. The reaction is
 5 acidified to pH 1 with conc. HCl and the mixture is extracted with EtOAc (3x100 mL). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated to give the title compound (1.05 g, 97%) as an orange oil. This material is used directly without further purification.

The following compounds in Table 3 are prepared essentially as described for 3-oxo-
 10 3-[2-(trifluoromethyl)spiro[3.3]heptan-2-yl]propanenitrile using the appropriate base (LDA or nBuLi in hexanes or THF) from 1.2-4.2 equivalents and adjusting reaction time to determine completion of the reaction.

Table 3

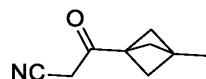
Prep. No.	Chemical name	Structure
21	3-Oxo-4-[1-(trifluoromethyl)cyclopropyl]butanenitrile	
22	3-Oxo-3-(4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl)propanenitrile	
¹ 23	3-(4-Fluorobicyclo[2.2.2]octan-1-yl)-3-oxopropanenitrile	
24	3-(2,2-Difluorospiro[3.3]heptan-6-yl)-3-oxo-propanenitrile	

¹nBuLi used instead of LDA.

-63-

Preparation 25

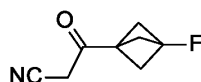
3-[3-Methylbicyclo[1.1.1]pentan-1-yl]-3-oxopropanenitrile



To THF (5 mL) is added n-BuLi (1.71 mL, 4.28 mmol, 2.5 M in THF) at 0 °C under N₂. To the mixture is added ACN (0.24 mL, 4.59 mmol) in THF (5 mL) dropwise over 5 min at -78 °C under N₂. The mixture is stirred for 1 hr at -78 °C. To the mixture is added methyl 3-methylbicyclo[1.1.1]pentane-1-carboxylate (0.40 g, 2.85 mmol) in THF (5 mL) dropwise at -78 °C under N₂. The mixture is stirred for 1 hr at RT. The reaction is quenched by the addition of saturated aq. NH₄Cl (20 mL) at 0 °C. The mixture is acidified to pH 4 with 1 N aq. HCl and extracted with DCM (3x50 mL). The combined organic extracts are washed with brine (2x100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (0.36 g, 85%) as a brown liquid. The crude product is used without further purification.

Preparation 26

3-(3-Fluorobicyclo[1.1.1]pentan-1-yl)-3-oxopropanenitrile

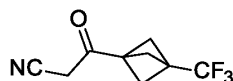


To a stirred solution of n-BuLi (2.0 mL, 2.5 M in n-hexanes, 5.00 mmol) in THF (20 mL) is added a solution of ACN (0.28 mL, 5.36 mmol) in THF (4 mL) dropwise at -78 °C under N₂. The mixture is stirred for 30 min at -78 °C. To the mixture is added a solution of methyl 3-fluorobicyclo[1.1.1]pentane-1-carboxylate (0.48 g, 3.33 mmol) in THF (4 mL) dropwise over 10 min at -78 °C. The mixture is allowed to warm to RT and stirred for an additional 3 hr. The reaction is quenched with saturated aq. NH₄Cl, acidified to pH 4 with 2 N aq. HCl, and extracted with DCM (3x50 mL). The combined organic extracts are washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (0.50 g, crude) as a brown oil. The crude product is used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 3.57 (s, 2H), 2.50 (d, 6H).

-64-

Preparation 27

3-Oxo-3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]propanenitrile



n-BuLi (0.83 mL, 2.08 mmol, 2.5 M in hexanes) is added to THF (10 mL) at 0 °C under N₂. ACN (0.12 mL, 2.30 mmol) in THF (2 mL) is added dropwise over 2 min at -78 °C under N₂ and the reaction is stirred for 1 hr at -78 °C. Methyl 3-(trifluoromethyl)bicyclo[1.1.1]pentane-1-carboxylate (0.27 g, 1.39 mmol) in THF (2 mL) is added dropwise to the reaction mixture at -78 °C and the reaction is stirred at RT for 12 hr. The reaction is quenched by the addition of saturated aq. NH₄Cl (20 mL), acidified to pH 4 with conc. HCl, and extracted with DCM (3x50 mL). The combined organic extracts are washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (0.29 g, crude). The crude product is used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 3.54 (s, 2H), 2.39 (s, 6H).

The following compounds in Table 4 are prepared essentially as described for 3-oxo-3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]propanenitrile, adjusting reaction time to determine completion of the reaction, and purification conditions as appropriate. The reaction can be allowed to warm to RT after the carboxylate is added. n-BuLi can be in hexanes or THF.

Table 4

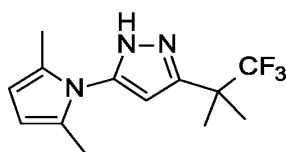
Prep. No.	Chemical name	Structure
28	3-(2-Cyanoacetyl)bicyclo[1.1.1]pentane-1-carbonitrile	
29	3-Oxo-3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]propanenitrile	
30	3-(3-Chloropyridin-2-yl)-3-oxopropanenitrile	

-65-

31	3-(2,2-Dimethylcyclopropyl)-3-oxo-propanenitrile	
32	4-(1-Methylcyclobutyl)-3-oxo-butanenitrile	
33	3-Oxo-3-spiro[2.2]pentan-2-yl-propanenitrile	
34	4-(2,2-Difluorocyclopropyl)-3-oxo-butanenitrile	
35	3-Oxo-3-spiro[2.3]hexan-2-yl-propanenitrile	
36	3-(2,2-Dimethylcyclobutyl)-3-oxo-propanenitrile	
37	3-(3,3-Difluoro-1-methyl-cyclobutyl)-3-oxo-propanenitrile	
38	4,4-Difluoro-5,5-dimethyl-3-oxo-hexanenitrile	

Preparation 39

5-(2,5-Dimethyl-1H-pyrrol-1-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazole



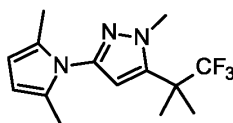
A solution of 3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-5-amine (0.50 g, 2.59 mmol), hexane-2,5-dione (0.91 mL, 7.76 mmol) and HOAc (0.015 mL, 0.26 mmol) in toluene (10 mL) is stirred for 2 hr at 100 °C under N₂. The mixture is concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 gel

-66-

column), eluting with a gradient of 30% to 50% ACN in H₂O (0.1% FA) to give the title compound (0.61 g, 87%) as a yellow solid. ES/MS (m/z) 272.1 (M+H).

Preparation 40

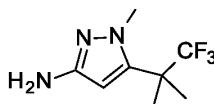
3-(2,5-Dimethyl-1H-pyrrol-1-yl)-1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazole



A solution of 5-(2,5-dimethyl-1H-pyrrol-1-yl)-3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazole (0.50 g, 1.84 mmol), MeI (0.46 mL, 7.39 mmol) and K₂CO₃ (0.51 g, 3.69 mmol) in ACN (10 mL) is stirred for 4 hr at 80 °C under N₂. The mixture is concentrated under reduced pressure. The residue is purified by preparative TLC, eluting with 5:1 PE:EtOAc to give the title compound (95 mg, 18%) as a white solid. ES/MS (m/z) 286.2 (M+H).

Preparation 41

1-Methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-amine

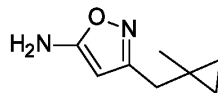


A solution of KOH (53 mg, 0.94 mmol) in EtOH (1 mL) and H₂O (1 mL) is added to a solution of hydroxylamine HCl (0.13 g, 1.87 mmol) in EtOH (2 mL). 3-(2,5-Dimethyl-1H-pyrrol-1-yl)-1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazole (90 mg, 0.32 mmol) is added and the mixture is stirred for 4 hr at 100 °C under N₂. The mixture is concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 10% to 30% ACN in H₂O (0.1% FA) to give the title compound (45 mg, 68%) as a white solid. ES/MS (m/z) 208.1 (M+H).

Preparation 42

3-[(1-Methylcyclopropyl)methyl]isoxazol-5-amine

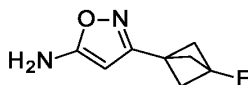
-67-



4-(1-Methylcyclopropyl)-3-oxobutanenitrile (1.40 g, 10.2 mmol) is dissolved in H₂O (15 mL). NaOH (0.45 g, 11.3 mmol) is added followed by hydroxylamine sulfate (1.84 g, 11.2 mmol). The pH is adjusted to ~10 with 2 M aq. NaOH (5.0 mL, 10.0 mmol). The mixture is heated to 100 °C for 1.5 hr. Conc. HCl (1 mL) is added and the mixture is stirred for 15 min. The mixture is diluted with H₂O (30 mL) and extracted with EtOAc (2x30 mL). The combined organic extracts are dried over anhydrous NH₂SO₄ and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 10% to 70% EtOAc in hexanes to give the title compound (0.54 g, 35%). ES/MS (m/z) 153.0 (M+H).

Preparation 43

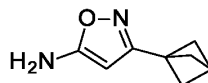
3-(3-Fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine



To a stirred solution of 3-(3-fluorobicyclo[1.1.1]pentan-1-yl)-3-oxopropanenitrile (0.50 g, 3.26 mmol) in MeOH (5 mL) is added hydroxylamine HCl (0.68 g, 9.79 mmol) and KOAc (0.96 g, 9.78 mmol) at 0 °C under N₂. The mixture is stirred for 5 hr at RT under N₂. The mixture is poured into H₂O (50 mL) and extracted with DCM (3x50 mL). The combined organic extracts are dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 25% to 45% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (0.22 g, 40%) as a light yellow solid. ES/MS (m/z) 169.1 (M+H).

Preparation 44

3-(Bicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine

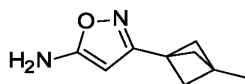


-68-

To a stirred solution of 3-(bicyclo[1.1.1]pentan-1-yl)-3-oxopropanenitrile (0.87 g, 6.44 mmol) in MeOH (10 mL) is added hydroxylamine HCl (1.34 g, 19.3 mmol) and KOAc (1.89 g, 19.3 mmol) at 0 °C under N₂. The mixture is stirred for 5 hr at RT under N₂. The mixture is poured into H₂O (50 mL) and extracted with DCM (3x50 mL). The combined organic extracts are dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is washed with hexanes (2x5 mL) to give the title compound (0.73 g, 75%) as a light yellow solid. ES/MS (m/z) 151.3 (M+H).

Preparation 45

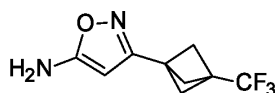
3-(3-Methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-amine



To a stirred mixture of 3-[3-methylbicyclo[1.1.1]pentan-1-yl]-3-oxopropanenitrile (0.35 g, 2.35 mmol) and hydroxylamine HCl (0.18 g, 2.59 mmol) in H₂O (8 mL) is added NaOH (0.19 g, 4.75 mmol) in portions at RT under N₂. The mixture is stirred for 1 hr at 100 °C under N₂. The mixture is allowed to cool to RT. The precipitated solids are collected by filtration and washed with H₂O (3x20 mL) to give the title compound (0.30 g, 78%) as a light yellow solid. ES/MS (m/z) 165.1 (M+H).

Preparation 46

3-(3-(Trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine



A mixture of 3-oxo-3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]propanenitrile (0.28 g, 1.38 mmol), hydroxylamine HCl (0.11 g, 1.58 mmol) and H₂O (10 mL) is added NaOH (0.11 g, 2.75 mmol) in portions at RT under N₂. The mixture is heated to 100 °C for 1 hr. The mixture is allowed to cool to RT and is extracted with DCM (3x50 mL). The combined organic extracts are washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting solid is triturated with Et₂O (10 mL).

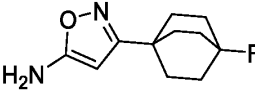
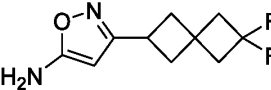
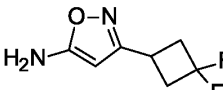
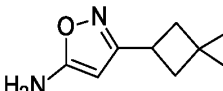
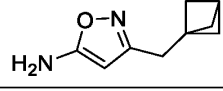
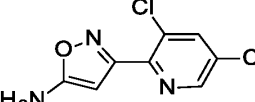
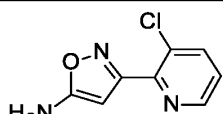
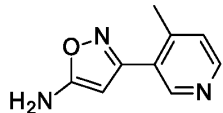
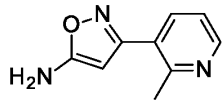
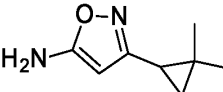
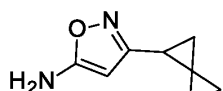
The solids are collected by filtration and washed with Et₂O to give the title compound (0.22 g, 73%). ES/MS (m/z) 219.2 (M+H).

The following compounds in Table 5 are prepared essentially as described for 3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine using the appropriate reagents (hydroxylamine sulfate or hydroxylamine HCl) about 1-6 equivalents, bases (NaOH, NaOAc, or KOAc) about 1-6 equivalents in the appropriate solvent (EtOH, MeOH, H₂O, or 1,4-dioxane), adjusting the reaction time to determine completion of the reaction and using appropriate chromatography conditions or precipitation for purification. The reaction temperature can range from 0 to 100 °C and the reaction mixture can be acidified in work-up if appropriate. The reagents can be added together at 0 °C in portions or all at once.

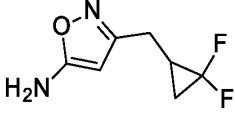
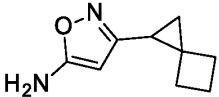
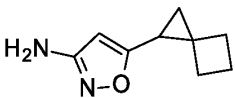
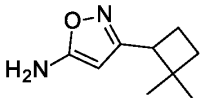
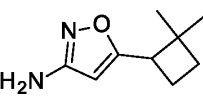
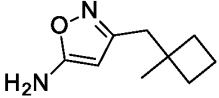
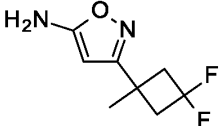
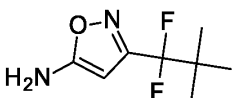
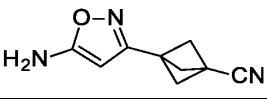
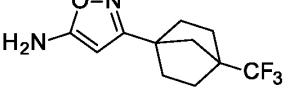
Table 5

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
47	3-Spiro[3.3]heptan-2-ylisoxazol-5-amine		179.1
48	3-[2-(Trifluoromethyl)spiro[3.3]heptan-2-yl]isoxazol-5-amine		247.1
49	3-[[1-(Trifluoromethyl)cyclopropyl]methyl]isoxazol-5-amine		207.1
50	3-(4-(Trifluoromethyl)bicyclo[2.2.1]heptan-1-yl)isoxazol-5-amine		247.1
51	3-(3,3,3-Trifluoro-2,2-dimethylpropyl)isoxazol-5-amine		209.0
52	3-(3,3-Dimethylcyclobutyl)isoxazol-5-amine		167.1

-70-

53	3-(4-Fluorobicyclo[2.2.2]octan-1-yl)isoxazol-5-amine		211.2
54	3-(2,2-Difluorospiro[3.3]heptan-6-yl)isoxazol-5-amine		215.1
55	3-(3,3-Difluorocyclobutyl)isoxazol-5-amine		175.1
56	3-Spiro[2.3]hexan-5-ylisoxazole-5-amine		165.1
57	3-(3-Bicyclo[1.1.1]pentan-1-ylmethyl)isoxazol-5-amine		165.1
58	3-(3,5-Dichloropyridin-2-yl)-1,2-oxazol-5-amine		230
59	3-(3-Chloropyridin-2-yl)isoxazol-5-amine		195.0
60	3-(4-Methylpyridin-3-yl)-1,2-oxazol-5-amine		176.1
¹ 61	3-(2-Methylpyridin-3-yl)-1,2-oxazol-5-amine ¹		
62	3-(2,2-Dimethylcyclopropyl)isoxazol-5-amine		152
63	3-Spiro[2.2]pentan-2-ylisoxazol-5-amine		151

-71-

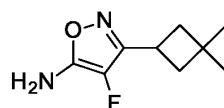
64	3-[(2,2-Difluorocyclopropyl)methyl]isoxazol-5-amine		175
65	3-Spiro[2.3]hexan-2-ylisoxazol-5-amine		165.3
66	5-Spiro[2.3]hexan-2-ylisoxazol-3-amine		165.3
67	3-(2,2-Dimethylcyclobutyl)isoxazol-5-amine		167
68	5-(2,2-Dimethylcyclobutyl)isoxazol-3-amine		167
² 69	3-[(1-Methylcyclobutyl)methyl]isoxazol-5-amine		166
² 70	3-(3,3-Difluoro-1-methylcyclobutyl)isoxazol-5-amine		189
² 71	3-(1,1-Difluoro-2,2-dimethylpropyl)isoxazol-5-amine		191
72	3-(5-Amino-1,2-oxazol-3-yl)bicyclo[1.1.1]pentane-1-carbonitrile		176.3
73	3-[4-(Trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-amine		247.2

¹ No base is used and after work-up, the product is used without further purification,

² After heating for 2 hr at 70-100 °C, c HCl (0.9 equiv) is added and the mixture is heated at 60-100 °C for 30 min-24 hr. The mixture is cooled to 0 °C and the pH adjusted to 9-11 with 30% aq NaOH or NaHCO₃ and worked up as above.

Preparation 74

3-(3,3-dimethylcyclobutyl)-4-fluoro-isoxazol-5-amine



- 5 To 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane;ditetrafluoroborate (0.46 g, 1.30 mmol) and 3-(3,3-dimethylcyclobutyl)isoxazol-5-amine (0.20 g, 1.20 mmol) in a sealed vial is added ACN (12 mL). The mixture is irradiated at 100 °C for 20 min under microwave conditions. The reaction is cooled to RT and concentrated under reduced pressure. The crude material is purified by reversed-phase chromatography (C18Aq
- 10 column), eluting with a gradient of 0% to 100% ACN in H₂O (0.1% HOAc). The desired fractions are combined and concentrated to remove ACN. To the remaining aqueous solution is added saturated aq. NaHCO₃ until a pH of 9 is reached. The mixture is extracted with DCM (2x10 mL). The organic extracts are combined, dried over anhydrous Na₂SO₄, diatomaceous earth is added, and the mixture is concentrated under vacuum. The material is
- 15 further purified by silica gel chromatography, eluting with a gradient of 5% to 40% EtOAc in cyclohexane to give the title compound (48 mg, 22%). ES/MS (m/z) 185.3 (M+H).

The following compounds in Table 6 are prepared essentially as described for 3-(3,3-dimethylcyclobutyl)-4-fluoro-isoxazol-5-amine using the appropriate adjusting reaction time to determine completion of the reaction, and purification conditions as appropriate.

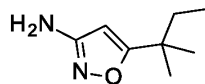
20 Table 6

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
75	3-(2,2-Dimethylpropyl)-4-fluoro-isoxazol-5-amine		173.3
76	4-Fluoro-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-amine		183

-73-

Preparation 77

5-(2-Methylbutan-2-yl)-1,2-oxazol-3-amine

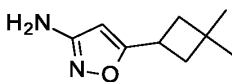


To a stirred mixture of 4,4-dimethyl-3-oxohexanenitrile (3.00 g, 21.6 mmol) and
5 hydroxylamine sulfate (3.89 g, 23.7 mmol) in MeOH (5 mL) and H₂O (45 mL) is added
NaHCO₃ (4.53 g, 53.9 mmol) in portions at RT under N₂. The mixture is stirred for 5 hr at
65 °C under N₂. The mixture is allowed to cool to RT. The mixture is acidified to pH 1 with
conc. HCl and stirred for 20 min at reflux under N₂. The mixture is allowed to cool to RT
and the pH adjusted to 8 with NaOH. The mixture is extracted with DCM (3x200 mL). The
10 combined organic extracts are washed with brine (2x200 mL), dried over anhydrous Na₂SO₄,
filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase
chromatography (C18 column), eluting with a gradient of 30% to 40% ACN in H₂O (0.1%
NH₄HCO₃), to give the title compound (1.20 g, 36%) as a light yellow solid. ¹H NMR
(CDCl₃) δ 5.53 (s, 1H), 1.66 (q, 2H), 1.27 (s, 6H), 0.82 (t, 3H).

15

Preparation 78

5-(3,3-Dimethylcyclobutyl)isoxazol-3-amine



To a sealed vial is added hydroxylamine HCl (0.79 g, 11.4 mmol) in MeOH (0.5 mL)
and 7 M NH₃ in MeOH (2.0 mL, 14.0 mmol). The suspension is stirred at 25 °C for 30 min.
20 A solution of 2-[2-(3,3-dimethylcyclobutyl)-1,3-dioxolan-2-yl]acetonitrile (0.56 g, 2.87
mmol) in MeOH (0.5 mL) and quinolin-8-ol (42 mg, 0.29 mmol) are added and the mixture
is stirred at 65 °C for 12 hr and cooled to RT. The mixture is filtered, the filtrate is
concentrated under reduced pressure, and re-concentrated from toluene (3x) to give the
intermediate 2-[2-(3,3-dimethylcyclobutyl)-1,3-dioxolan-2-yl]-N'-hydroxy-acetamidine as a
25 yellow solid which is used without further purification. In a sealed vial, 2-[2-(3,3-
dimethylcyclobutyl)-1,3-dioxolan-2-yl]-N'-hydroxy-acetamidine is dissolved in EtOH (2 mL)
and acidified to pH 1 with conc. HCl. The reaction mixture is stirred at 80 °C for 12 hr. The

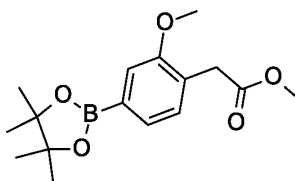
-74-

mixture is concentrated under reduced pressure and the residue is diluted with DCM. Saturated aq. NaHCO_3 is added until the solution is basic (pH 11). The organic layer is separated and the aqueous phase is extracted with DCM. The combined organic extracts are washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure.

- 5 The crude material is purified by silica gel chromatography, eluting with a gradient of 0% to 5% MeOH in DCM to give the title compound as a yellow solid (30 mg, 6.3%). ES/MS (m/z) 167 (M+H).

Preparation 79

Methyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate



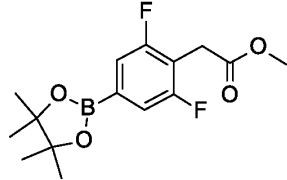
10

Methyl 2-(4-bromo-2-methoxy-phenyl)acetate (0.15 g, 0.579 mmol), bis(pinacolato)diboron (0.18 g, 0.709 mmol), KOAc (95%, 0.18 g, 1.74 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (95%, 22 mg, 0.029 mmol) and 1,4-dioxane (2.7 mL) are added together. The reaction mixture is stirred at 80 °C overnight. The reaction is quenched with

15 H_2O and DCM is added. The two layers are separated and the aqueous phase is extracted with DCM (3x10 mL). The combined organic extracts are dried over Na_2SO_4 , filtered, and concentrated under vacuum to give the title compound as a brown oil which is used crude without further purification. ES/MS (m/z) 307.2 (M+H).

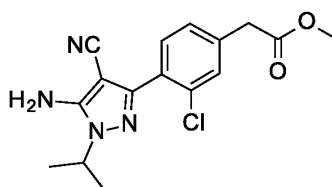
- 20 The following compound in Table 7 is prepared essentially as described for methyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate using the appropriate reagents, adjusting reaction time to determine completion of the reaction and purifying by chromatography as appropriate. The reaction temperature can range from about 80-100 °C, filtered through talcum powder, and purified as appropriate.

Table 7

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
80	Methyl 2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate		313

Preparation 81

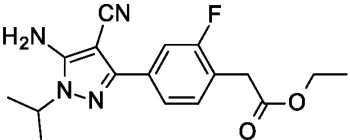
Methyl 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)-3-chlorophenyl]acetate



- 5 A solution of methyl 2-(3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.00 g, 3.22 mmol), 5-amino-3-bromo-1-isopropylpyrazole-4-carbonitrile (0.73 g, 3.22 mmol), Pd(dppf)Cl₂ (0.47 g, 0.64 mmol), and K₃PO₄ (2.05 g, 9.66 mmol) in 1,4-dioxane:H₂O (12 mL, 5:1) is stirred for 2 hr at 120 °C under N₂ and cooled to RT. The solution is filtered through diatomaceous earth and washed with EtOAc (200 mL), filtered,
- 10 and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 10% to 50% ACN in H₂O, to give the title compound (0.30 g, 28%) as a white solid. ES/MS (m/z) 333.1 (M+H).

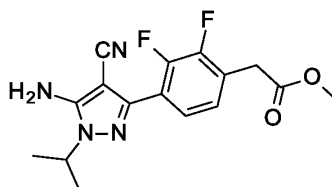
- The following compound in Table 8 is prepared essentially as described for methyl 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)-3-chlorophenyl]acetate, adjusting reaction
- 15 time to determine completion of the reaction and purifying by titration or chromatography as appropriate. The reaction temperature can range from RT to 120 °C.

Table 8

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
82	Ethyl 2-[4-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-fluoro-phenyl]acetate		331.1

Preparation 83

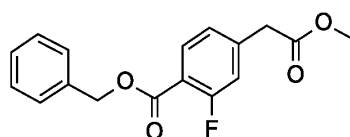
Methyl 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)-2,3-difluorophenyl]acetate



- 5 To a stirred mixture of methyl 2-(4-bromo-2,3-difluorophenyl)acetate (5.00 g, 18.9 mmol) and bis(pinacolato)diboron (5.75 g, 22.6 mmol) in 1,4-dioxane (30 mL) is added KOAc (3.70 g, 37.7 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (1.54 g, 1.88 mmol) at RT. The mixture is stirred for 1 hr at 80 °C under N₂, filtered, and the filter cake is washed with 1,4-dioxane (5 mL). To the filtrate is added 5-amino-3-bromo-1-isopropylpyrazole-4-carbonitrile (4.75 g,
- 10 20.7 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (1.54 g, 1.88 mmol), K₂CO₃ (5.21 g, 37.7 mmol) and H₂O (7 mL) at RT. The mixture is stirred for 1 hr at 80 °C. The mixture is allowed to cool to RT and the residue is purified by silica gel chromatography, eluting with 3:1 to 2:1 PE:EtOAc to give the title compound (4.90 g, 78%) as a yellow solid. ES/MS (m/z) 335.1 (M+H).

Preparation 84

- 15 Benzyl 2-fluoro-4-(2-methoxy-2-oxoethyl)benzoate



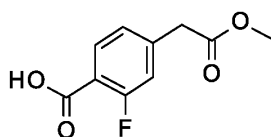
To a solution of methyl 2-(4-bromo-3-fluorophenyl)acetate (5.45 g, 22.1 mmol), TEA (9.2 mL, 66.0 mmol) and benzyl alcohol (2.5 mL, 24.0 mmol) in toluene (150 mL) is added

-77-

Pd(dppf)Cl₂ (0.32 g, 0.44 mmol) in a pressure tank. The mixture is purged with N₂ for 1 min and then is pressurized to 30 atm with CO. The mixture is stirred for 24 hr at 115 °C under a CO atmosphere. The mixture is allowed to cool to RT, filtered, and the filter cake is washed with EtOAc (2x50 mL). The filtrate is concentrated under reduced pressure and the residue is purified by silica gel chromatography, eluting with a gradient of 10:1 to 3:1 PE:EtOAc to give the title compound (2.63 g, 39%) as a colorless oil. ES/MS (m/z) 320.05 (M+NH₃+H).

Preparation 85

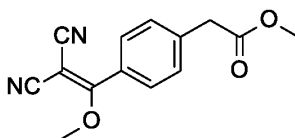
2-Fluoro-4-(2-methoxy-2-oxoethyl)benzoic acid



To a solution of benzyl 2-fluoro-4-(2-methoxy-2-oxoethyl)benzoate (2.63 g, 8.70 mmol) in MeOH (25 mL) is added Pd/C (10%, 0.90 g, 0.85 mmol) at RT under N₂. The mixture is stirred for 2 hr at RT under H₂. The mixture is filtered, the filter cake is washed with MeOH (2x10 mL), and the filtrate is concentrated under reduced pressure to give the title compound (1.51 g, 82%) as a white solid which is used without further purification.

Preparation 86

Methyl 2-[4-(2,2-dicyano-1-methoxyeth-1-en-1-yl)phenyl]acetate



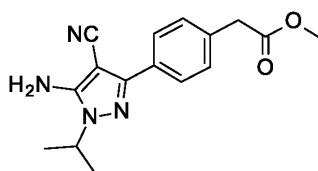
To a stirred solution of 4-(2-methoxy-2-oxoethyl)benzoic acid (40.0 g, 206 mmol) and a few drops of DMF in DCM (300 mL) is added oxalyl chloride (21.2 mL, 247 mmol) dropwise at 0 °C. The mixture is stirred for 2 hr at RT. The mixture is concentrated under reduced pressure to give the intermediate methyl 2-(4-(chlorocarbonyl)phenyl)acetate. In another vessel, a solution of malononitrile (13.6 g, 206 mmol) in THF (100 mL) is added dropwise to a stirred suspension of NaH (16.5 g, 412 mmol, 60% in mineral oil) in THF (100 mL) at 0-10 °C under N₂. The mixture is stirred for 20 min at RT. To this mixture is added

-78-

methyl 2-(4-(chlorocarbonyl)phenyl)acetate in THF (200 mL) dropwise at 0-10 °C. The mixture is stirred for 1 hr at RT. Dimethyl sulfate (23.4 mL, 247 mmol) is added and the mixture is refluxed overnight at 80 °C under N₂. H₂O (300 mL) is added and the mixture is extracted with EtOAc (3x200 mL). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 4:1 to 1:1 PE:EtOAc to give the title compound (42.0 g, 80%) as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.51-7.40 (m, 4H), 3.96 (s, 3H), 3.75 (s, 3H), 3.74 (s, 2H).

Preparation 87

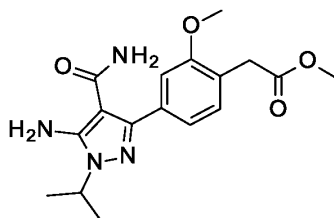
10 Methyl 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]acetate



A solution of methyl 2-[4-(2,2-dicyano-1-methoxyeth-1-en-1-yl)phenyl]acetate (2.50 g, 9.76 mmol) and isopropylhydrazine HCl (1.29 g, 11.7 mmol) and TEA (4.1 mL, 29.4 mmol) in EtOH (40 mL) is stirred for 1 hr at RT under N₂. The mixture is concentrated under reduced pressure and extracted with EtOAc (3x100 mL). The combined organic extracts are washed with brine (2x100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by trituration with Et₂O (50 mL) to give the title compound (2.00 g, 69%) as a yellow solid. ES/MS (m/z) 299.0 (M+H).

Preparation 88

20 Methyl 2-[4-(5-amino-4-carbamoyl-1-isopropylpyrazol-3-yl)-2-methoxyphenyl]acetate



-79-

Methyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate (67%, 0.21 g, 0.460 mmol), 5-amino-3-bromo-1-isopropyl-pyrazole-4-carboxamide (0.14 g, 0.567 mmol), K₂CO₃ (0.13 g, 0.941 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (19 mg, 0.0231 mmol) are added together in a mixture of 1,4-dioxane (3.7 mL) and H₂O (0.73 mL). The reaction is heated at 140 °C for 1 hr under microwave irradiation. The reaction mixture is filtered through diatomaceous earth, washed with EtOAc, and evaporated to dryness. The crude material is purified by silica gel chromatography, eluting with a gradient of 0% to 8% MeOH in DCM to give the title compound (0.17 g, quantitative yield). ES/MS (m/z) 347.2 (M+H).

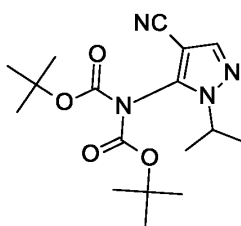
The following compound in Table 9 is prepared essentially as described for methyl 2-[4-(5-amino-4-carbamoyl-1-isopropyl-pyrazol-3-yl)-2-methoxy-phenyl]acetate adjusting the reaction time to determine completion of the reaction and purification as appropriate.

Table 9

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
89	Methyl 2-[4-(5-amino-4-carbamoyl-1-isopropyl-pyrazol-3-yl)-2,6-difluoro-phenyl]acetate		353

Preparation 90

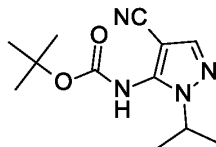
tert-Butyl N-*tert*-butoxycarbonyl-N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate



Preparation 91

tert-Butyl N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate

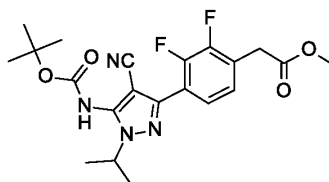
-80-



To a stirred solution of 5-amino-1-isopropyl-pyrazole-4-carbonitrile (4.80 g, 32.0 mmol) in THF (205 mL) is added successively N,N-dimethylpyridin-4-amine (0.38 g, 3.11 mmol), TEA (13 mL, 93.3 mmol) and *tert*-butoxycarbonyl *tert*-butyl carbonate (14.7 g, 67.4 mmol). The reaction mixture is stirred at RT overnight. The reaction mixture is quenched with saturated aq. NH₄Cl (15 mL) and extracted with EtOAc (3x20 mL). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 2% to 30% EtOAc in cyclohexane to give *tert*-butyl N-*tert*-butoxycarbonyl-N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate as an off white solid (7.67 g, 68%), ES/MS (m/z) 373 (M+Na) and *tert*-butyl N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate as an off-white solid (1.12 g, 14%), ES/MS (m/z) 251 (M+H).

Preparation 92

Methyl 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,3-difluorophenyl]acetate

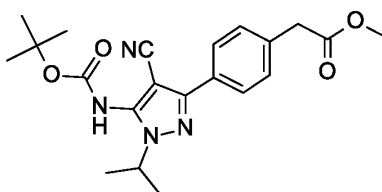


THF (4.8 mL) is added to *tert*-butyl N-*tert*-butoxycarbonyl-N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate (0.79 g, 2.25 mmol), bis(pinacolato)diboron (0.46 g, 1.81 mmol), [Ir(OMe)(1,5-cod)]₂ (31 mg, 0.047 mmol) and 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (26 mg, 0.093 mmol) under N₂. The mixture is stirred at reflux for 4 hr. The reaction mixture is cooled to RT and concentrated under reduced pressure. The residue is dissolved in a mixture of 4:1 DCM:EtOAc (20 mL) and this solution is passed through a pad of silica gel (2 g). The pad is washed with 3:1 DCM:EtOAc (2x10 mL). The filtrates are combined,

-81-

concentrated under reduced pressure, and dried under vacuum to give a crude residue. To the residue under N₂ is added Cs₂CO₃ (2.14 g, 6.57 mmol) and methyl 2-(4-bromo-2,3-difluorophenyl)acetate (0.50 g, 1.89 mmol) in 1,4-dioxane (10 mL). Pd(dppf)Cl₂·CH₂Cl₂ (0.10 g, 0.123 mmol) and 4Å molecular sieves are then added under Ar. The mixture is heated to 90 °C overnight. The mixture is cooled to RT, diluted with EtOAc, and filtered through diatomaceous earth. The filtrate is diluted with H₂O and the aqueous layer is extracted with EtOAc (2x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by silica gel chromatography, eluting with a gradient of 2% to 80% DCM in EtOAc to give the title compound (0.64 g, 94% purity, 73%) as a beige solid. ES/MS (m/z) 435 (M+H).

Preparation 93

Methyl 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]phenyl]acetate

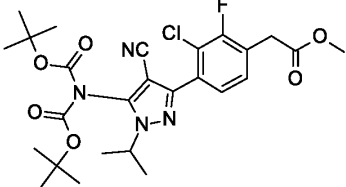
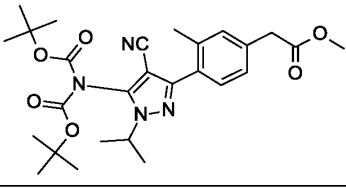
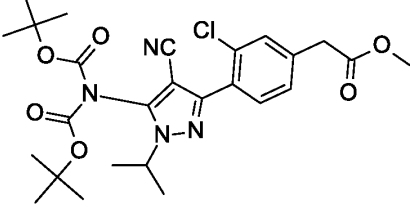
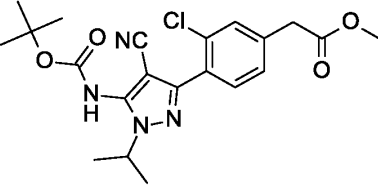
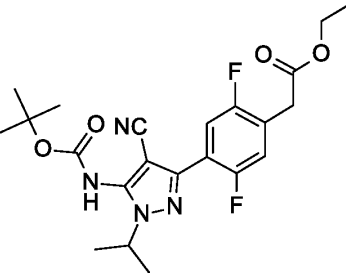
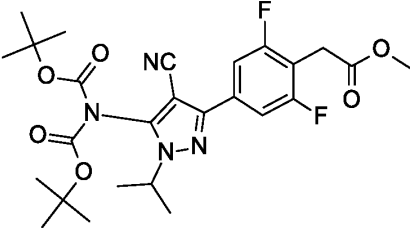
To *tert*-butyl N-*tert*-butoxycarbonyl-N-(4-cyano-2-isopropyl-pyrazol-3-yl)carbamate (4.50 g, 12.8 mmol), bis(pinacolato)diboron (2.61 g, 10.3 mmol), [Ir(Ome)(1,5-cod)]₂ (0.18 g, 0.267 mmol) and 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (0.15 g, 0.535 mmol) under N₂ is added THF (25 mL). The mixture is stirred at reflux for 4 hr. The mixture is cooled to RT and concentrated under reduced pressure. The residue is dissolved in a mixture of 4:1 DCM:EtOAc (20 mL) and the solution is passed through a pad of silica gel and washed with 3:1 DCM:EtOAc (2x10 mL). The filtrates are combined, concentrated under reduced pressure, and dried under vacuum to give a crude residue. To the residue under N₂ is added Cs₂CO₃ (10.5 g, 32.2 mmol) and methyl (4-bromophenyl)acetate (2.50 g, 10.9 mmol) in 1,4-dioxane (50 mL). Pd(dppf)Cl₂·CH₂Cl₂ (0.53 g, 0.642 mmol) and 4Å molecular sieves are then added under Ar. The mixture is heated to 90 °C for 12 hr, cooled to RT, diluted with EtOAc, and filtered through diatomaceous earth. To the filtrate is added H₂O and the aqueous layer is extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered, and

concentrated under reduced pressure. The crude brown oil is purified by silica gel chromatography, eluting with a gradient of 2% to 80% DCM in EtOAc to give the title compound as a white solid (3.80 g, 87%). ES/MS (m/z) 399 ($M+H$).

The following compounds in Table 10 are prepared essentially as described for methyl 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]phenyl]acetate using the appropriate reagents, adjusting reaction time to determine completion of the reaction and purifying by chromatography as appropriate. K_2CO_3 can be substituted for Cs_2CO_3 . Temperature can range from about 50-90 ° for the second coupling reaction. The mono and bis *tert*-butoxycarbonyl amino compounds can be isolated and both carried on to give a common product at a later step.

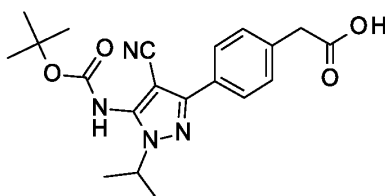
Table 10

Prep No.	Chemical Name	Structure	ES/MS m/z ($M+H$)
94	Methyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-3-fluoro-phenyl]acetate		517.4
95	Ethyl 2-[4-[5-(<i>tert</i> -butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2-chloro-3-fluoro-phenyl]acetate		465
96	Ethyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-2-chloro-3-fluoro-phenyl]acetate		565

97	Methyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-3-chloro-2-fluoro-phenyl]acetate		551
98	Methyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-3-methyl-phenyl]acetate		512
99	Methyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-3-chloro-phenyl]acetate		533
100	Methyl 2-[4-[5-(<i>tert</i> -butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-3-chloro-phenyl]acetate		433
101	Ethyl 2-[4-[5-(<i>tert</i> -butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,5-difluoro-phenyl]acetate		449
102	Methyl 2-[4-[5-[bis(<i>tert</i> -butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-2,6-difluoro-phenyl]acetate		557 M+Na

-84-

Preparation 103

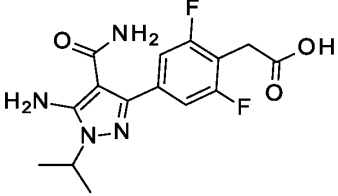
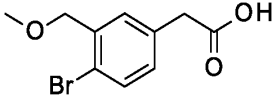
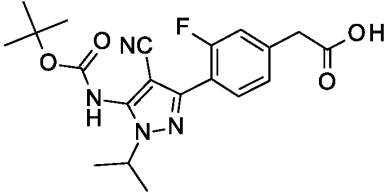
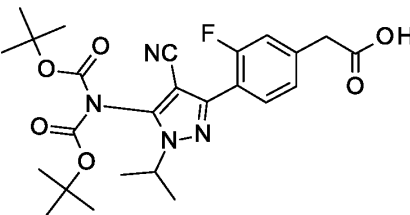
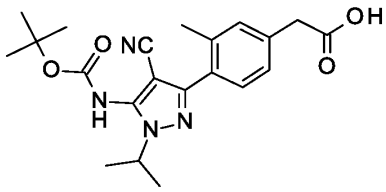
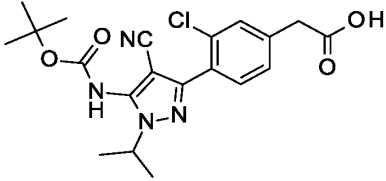
2-[4-[5-(*tert*-Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]phenyl]acetic acid

To a stirred solution of methyl 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]phenyl]acetate (3.80 g, 9.54 mmol) in MeOH (40 mL) is added 2 M NaOH (14 mL, 28 mmol). The reaction mixture is stirred at 25 °C for 1 hr. The organic layer is concentrated. H₂O is added and KHSO₄ (3.92 g, 28.8 mmol) in H₂O is added dropwise. The precipitate formed is filtered, washed with H₂O, and dried under vacuum to give the title compound (2.88 g, 79%) which is used without further purification. ES/MS (m/z) 385 (M+H).

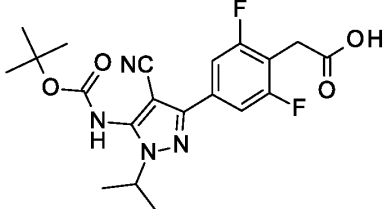
The following compounds in Table 11 are prepared essentially as described for 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]phenyl]acetic acid and adjusting reaction time to determine completion of the reaction. 1,4-Dioxane can be substituted for MeOH, NH₄Cl can be substituted for KHSO₄ and the product can be extracted from H₂O if appropriate. The mono and bis *tert*-butoxycarbonyl amino compounds can be isolated and both carried on to give a common product at a later step.

Table 11

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
104	2-[4-(5-Amino-4-carbamoyl-1-isopropyl-pyrazol-3-yl)-2-methoxy-phenyl]acetic acid		333.1

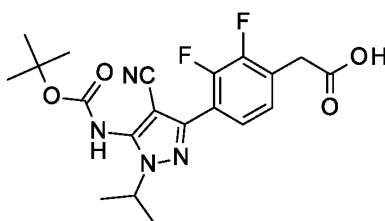
105	2-[4-(5-Amino-4-carbamoyl-1-isopropyl-pyrazol-3-yl)-2,6-difluorophenyl]acetic acid		339
106	2-[4-Bromo-3-(methoxymethyl)phenyl]acetic acid		283 M+Na
107	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-3-fluorophenyl]acetic acid		403.4
108	2-[4-[5-[bis(<i>tert</i> -Butoxycarbonyl)amino]-4-cyano-1-isopropyl-pyrazol-3-yl]-3-fluorophenyl]acetic acid		503
109	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-3-methylphenyl]acetic acid		399
110	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-3-chlorophenyl]acetic acid		418

-86-

111	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,6-difluorophenyl]acetic acid		421
-----	--	--	-----

Preparation 112

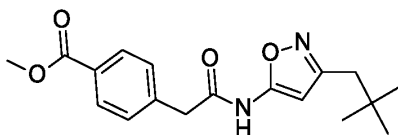
2-[4-[5-(*tert*-Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,3-difluorophenyl]acetic acid



- 5 To methyl 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,3-difluorophenyl]acetate (0.64 g, 1.47 mmol) in 1,4-dioxane (6.5 mL) and H₂O (2 mL) is added 1 M LiOH hydrate (4.4 mL, 4.40 mmol). The mixture is stirred at RT overnight. The reaction mixture is concentrated and poured into H₂O and washed with EtOAc. The aqueous layer is acidified with 1 M aq. KHSO₄ to pH 2-3 then extracted with EtOAc (3x). The
- 10 combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound as a beige solid (0.54 g, 94% purity, 82%). ES/MS (m/z) 421 (M+1).

Preparation 113

Methyl 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]benzoate



15

To a stirred solution of [4-(methoxycarbonyl)phenyl]acetic acid (20.0 g, 103 mmol) and 3-(2,2-dimethylpropyl)-1,2-oxazol-5-amine (17.5 g, 113 mmol) and DIPEA (89.5 mL, 514 mmol) in DMF (200 mL) is added T3P[®] (328 g, 515 mmol, 50% in DMF) in portions at

-87-

0 °C. The mixture is stirred for 2 hr at 50 °C. To the mixture is added EtOAc (1 L). The mixture is washed with H₂O (3x300 mL). The organic layer is separated, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 8:1 to 4:1 PE:EtOAc to give the title compound (31.0 g, 91%) as a light yellow solid. ES/MS (m/z) 331.2 (M+H).

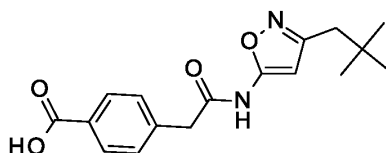
The following compounds in Table 12 are prepared essentially as described for methyl 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoate using the appropriate reagents, adjusting the reaction time to determine completion of the reaction and using appropriate chromatography conditions for purification or used without further purification. The reaction temperature can range from RT to 100 °C. T3P[®] can be added in DCM instead of DMF.

Table 12

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
114	Methyl 4-([3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoate		389.2
115	Methyl 4-([3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl)benzoate		423.1
116	Methyl 4-([3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl)benzoate		341.3

Preparation 117

4-([3-(2,2-Dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoic acid



To a stirred solution of methyl 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoate (31.0 g, 93.8 mmol) in THF (240 mL) and H₂O (80 mL) is

added LiOH (11.2 g, 468 mmol) in portions at RT. The mixture is stirred overnight. The mixture is acidified to pH 5 with 2 N HCl and extracted with EtOAc (3x200 mL). The combined organic extracts are washed with brine (3x50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the title compound (28.5 g, 96%) as a white solid. ES/MS (m/z) 317.2 (M+1).

The following compounds in Table 13 are prepared essentially as described for 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]benzoic acid using the appropriate ester, adjusting the reaction time to determine completion of the reaction, adjusting the pH to 1-5 after completion, and collecting by extraction or precipitation as appropriate. A solvent mixture of 1,4-dioxane/H₂O or MeOH/H₂O can be used if needed for solubility and the temperature can range from about RT to 50 °C. 1 M NaOH can be substituted for LiOH and citric acid or KHSO₄ can be substituted for HCl.

Table 13

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
118	4-([3-(2-Chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]benzoic acid		375.1
119	4-([3-(4-(Trifluoromethyl)bicyclo[2.2.1]heptan-1-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]benzoic acid		409.1
120	2-[4-Bromo-3-(tert-butoxymethyl)phenyl]acetic acid		323.1 M+Na
121	2-[4-[5-(tert-Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2-chloro-3-fluorophenyl]acetic acid		437

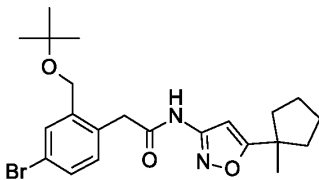
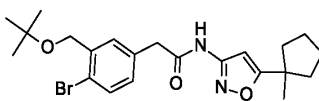
122	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-3-chloro-2-fluorophenyl]acetic acid		437
123	2-[4-[5-(<i>tert</i> -Butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,5-difluorophenyl]acetic acid		421
124	4-[[[3-(3-Methylbicyclo[1.1.1]pentan-1-yl)-1,2-oxazol-5-yl]carbamoyl]methyl]benzoic acid		327.1

The following compounds in Table 14 are prepared essentially as described for methyl 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]benzoate using the appropriate reagents, adjusting the reaction time to determine completion of the reaction and using appropriate chromatography conditions for purification or used without further purification. The reaction temperature can range from RT to 100 °C. T3P® can be added in DCM or EtOAc instead of DMF.

Table 14

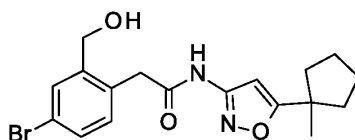
Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
125	2-[4-Bromo-3-(methoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide		407
126	2-[4-Bromo-2-(methoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide		408

-90-

127	2-[4-Bromo-2-(<i>tert</i> -butoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide		449
128	2-[4-Bromo-3-(<i>tert</i> -butoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide		449.2

Preparation 129

2-[4-Bromo-2-(hydroxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide

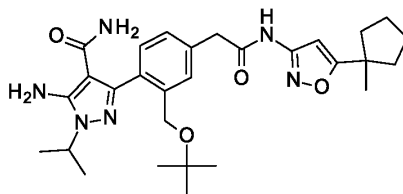


To TFA (16.6 mL), (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (5.42 g, 25.8 mmol) and triethylsilane (1.0 mL, 6.26 mmol) under N₂ is added 2-[4-bromo-2-(*tert*-butoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide (0.29 g, 0.645 mmol) in DCM (8.29 mL). The reaction is stirred for 4 hr. The reaction mixture is concentrated under reduced pressure and dried under vacuum. The material is dissolved in THF (9 mL) and H₂O (4.5 mL). Saturated aq. NaHCO₃ (4 mL) is added and the mixture is stirred at RT for 1 hr. THF is removed under vacuum. The mixture is diluted with DCM (10 mL) and the organic layer is separated, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 1% to 10% MeOH in DCM to give the title compound (0.20 g, 79%). ES/MS (m/z) 394 (M+H).

Preparation 130

5-Amino-3-[2-(*tert*-butoxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide

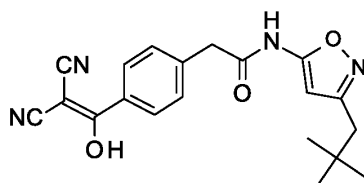
-91-



To bis(pinacolato)diboron (93 mg, 0.366 mmol), 2-[4-bromo-3-(*tert*-butoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide (0.15 g, 0.334 mmol), KOAc (0.11 g, 1.12 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (28 mg, 0.033 mmol) under N₂ is added dry THF (4 mL). The reaction mixture is degassed with Ar for 15 min and then heated to 50 °C. The reaction is stirred at 50 °C overnight, at 65 °C for a second night and then at 80 °C for 24 hr. The reaction mixture is cooled to RT. 5-Amino-3-bromo-1-isopropyl-pyrazole-4-carboxamide (0.11 g, 0.445 mmol) in THF (1.3 mL) and K₃PO₄ (0.22 g, 1.04 mmol) in H₂O (1.3 mL) are added. The reaction mixture is degassed with Ar and XantPhos Pd G3 (17 mg, 0.0167 mmol) is added. The mixture is heated to 50 °C overnight. The mixture is filtered through a pad of talcum powder; H₂O is added to the filtrate and the mixture is extracted with EtOAc (2x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 1% to 10% MeOH in DCM to give the title compound as a brown powder (67 mg, 37%). ES/MS (m/z) 537 (M+H).

Preparation 131

2-[4-(2,2-Dicyano-1-hydroxyeth-1-en-1-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide



To a stirred solution of 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoic acid (32.0 g, 101 mmol) and DMF (0.16 mL, 2.14 mmol) in DCM (350 mL) is added oxalyl chloride (10.6 mL, 124 mmol) dropwise at 0 °C. The

mixture is stirred for 2 hr at RT. The mixture is concentrated under reduced pressure to give crude 4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoyl chloride. To a solution of malononitrile (6.31 g, 95.5 mmol) in THF (100 mL) is added NaH (7.65 g, 191 mmol, 60% in mineral oil) at 0 °C. The mixture is stirred for 15 min. 4-([3-(2,2-

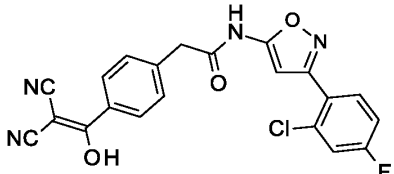
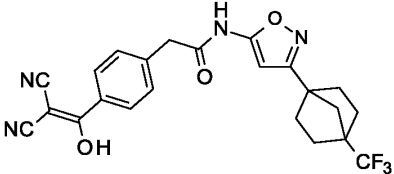
5 Dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl)benzoyl chloride (32.0 g, 95.6 mmol) in THF (150 mL) is added dropwise to the 0 °C solution and the mixture is stirred for 2 hr and allowed to warm to RT. The mixture is diluted with H₂O (300 mL), acidified to pH 5 with 2 N HCl, and extracted with EtOAc (3x200 mL). The combined organic extracts are washed with brine (3x100 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure

10 to give the title compound (30.0 g, 82%). The crude product is used directly without further purification. ES/MS (m/z) 365.1 (M+H).

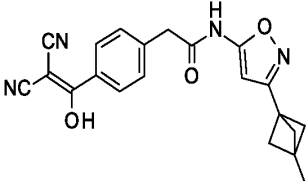
The following compounds in Table 15 are prepared essentially as described for 2-[4-(2,2-dicyano-1-hydroxyeth-1-en-1-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-

15 yl]acetamide under N₂ if desired and adjusting the reaction time to determine completion of the reactions. The malononitrile in THF and NaH can be stirred from 15-30 min at 0 ° to RT. The reaction can be acidified or concentrated to dryness and purified by chromatography as appropriate.

Table 15

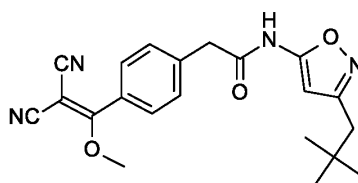
Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
132	N-[3-(2-Chloro-4-fluorophenyl)-1,2-oxazol-5-yl]-2-[4-(2,2-dicyano-1-hydroxyeth-1-en-1-yl)phenyl]acetamide		423.1
133	2-[4-(2,2-Dicyano-1-hydroxyeth-1-en-1-yl)phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		457

-93-

134	Methyl 2-(4-(2,2-dicyano-1-hydroxyvinyl)-3-fluorophenyl)acetate		
135	2-[4-(2,2-Dicyano-1-hydroxyeth-1-en-1-yl)phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		375.3

Preparation 136

2-[4-(2,2-Dicyano-1-methoxyeth-1-en-1-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide



- 5 To a stirred solution of 2-[4-(2,2-dicyano-1-hydroxyeth-1-en-1-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide (25.0 g, 68.6 mmol) and TEA (28.7 mL, 206 mmol) in ACN (240 mL) is added dimethyl sulfate (39.0 mL, 411 mmol) dropwise at RT under N₂. The mixture is stirred for 14 hr at 50 °C under N₂. The mixture is diluted with EtOAc (500 mL), washed with brine (3x50 mL), dried over anhydrous Na₂SO₄, filtered, and
- 10 concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 8:1 to 2:1 PE:EtOAc to give the title compound (9.0 g, 35%) as a light yellow solid. ES/MS (m/z) 379.1 (M+H).

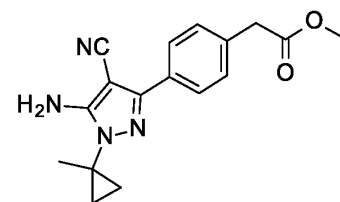
- The following compounds in Table 16 are prepared essentially as described for 2-[4-(2,2-dicyano-1-methoxyeth-1-en-1-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide adjusting the reaction time to determine completion of the reaction and
- 15 purification as appropriate. The temperature can range from about 50 °C to 80 °C.

Table 16

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
137	N-[3-(2-Chloro-4-fluorophenyl)-1,2-oxazol-5-yl]-2-[4-(2,2-dicyano-1-methoxyethyl-en-1-yl)phenyl]acetamide		437.1
138	2-[4-(2,2-Dicyano-1-methoxyethyl-en-1-yl)phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		471.2
139	Methyl 2-(4-(2,2-dicyano-1-methoxyvinyl)-3-fluorophenyl)acetate		292.2, M+NH ₃ ⁺ H
140	2-[4-(2,2-Dicyano-1-methoxyethyl-en-1-yl)phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		389.1

Preparation 141

Methyl 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetate

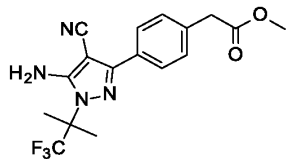
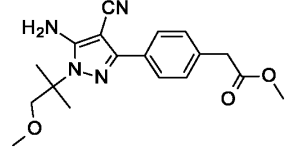
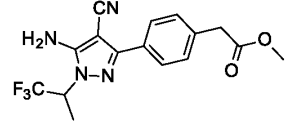
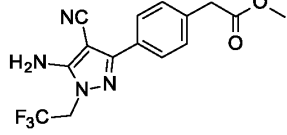
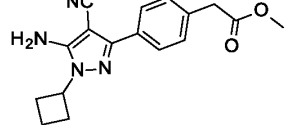


- 5 To a stirred mixture of (1-methylcyclopropyl)hydrazine HCl (crude, 2.00 g, 16.3 mmol) and TEA (1.6 mL, 11.5 mmol) in EtOH (20 mL) is added methyl 2-[4-(2,2-dicyano-1-methoxyethyl-1-en-1-yl)phenyl]acetate (0.48 g, 1.87 mmol) in portions at RT under N₂. The mixture is stirred for 2 hr at 50 °C under N₂. The mixture is allowed to cool to RT and

concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 30% to 50% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (0.50 g, 86%) as a white solid. ES/MS (m/z) 311.3 (M+H).

- 5 The following compounds in Table 17 are prepared essentially as described for methyl 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetate using the appropriate reagents, adjusting reaction time to determine completion of the reaction and purifying by chromatography as appropriate. The reaction temperature can range from RT to 80 °C, the solvent can be THF if appropriate, and the base can be DIPEA
- 10 or TEA.

Table 17

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
142	Methyl 2-[4-[5-amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]acetate		367.2
143	Methyl 2-[4-[5-amino-4-cyano-1-(1-methoxy-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]acetate		343.3
144	Methyl 2-[4-[5-amino-4-cyano-1-(1,1,1-trifluoropropan-2-yl)pyrazol-3-yl]phenyl]acetate		353.2
145	Methyl 2-[4-[5-amino-4-cyano-1-(2,2,2-trifluoroethyl)pyrazol-3-yl]phenyl]acetate		339.1
146	Methyl 2-[4-(5-amino-4-cyano-1-cyclobutylpyrazol-3-yl)phenyl]acetate		311.2

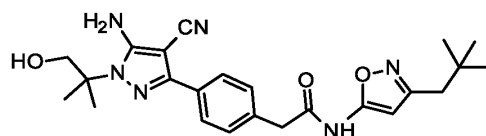
-96-

147	2-[4-[5-Amino-4-cyano-1-(1-hydroxypropan-2-yl)pyrazol-3-yl]phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		447.3
148	2-[4-[5-Amino-4-cyano-1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		461.2
149	Methyl 2-[4-[5-amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]acetate		367.1
150	Methyl 2-[4-(5-amino-1-tert-butyl-4-cyanopyrazol-3-yl)phenyl]acetate		313.2
151	2-(4-(5-Amino-4-cyano-1-cyclopentyl-1H-pyrazol-3-yl)phenyl)acetate		325
152	Methyl 2-(4-(5-amino-4-cyano-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetate		375.1 M+Na
153	Methyl 2-[4-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)phenyl]acetate		299
154	Methyl 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-3-fluorophenyl)acetate		329.1

Preparation 155

2-(4-(5-Amino-4-cyano-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide

-97-



2-Hydrazino-2-methylpropan-1-ol HCl (43 mg, 0.306 mmol), EtOH (1.5 mL), TEA (0.12 mL, 0.861 mmol), and 2-(4-(2,2-dicyano-1-methoxyvinyl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide (0.11 g, 0.291 mmol) are added together and stirred for 18 hr at 45 °C. The mixture is diluted with H₂O (1 mL) and extracted with EtOAc (3×3 mL). The organic extracts are concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 0% to 100% EtOAc in hexanes to give the title compound (39 mg, 30%) as a white solid. ES/MS (m/z) 451.3 (M+H).

The following compounds in Table 18 are prepared essentially as described for 2-(4-(5-amino-4-cyano-1-(1-hydroxy-2-methylpropan-2-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide using the appropriate hydrazine from 1-3 equivalents, adjusting reaction time to determine completion of the reaction, and purification conditions as appropriate. The reaction temperature can range from RT to 45 °C, and THF can be substituted for the solvent based on solubility.

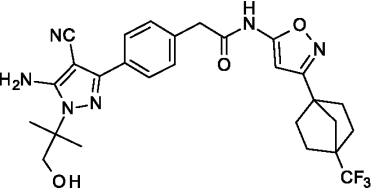
Table 18

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
156	2-(4-(5-Amino-4-cyano-1-(1-cyclopropylethyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		447.2
157	2-(4-(5-Amino-4-cyano-1-(tetrahydrofuran-3-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		449.2

158	2-(4-(5-Amino-4-cyano-1-cyclopentyl-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		447.2
159	2-(4-(5-Amino-4-cyano-1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		463.2
160	2-(4-(5-Amino-4-cyano-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		463.2
161	2-(4-(5-Amino-4-cyano-1-((1R,3R)-3-ethoxycyclobutyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		477.2
162	2-(4-(5-Amino-4-cyano-1-(3-hydroxypropyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		437.2
163	2-(4-(5-Amino-4-cyano-1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		463.2
164	2-(4-(5-Amino-4-cyano-1-(1-hydroxypropan-2-yl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		437.2

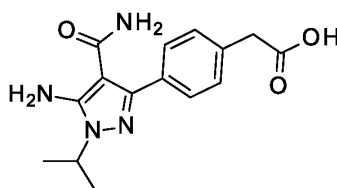
165	2-(4-(5-Amino-1-(<i>tert</i> -butyl)-4-cyano-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		435.2
166	2-[4-(5-Amino-4-cyano-1-cyclopropyl-pyrazol-3-yl)phenyl]-N-[3-(2,2-dimethylpropyl)isoxazol-5-yl]acetamide		419.2
167	2-(4-(5-Amino-1-(bicyclo[1.1.1]pentan-1-yl)-4-cyano-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		445.2
168	2-(4-(5-Amino-4-cyano-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		461.1
169	2-[4-[5-Amino-4-cyano-1-(1-hydroxypropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]acetamide		495.1
170	2-[4-[5-Amino-4-cyano-1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]acetamide		509.3
171	2-[4-[5-Amino-4-cyano-1-(1-hydroxypropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		529.1

-100-

172	2-[4-[5-Amino-4-cyano-1-(1-hydroxy-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		543.4
-----	---	--	-------

Preparation 173

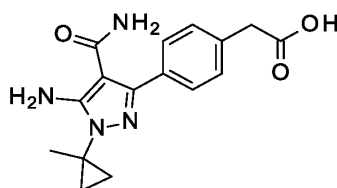
2-(4-(5-Amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid



To a mixture of methyl 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]acetate (7.40 g, 24.8 mmol), NaOH (5.96 g, 149 mmol), H₂O (24 mL), DMSO (12 mL) and EtOH (60 mL) is added H₂O₂ (38.0 mL, 372 mmol, 30% in H₂O) at RT. The mixture is heated to 40 °C and stirred for 6 hr. The mixture is quenched with saturated aq. Na₂S₂O₃ and adjusted to pH 4 with dilute aq. HCl. The mixture is extracted with EtOAc (3x200 mL). The combined organic extracts are concentrated under reduced pressure and the resulting solid is triturated with EtOAc (20 mL). The precipitated solid is collected by filtration, washed with water (3x60 mL), and dried under reduced pressure to give the title compound (4.30 g, 57%) as a yellow solid. ES/MS (m/z) 303.1 (M+H).

Preparation 174

2-(4-(5-Amino-4-carbamoyl-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid



15

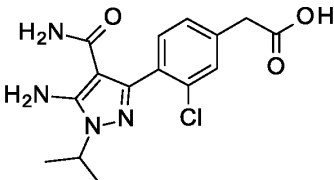
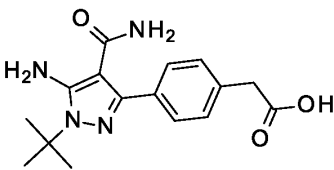
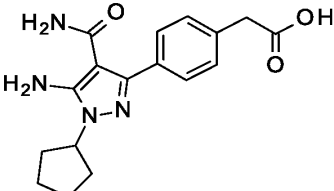
To a stirred mixture of methyl 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetate (0.50 g, 1.61 mmol) and NaOH (0.32 g, 8.00 mmol) in EtOH/H₂O/DMSO (5 mL/2 mL/1 mL) is added H₂O₂ (2.43 mL, 23.8 mmol, 30% in H₂O)

-101-

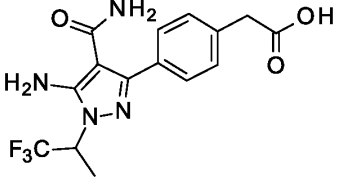
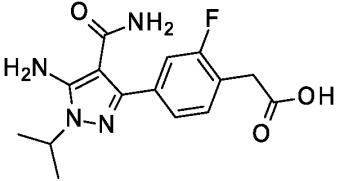
dropwise at RT under N₂. The mixture is stirred overnight at 50 °C. The reaction is quenched with saturated aq. Na₂SO₃ (10 mL) at RT. The residue is adjusted to pH 4 with 1 N aq. HCl and extracted with EtOAc (5x50 mL). The combined organic extracts are washed with brine (2x100 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate is concentrated under reduced pressure. The resulting solid is triturated with EtOAc (10 mL) and the precipitated solids are collected by filtration and washed with EtOAc (3x5 mL) to give the title compound (0.20 g, 40%) as a white solid. ES/MS (m/z) 315.2 (M+H).

The following compounds in Table 19 are prepared essentially as described for 2-(4-(5-amino-4-carbamoyl-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid, adjusting the reaction time to determine completion of the reaction and purifying by titration or chromatography as appropriate. The reaction temperature can range from about RT to 50 °C and about 15-30 equiv of H₂O₂ can be used. The reagents can also be added together at about 0 °C.

Table 19

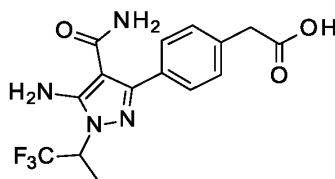
Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
175	[4-(5-Amino-4-carbamoyl-1-isopropylpyrazol-3-yl)-3-chlorophenyl]acetic acid		337.1
176	[4-(5-Amino-1- <i>tert</i> -butyl-4-carbamoylpyrazol-3-yl)phenyl]acetic acid		317.1
177	2-(4-(5-Amino-4-carbamoyl-1-cyclopentyl-1H-pyrazol-3-yl)phenyl)acetic acid		329

-102-

178	2-(4-(5-Amino-4-carbamoyl-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetic acid		357.1
179	[4-(5-Amino-4-carbamoyl-1-isopropylpyrazol-3-yl)-2-fluorophenyl]acetic acid		321.1

Preparation 180

2-(4-(5-Amino-4-carbamoyl-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetic acid, Isomer 1



5

Preparation 181

2-(4-(5-Amino-4-carbamoyl-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetic acid, Isomer 2

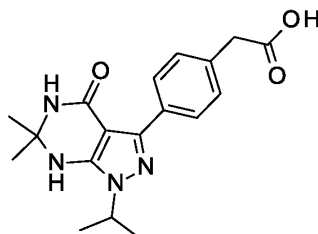
2-(4-(5-Amino-4-carbamoyl-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetic acid (0.500 g, 1.40 mmol) is separated by Chiral-HPLC with the following conditions: Column: CHIRALPAK IG, 2*25 cm, 5 μ m; mobile phase A: hexanes (0.1% TFA), Mobile Phase B: IPA with a flow rate of 20 mL/min eluting with 25% B in 12.5 min; to give the title compound of Isomer 1 as a light yellow solid $t_{(R)}$ 6.7 min, (0.240 g, 48%), ES/MS (m/z) 357.1 (M+H), $[\alpha]_D^{25} = -15.789$ (C=0.304, MeOH) and Isomer 2 as a light yellow solid $t_{(R)}$ 9.5 min (0.210 g, 42%), ES/MS (m/z) 357.1 (M+H), $[\alpha]_D^{25} = 17.197$ (C=0.314, MeOH).

15

Preparation 182

2-[4-(1-Isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetic acid

-103-



To 2-[4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl]acetic acid (0.100 g, 0.331 mmol) in acetone (5 mL) is added TFA (0.005 mL). The mixture is stirred for 2 hr at 50 °C, concentrated under reduced pressure, and dried under vacuum to give the title compound as a yellow solid (0.113 g, 100%) which is used without further purification. ES/MS (m/z) 343.2 (M+H).

The following compounds in Table 20 are prepared essentially as described for 2-[4-(1-isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetic acid and adjusting reaction time to determine completion of the reaction.

10 Table 20

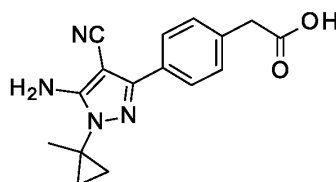
Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
183	2-[4-(1-Isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]acetic acid; ½ TFA	 1/2 TFA	373.2
¹ 184	2-[2,6-Difluoro-4-(1-isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)phenyl]acetic acid		379

¹Ethoxyethane HCl is substituted for TFA and the mixture is stirred at RT for 30 min.

-104-

Preparation 185

2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid



A solution of methyl 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetate (4.30 g, 13.9 mmol) and LiOH (1.66 g, 69.3 mmol) in THF (40 mL) and H₂O (10 mL) is stirred for 3 hr at RT under N₂. The mixture is concentrated under reduced pressure, diluted with H₂O (10 mL) and acidified to pH 3 with 1 N aq. HCl. The precipitated solids are collected by filtration and washed with H₂O (3x30 mL) to give the title compound (4.00 g, 97%) as a white solid. ES/MS (m/z) 297.3 (M+H).

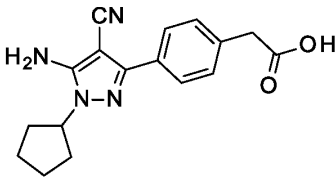
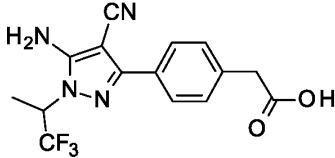
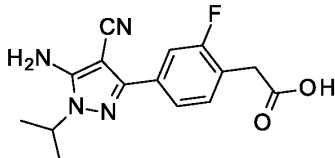
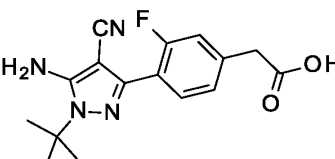
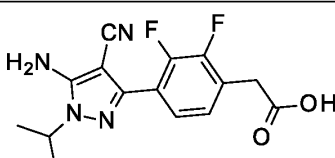
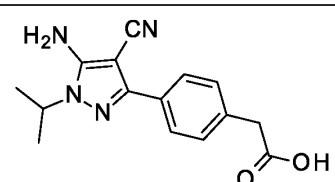
The following compounds in Table 21 are prepared essentially as described for 2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid using the appropriate ester, adjusting the reaction time to determine completion of the reaction, adjusting the pH to 1-5 after completion, and collecting by extraction or precipitation as appropriate. A solvent mixture of 1,4-dioxane/H₂O or MeOH/H₂O can be used if needed for solubility and the temperature can range from about RT to 50 °. 1 M NaOH can be substituted for LiOH and citric acid or KHSO₄ can be substituted for HCl.

Table 21

Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
186	[4-[5-Amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]acetic acid:		353.1

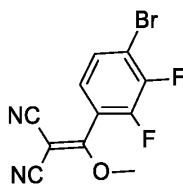
187	2-[4-[5-Amino-4-cyano-1-(2-methoxy-1,1-dimethyl-ethyl)pyrazol-3-yl]phenyl]acetic acid		329.2
188	2-[4-[5-Amino-4-cyano-1-(2,2,2-trifluoro-1-methyl-ethyl)pyrazol-3-yl]phenyl]acetic acid		339.2 M+Na
189	[4-[5-Amino-4-cyano-1-(2,2,2-trifluoroethyl)pyrazol-3-yl]phenyl]acetic acid		325.1
190	[4-(5-Amino-4-cyano-1-cyclobutylpyrazol-3-yl)phenyl]acetic acid		297.2
191	4-[5-Amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]acetic acid		353.2
192	[4-(5-Amino-1-tert-butyl-4-cyanopyrazol-3-yl)phenyl]acetic acid		299.2
193	[4-(5-Amino-1-tert-butyl-4-cyanopyrazol-3-yl)phenyl]acetic acid		299.2

-106-

194	2-(4-(5-Amino-4-cyano-1-cyclopentyl-1H-pyrazol-3-yl)phenyl)acetic acid		311
195	2-(4-(5-Amino-4-cyano-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazol-3-yl)phenyl)acetic acid		339.2
196	[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)-2-fluorophenyl]acetic acid		303.2
197	2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-3-fluorophenyl)acetic acid		315.2
198	[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)-2,3-difluorophenyl]acetic acid		321.1
199	[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]acetic acid		285.1

Preparation 200

2-[(4-Bromo-2,3-difluorophenyl)(methoxy)methylidene]propanedinitrile

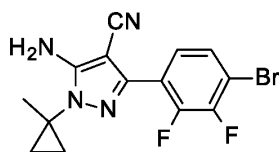


-107-

NaH (1.67 g, 41.8 mmol, 60% in mineral oil) and malononitrile (1.37 g, 20.7 mmol) are added to THF (50 mL) at 0 °C. The mixture is stirred for 30 min at 0 °C under N₂. To this mixture is added 4-bromo-2,3-difluorobenzoyl chloride (5.30 g, 20.7 mmol) in THF (10 mL) dropwise at 0 °C. The mixture is stirred for 1 hr at RT. The intermediate mixture of 2-
5 [(4-bromo-2,3-difluoro-phenyl)-hydroxy-methylene]propanedinitrile is used directly without further purification. ES/MS (m/z) (⁷⁹Br/⁸¹Br) 282.9/284.9 (M-H). Dimethyl sulfate (2.4 mL, 25.3 mmol) is added to the solution of 2-[(4-bromo-2,3-difluoro-phenyl)-hydroxy-methylene]propanedinitrile (theoretical 5.90 g, 20.7 mmol) in THF (60 mL). The mixture is stirred overnight at reflux under N₂. The solution is cooled to RT and concentrated under
10 reduced pressure. The crude product is dissolved in EtOAc (200 mL) and diluted with H₂O (200 mL) and extracted with EtOAc (3x300 mL). The organic extracts are washed with brine (2x100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product is purified by silica gel chromatography, eluting with a gradient of 3:1 to 2:1 PE:EtOAc to give the title compound (3.00 g, 48%) as a yellow solid.

15 Preparation 201

5-Amino-3-(4-bromo-2,3-difluorophenyl)-1-(1-methylcyclopropyl)pyrazole-4-carbonitrile

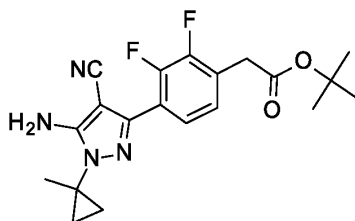


A solution of 2-[(4-bromo-2,3-difluorophenyl)(methoxy)methylidene]propanedinitrile (2.50 g, 8.36 mmol), (1-methylcyclopropyl)hydrazine HCl (3.07 g, 25.0 mmol), and TEA
20 (5.8 mL, 41.6 mmol) in THF (30 mL) is stirred for 1 hr at RT under N₂. The reaction is concentrated under reduced pressure and the residue is purified by silica gel chromatography, eluting with a gradient of 3:1 to 2:1 PE:EtOAc to give the title compound (2.50 g, 85%) as a light yellow solid. ES/MS (m/z) (⁷⁹Br/⁸¹Br) 353.1/355.1 (M+H).

Preparation 202

25 *tert*-Butyl 2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]acetate

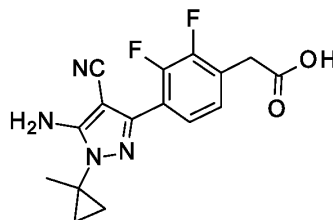
-108-



A solution of 5-amino-3-(4-bromo-2,3-difluorophenyl)-1-(1-methylcyclopropyl)pyrazole-4-carbonitrile (1.80 g, 5.10 mmol), *tert*-butyl 2-(bromozincio)acetate (3.98 g, 15.3 mmol) and Pd(*t*-Bu₃P)₂ (0.26 g, 0.509 mmol) in THF (20 mL) is stirred for 1 hr at 80 °C under N₂ and allowed to cool to RT. The solution is concentrated under reduced pressure and the residue is purified by silica gel chromatography, eluting with a gradient of 2:1 to 1:1 PE:EtOAc to give the title compound (0.50 g, 25%) as a yellow solid. ES/MS (m/z) 389.2 (M+H).

Preparation 203

2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluoro-phenyl]acetic acid

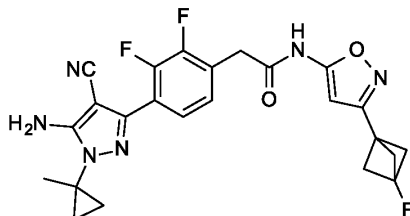


A solution of *tert*-butyl 2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]acetate (0.49 g, 1.26 mmol) and TFA (5 mL) in DCM (10 mL) is stirred for 2 hr at RT under N₂ and concentrated under reduced pressure. The mixture is diluted with Et₂O (20 mL) and concentrated under reduced pressure to give the title compound (0.40 g, 96%) as a yellow solid. ES/MS (m/z) 333.1 (M+H).

Preparation 204

2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-(3-[3-fluorobicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide

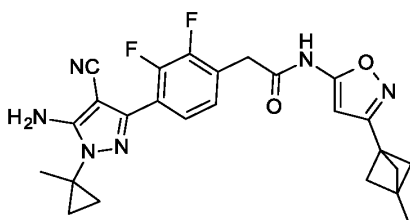
-109-



A solution of 2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluoro-phenyl]acetic acid (80 mg, 0.241 mmol), 3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine (49 mg, 0.291 mmol), DIPEA (0.25 mL, 1.44 mmol), and T3P® (0.46 g, 0.723 mmol, 50% in EtOAc) in DCM (3.00 mL) is stirred for 1 hr at 50 °C under N₂. The mixture is cooled to RT and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 40% to 60% ACN in H₂O (0.1% FA) to give the title compound (60 mg, 52%) as a yellow solid. ES/MS (m/z) 483.1 (M+H).

Preparation 205

2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide

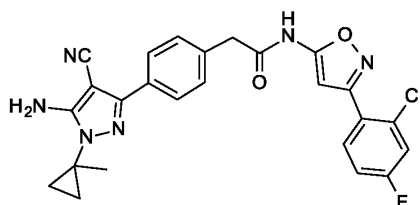


To a solution of 2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluoro-phenyl]acetic acid (80 mg, 0.241 mmol), 3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-amine (47 mg, 0.286 mmol) and DIPEA (0.13 mL, 0.746 mmol) in DCM (3 mL) is added T3P® (0.46 g, 0.723 mmol, 50% in EtOAc). The reaction is stirred for 2 hr at 50 °C in a sealed tube. The mixture is cooled to RT and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 40% to 60% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (70 mg, 61%) as a white solid. ES/MS (m/z) 479.1 (M+H).

-110-

Preparation 206

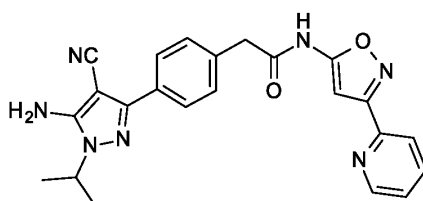
2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)-N-(3-(2-chloro-4-fluorophenyl)isoxazol-5-yl)acetamide



2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid (60 mg, 0.202 mmol) is dissolved in DCM (0.41 mL) and treated with 3-(2-chloro-4-fluorophenyl)isoxazol-5-amine (47 mg, 0.221 mmol), T3P® (0.77 g, 1.21 mmol, 50% in EtOAc), and DIPEA (0.21 mL, 1.18 mmol) at 0 °C. The mixture is stirred for about 20 min, evaporated to dryness, and used without further purification. ES/MS (m/z) 491.1 (M+H).

Preparation 207

2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[3-(pyridin-2-yl)-1,2-oxazol-5-yl]acetamide



To a stirred mixture of [4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]acetic acid (0.100 g, 0.352 mmol) and 3-(pyridin-2-yl)-1,2-oxazol-5-amine (62 mg, 0.385 mmol) in DCM (3 mL) is added T3P® (0.337 g, 0.530 mmol, 50% in EtOAc) and DIPEA (0.31 mL, 1.78 mmol). The mixture is stirred for 2 hr at RT and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 10% to 50% ACN in H₂O (0.1% FA) to give the title compound (70 mg, 47%) as a light yellow solid. ES/MS (m/z) 428.2 (M+H).

The following compounds in Table 22 are prepared essentially as described for 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[3-(pyridin-2-yl)-1,2-oxazol-5-

-111-

yl]acetamide using the appropriate amine and carboxylic acid with a coupling reagent, about 1-6 equivalents, base, about 1-4 equiv, and solvent, about 0.3-6 mL, adjusting the reaction time to determine completion of the reaction, and purification conditions as appropriate. The reaction temperature can range from -20 °C to 50 °C, T3P[®] can be added in 50% EtOAc, 50% DMF, or 50% MeTHF. TCFH can be added in portions and the reaction can be done under N₂ and in a sealed tube.

*Coupling reagents: 1 T3P[®], 2 TCFH, 3 BTFFH, 4 COMU[®], 5 TBTU, 6 TFFH, 7 HATU 8 EDCI/HOBT

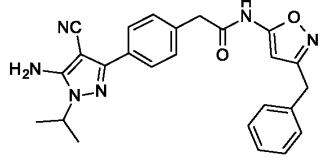
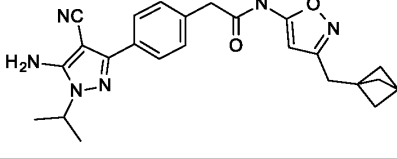
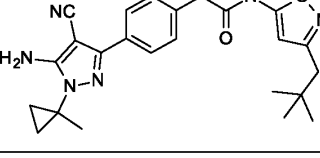
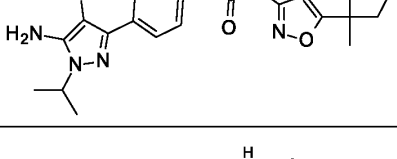
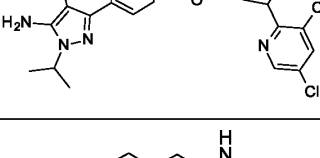
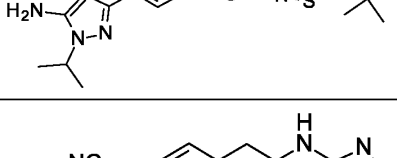
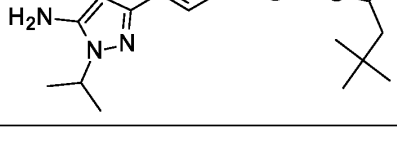
10 Bases: a NMI, b pyridine, c DIPEA

Solvents: I EtOAc, II ACN, III DMF, IV DCM, V MeTHF

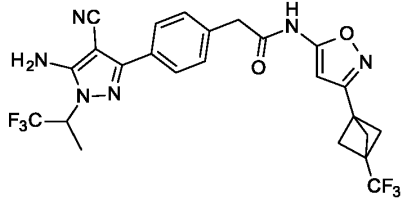
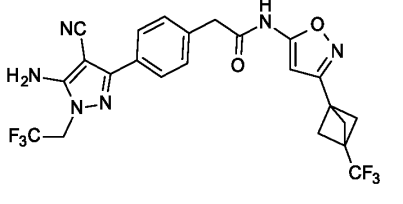
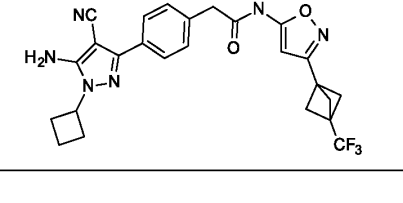
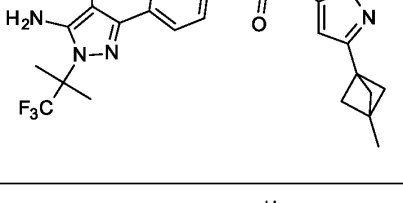
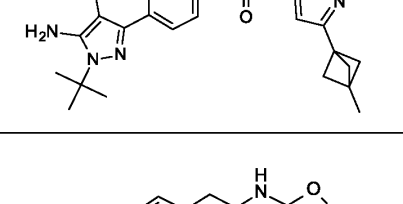
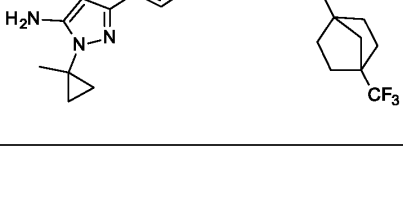
Table 22

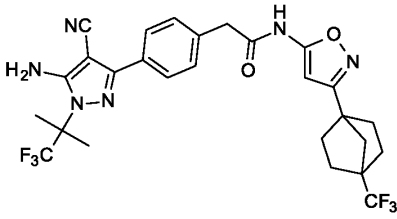
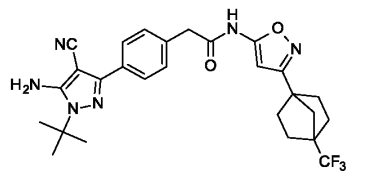
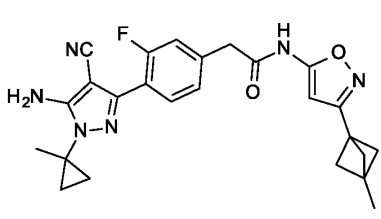
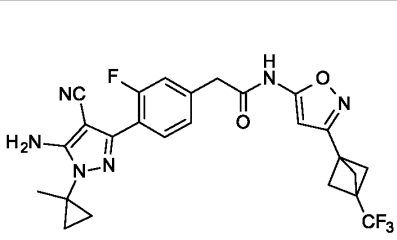
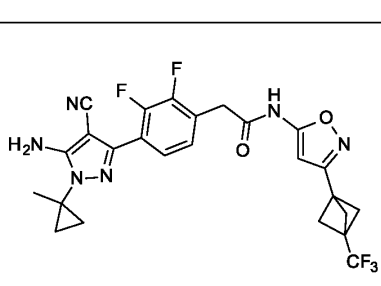
Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)	*
208	2-(4-(5-Amino-4-cyano-1-isopropyl-1H-pyrazol-3-yl)phenyl)-N-(3-(3,3,3-trifluoro-2,2-dimethylpropyl)isoxazol-5-yl)acetamide		474.9	1, b, I
209	2-(4-(5-Amino-4-cyano-1-isopropyl-1H-pyrazol-3-yl)phenyl)-N-(3-(4-fluorobicyclo[2.2.2]octan-1-yl)isoxazol-5-yl)acetamide		477.2	1, b, I
210	2-(4-(5-Amino-4-cyano-1-cyclobutyl-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		433.2	1, c, III
211	2-(4-(5-Amino-4-cyano-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		461.1	1, c, III

-112-

212	2-(4-(5-Amino-4-cyano-1-isopropyl-1H-pyrazol-3-yl)phenyl)-N-(3-benzylisoxazol-5-yl)acetamide		441.1	1, c, III
213	2-(4-(5-Amino-4-cyano-1-isopropyl-1H-pyrazol-3-yl)phenyl)-N-(3-(bicyclo[1.1.1]pentan-1-ylmethyl)isoxazol-5-yl)acetamide		431.2	1, b, I & III
214	2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)-N-(3-neopentylisoxazol-5-yl)acetamide		433.2	1, c, III
215	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[5-(2-methylbutan-2-yl)-1,2-oxazol-3-yl]acetamide		421.2	1, c, IV
216	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[3-(3,5-dichloropyridin-2-yl)-1,2-oxazol-5-yl]acetamide		496.1	1, c, IV
217	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[5-(2,2-dimethylpropyl)-1,2-thiazol-3-yl]acetamide		437.1	2, a, II
219	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[5-(2,2-dimethylpropyl)-1,3-thiazol-2-yl]acetamide		437.1	1, c, IV

219	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[5-(2,2-dimethylpropyl)-4-methyl-1,3-thiazol-2-yl]acetamide		451.1	2, a, II
220	2-[4-[5-Amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide		489.3	1, c, IV
221	2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]phenyl]-N-[3-(3,3-dimethylcyclobutyl)-1,2-oxazol-5-yl]acetamide		445.4	1, c, IV
222	2-(4-(5-amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)-N-(5-neopentylisoxazol-3-yl)acetamide		433.2	1, c, IV
223	2-[4-[5-Amino-4-cyano-1-(1-methoxy-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide		487.2 M+Na	1, c, IV
224	2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]phenyl]-N-[3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)-1,2-oxazol-5-yl]acetamide		497.3	1, c, IV

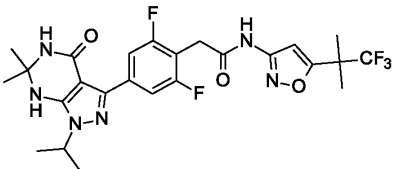
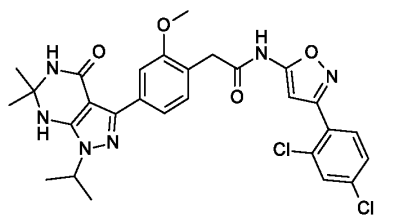
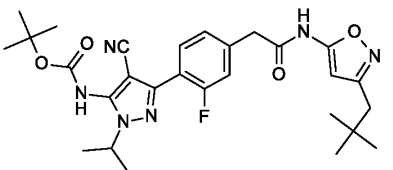
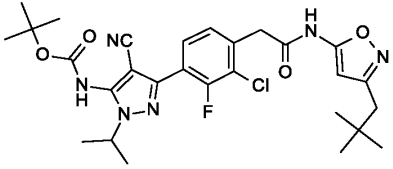
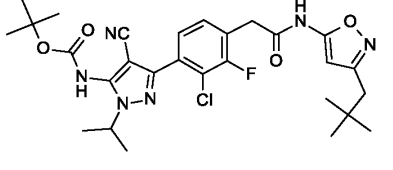
225	2-[4-[5-Amino-4-cyano-1-(1,1,1-trifluoropropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]acetamide		539.2	1, c, IV
226	2-(4-(5-Amino-4-cyano-1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)phenyl)-N-(3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)acetamide		525.2	1, c, IV
227	2-[4-(5-amino-4-cyano-1-cyclobutylpyrazol-3-yl)phenyl]-N-[3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]acetamide		497.2	1, c, IV
228	2-[4-[5-Amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		499.2	1, c, IV
229	2-[4-(5-Amino-1-tert-butyl-4-cyanopyrazol-3-yl)phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		445.3	1, c, IV
230	2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		525.2	1, c, IV

231	2-[4-[5-Amino-4-cyano-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl]phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		581.1	1, c, IV
232	2-[4-(5-Amino-1- <i>tert</i> -butyl-4-cyanopyrazol-3-yl)phenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		527.3	1, c, IV
233	2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-3-fluorophenyl)-N-(3-(3-methylbicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)acetamide		461.1	1, c, IV
234	2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-3-fluorophenyl)-N-(3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)acetamide		515.1	1, c, IV
235	2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-[3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]acetamide		533.2	1, c, IV

236	2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		561.1	1, c, IV
237	2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)-3-fluorophenyl)-N-(3-(4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl)isoxazol-5-yl)acetamide		543.1	1, c, IV
238	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)-2,3-difluorophenyl]-N-[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]acetamide		549.3	1, c, IV
239	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)-2,3-difluorophenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		467.2	1, c, IV
240	2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]phenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide		443.2	1, c, IV

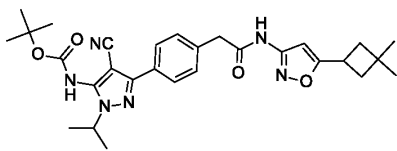
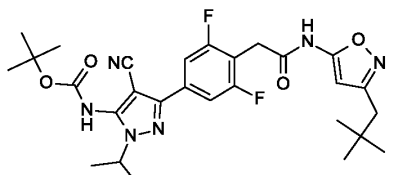
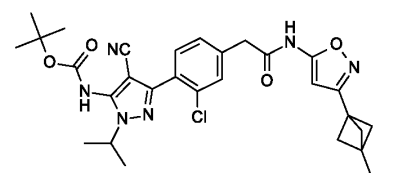
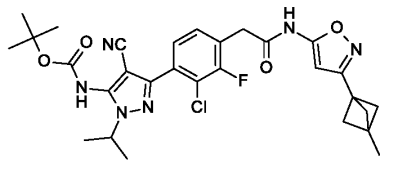
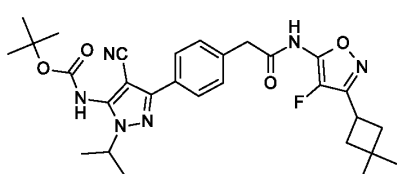
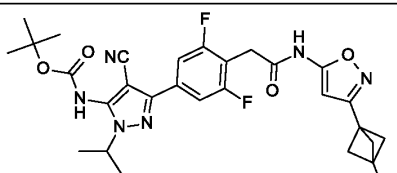
241	2-(4-(5-Amino-4-cyano-1-isopropyl-1H-pyrazol-3-yl)phenyl)-N-(3-(1,1-difluoroethyl)isoxazol-5-yl)acetamide		415.2	1, c, IV
242	2-[4-(5-Amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]acetamide		421.1	1, c, IV
243	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		518	1, b, V
244	<i>tert</i> -Butyl N-[4-cyano-2-isopropyl-5-[4-[2-oxo-2-[(3-spiro[2.2]pentan-2-yl)isoxazol-5-yl]amino]ethyl]phenyl]pyrazol-3-yl]carbamate		517	1, b, V
245	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-difluorocyclopropyl)methyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		541	1, b, V
246	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-difluorocyclopentyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		555	1, b, V

247	<i>tert</i> -Butyl N-[4-cyano-2-isopropyl-5-[4-[2-oxo-2-[(3-spiro[2.3]hexan-2-ylisoxazol-5-yl)amino]ethyl]phenyl]pyrazol-3-yl]carbamate		531.5	1, b, V
248	<i>tert</i> -Butyl N-[4-cyano-2-isopropyl-5-[4-[2-oxo-2-[(5-spiro[2.3]hexan-2-ylisoxazol-3-yl)amino]ethyl]phenyl]pyrazol-3-yl]carbamate		531	1, b, V
249	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[5-(2,2-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		533	1, b, V
250	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		533.5	1, b, V
251	2-[4-(1-Isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)phenyl]-N-[5-[1-(trifluoromethyl)cyclopropyl]isoxazol-3-yl]acetamide		517.4	1, c, III
252	2-[4-(1-Isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxy-phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide		520	1, c, III

253	2-[2,6-Difluoro-4-(1-isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)phenyl]-N-[5-(2,2,2-trifluoro-1,1-dimethylethyl)isoxazol-3-yl]acetamide		555	1, c, III
254	N-[3-(2,4-Dichlorophenyl)isoxazol-1-5-yl]-2-[4-(1-isopropyl-6,6-dimethyl-4-oxo-5,7-dihydropyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]acetamide		583	1, c, III
255	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-2-fluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		539	1, b, V
256	<i>tert</i> -Butyl N-[5-[3-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-2-fluoro-phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		573.4	1, b, V
257	<i>tert</i> -Butyl N-[5-[2-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-3-fluoro-phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		573.4	1, b, V

258	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-2-methylphenyl]-2-isopropylpyrazol-3-yl]carbamate		535.5	1, c, III
259	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(cyclobutylmethyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropylpyrazol-3-yl]carbamate		519.4	1, c, III
260	<i>tert</i> -Butyl N-[5-[2-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-4-cyano-2-isopropylpyrazol-3-yl]carbamate		555.4	1, c, III
261	<i>tert</i> -Butyl N-[4-cyano-2-isopropyl-5-[4-[2-[[3-[(1-methylcyclobutyl)methyl]isoxazol-5-yl]amino]-2-oxoethyl]phenyl]pyrazol-3-yl]carbamate		533.5	1, b, V
262	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-difluoro-1-methylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropylpyrazol-3-yl]carbamate		555	1, b, V
263	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]-2-fluorophenyl]-2-isopropylpyrazol-3-yl]carbamate		551.5	1, b, V

264	<i>tert</i> -Butyl N-[5-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		567.4	1, b, V
265	<i>tert</i> -Butyl N-[5-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]-3-fluoro-phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		585.4	1, b, V
266	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(1,1-difluoro-2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		557.4	1, b, V
267	<i>tert</i> -Butyl N-[4-cyano-5-[2-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		549.5	1, b, V
268	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxoethyl]-2,3-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		569.4	1, b, V
269	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-2,5-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		557	1, b, V

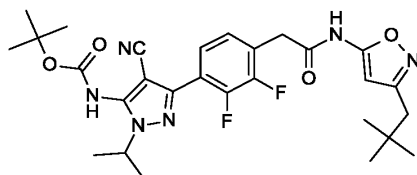
270	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		533	1, b, V
271	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]-3,5-difluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		557	1, b, V
272	<i>tert</i> -Butyl N-[5-[2-chloro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		565	1, b, V
273	<i>tert</i> -Butyl N-[5-[2-chloro-3-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-4-cyano-2-isopropyl-pyrazol-3-yl]carbamate		583	1, b, V
274	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)-4-fluoro-isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		551.4	1, b, V
275	<i>tert</i> -Butyl N-[4-cyano-5-[3,5-difluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		567	1, b, V

-123-

	isopropyl-pyrazol-3-yl]carbamate			
276	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)-4-fluoro-isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		539	1, b, V
277	<i>tert</i> -Butyl N-[4-cyano-5-[4-[2-[[4-fluoro-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		549	1, b, V

Preparation 278

tert-Butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate

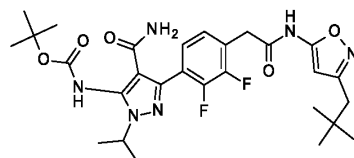


- 5 3-(2,2-Dimethylpropyl)-1,2-oxazol-5-amine (58 mg, 0.376 mmol), 2-[4-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]-2,3-difluoro-phenyl]acetic acid (0.100 g, 0.238 mmol) and DIPEA (98 μ L, 0.563 mmol) are added together in DMF (0.69 mL) under N₂. T3P® (0.454 g, 0.713 mmol, 50% in MeTHF) is added and the reaction is stirred at RT overnight. The mixture is quenched with saturated aq. NH₄Cl and the aqueous
- 10 layer is extracted with EtOAc (3x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 10% to 50% EtOAc in cyclohexane to give the title compound (45 mg, 95% purity, 32%) as a white solid. ES/MS (m/z) 557 (M+H).

-124-

Preparation 279

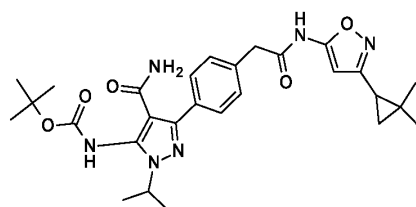
tert-Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate



5 To *tert*-butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate (75 mg, 0.135 mmol) and Parkins catalyst (5.8 mg, 0.0135 mmol) under N₂ is added a mixture of *tert*-BuOH (1.8 mL) and H₂O (0.9 mL). The mixture is heated to 65 °C for 16 hr. The reaction mixture is cooled to RT and diluted with EtOAc. The organic layer is washed with brine, dried over
10 Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by silica gel chromatography, eluting with a gradient of 1% to 10% DCM in MeOH to give the title compound (48 mg, 62%) as a white solid. ES/MS (m/z) 597 (M+Na).

Preparation 280

15 *tert*-Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate

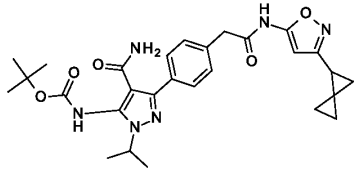
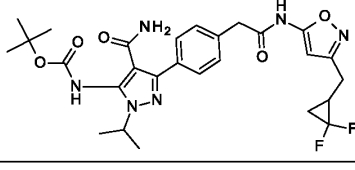
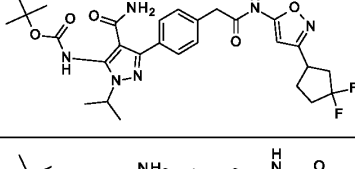
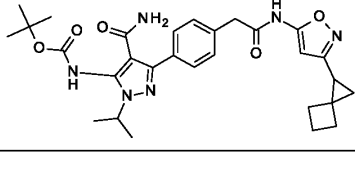
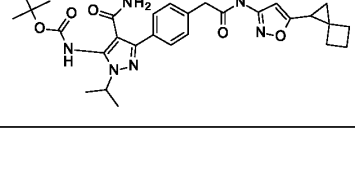


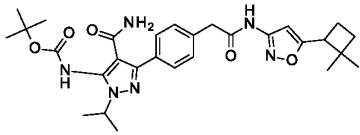
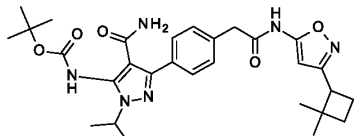
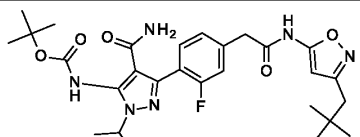
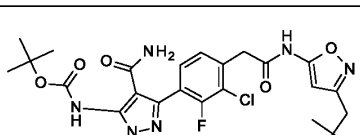
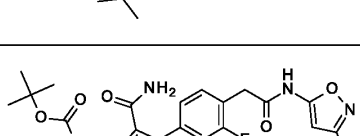
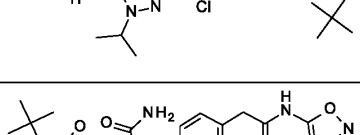
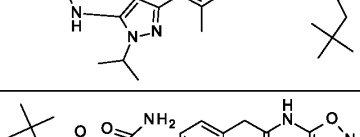
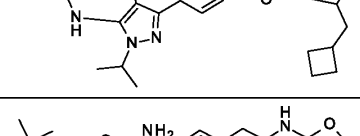
To a stirred solution of *tert*-butyl N-[4-cyano-5-[4-[2-[[3-(2,2-dimethylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate (0.365 g, 0.704 mmol) in *tert*-BuOH (10 mL) and H₂O (5 mL) under N₂ is added Parkins catalyst (15 mg, 0.0352 mmol). The reaction mixture is stirred at 60 °C for 4
20 hr. The reaction mixture is quenched with saturated aq. NH₄Cl. The aqueous layer is extracted with EtOAc (3x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The material is purified by silica

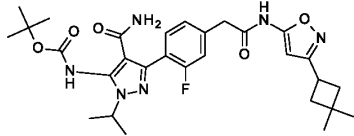
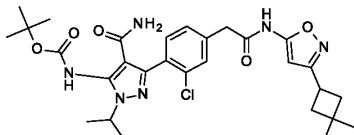
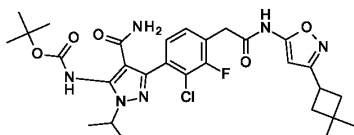
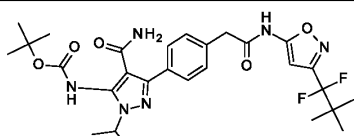
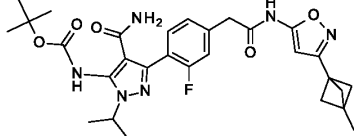
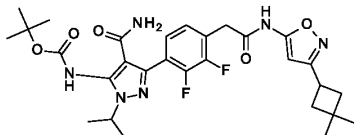
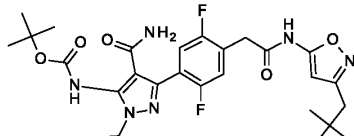
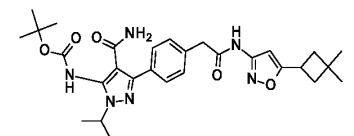
gel chromatography, eluting with a gradient of 30% to 80% EtOAc in cyclohexane to give the title compound (0.363 g, 96%) as a white solid. ES/MS (m/z) 559.4 (M+Na).

The following compounds in Table 23 are prepared essentially as described for *tert*-butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate adjusting reaction time to determine completion of the reaction, using *t*-BuOH or 4:1 EtOH:H₂O as solvent, and using appropriate chromatography conditions for purification. Temperature can range from about 60-70 °C.

Table 23

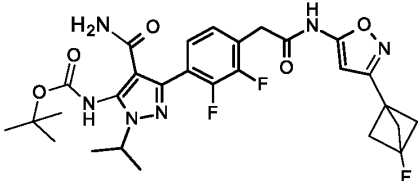
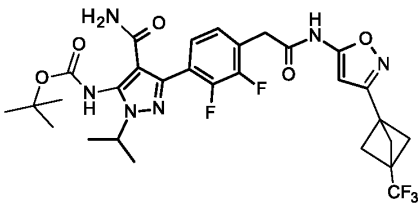
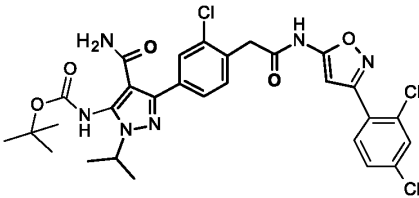
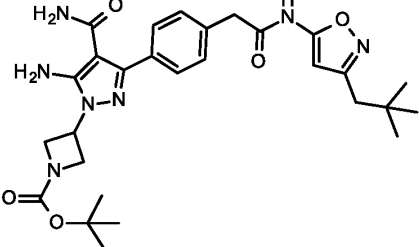
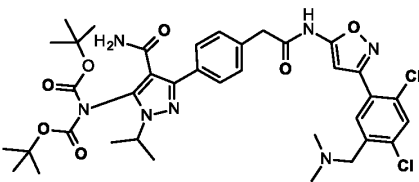
Prep. No.	Chemical name	Structure	ES/MS m/z (M+H)
281	<i>tert</i> -Butyl N-[4-carbamoyl-2-isopropyl-5-[4-[2-oxo-2-[(3-spiro[2.2]pentan-2-ylisoxazol-5-yl)amino]ethyl]phenyl]pyrazol-3-yl]carbamate		535
282	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-[(2,2-difluorocyclopropyl)methyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		581 M+Na
283	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(3,3-difluorocyclopentyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		595.4 M+Na
284	<i>tert</i> -Butyl N-[4-carbamoyl-2-isopropyl-5-[4-[2-oxo-2-[(3-spiro[2.3]hexan-2-ylisoxazol-5-yl)amino]ethyl]phenyl]pyrazol-3-yl]carbamate		549.4
285	<i>tert</i> -Butyl N-[4-carbamoyl-2-isopropyl-5-[4-[2-oxo-2-[(5-spiro[2.3]hexan-2-ylisoxazol-3-yl)amino]ethyl]phenyl]pyrazol-3-yl]carbamate		549

286	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[5-(2,2-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		551
287	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		551.4
288	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		557.5
289	<i>tert</i> -Butyl N-[4-carbamoyl-5-[3-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		613.4 M+Na
290	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-fluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		613.4 M+Na
291	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-methylphenyl]-2-isopropyl-pyrazol-3-yl]carbamate		575.4 M+Na
292	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(cyclobutylmethyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		559.4 M+Na
293	<i>tert</i> -Butyl N-[4-carbamoyl-2-isopropyl-5-[4-[2-[[3-[(1-methylcyclobutyl)methyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]pyrazol-3-yl]carbamate		573, M+Na

294	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		591.4 M+Na
295	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		607.4 M+Na
296	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-fluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		625.4 M+Na
297	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(1,1-difluoro-2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		575.4
298	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		589.4 M+Na
299	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		609.4, M+Na
300	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,5-difluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		575
301	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[5-(3,3-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		551

302	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3,5-difluorophenyl]-2-isopropyl-pyrazol-3-yl]carbamate		597 M+Na
303	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-chloro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		605 M+Na
304	<i>tert</i> -Butyl N-[4-carbamoyl-5-[2-chloro-3-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		623 M+Na
305	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(3,3-dimethylcyclobutyl)-4-fluoro-isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		569.5
306	<i>tert</i> -Butyl N-[4-carbamoyl-5-[3,5-difluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		607 M+Na
307	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)-4-fluoro-isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		557
308	<i>tert</i> -Butyl N-[4-carbamoyl-5-[4-[2-[[4-fluoro-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-2-isopropyl-pyrazol-3-yl]carbamate		589 M+Na

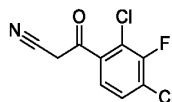
-129-

309	<i>tert</i> -Butyl (4-carbamoyl-3-(2,3-difluoro-4-(2-((3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazol-5-yl)carbamate		589.4
310	<i>tert</i> -Butyl (4-carbamoyl-3-(2,3-difluoro-4-(2-oxo-2-((3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1-isopropyl-1H-pyrazol-5-yl)carbamate		639.4
311	<i>tert</i> -Butyl N-[4-carbamoyl-5-[3-chloro-4-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropylpyrazol-3-yl]carbamate		649.1
312	<i>tert</i> -Butyl 3-(5-amino-4-carbamoyl-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazol-1-yl)azetidine-1-carboxylate		552.3
313	<i>tert</i> -Butyl N- <i>tert</i> -butoxycarbonyl-N-[4-carbamoyl-5-[4-[2-[[3-[2,4-dichloro-5-[(dimethylamino)methyl]phenyl]isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-2-isopropylpyrazol-3-yl]carbamate		771.7

Preparation 314

3-(2,4-Dichloro-3-fluoro-phenyl)-3-oxo-propanenitrile

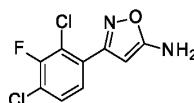
-130-



To a stirred solution of LDA (1.35 mL, 2.69 mmol) in THF (4 mL) is added ACN (0.13 mL, 2.47 mmol) dropwise at -78°C under N₂. The reaction is stirred 1 hr at -78 °C then a solution of methyl 2,4-dichloro-3-fluorobenzoate in THF is added dropwise. Once the addition is complete the reaction is stirred at RT for 2 hr. The reaction is quenched with saturated aq. NH₄Cl. The pH is adjusted to pH 5 with HCl (1N) then extracted with EtOAc. The organic layer is washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford the title compound (0.83 g). This crude material is used without further purification in the preparation of 3-(2,4-dichloro-3-fluoro-phenyl)isoxazol-5-amine.

Preparation 315

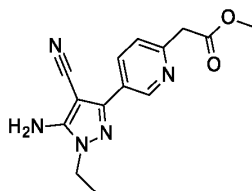
3-(2,4-Dichloro-3-fluoro-phenyl)isoxazol-5-amine



A solution of 3-(2,4-dichloro-3-fluoro-phenyl)-3-oxo-propanenitrile (0.27 g, 1.15 mmol) in EtOH (3.7 mL) and H₂O (3.7 mL) is treated with hydroxyamine HCl (0.40 g, 5.74 mmol) and KOAc (0.68 g, 6.89 mmol). The mixture is stirred at 60 °C for 1 hr. The reaction is extracted with EtOAc and the organic layer is concentrated in vacuo. The residue is purified by normal phase silica gel chromatography, eluting with 0% to 100% EtOAc in hexanes followed by 0% to 20% MeOH in EtOAc to afford the title compound (0.18 g, 65%). ES/MS (m/z) 247.0 (M+H).

Preparation 316

2-[5-(5-amino-4-cyano-1-ethyl-pyrazol-3-yl)-2-pyridyl]acetate

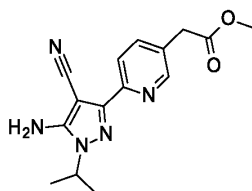


-131-

A mixture of 5-amino-3-bromo-1-ethyl-pyrazole-4-carbonitrile (233.58 mg, 1.09 mmol), K₂CO₃ (299.78 mg, 2.17mmol) , Pd(dppf)Cl₂ (79.48 mg, 0.11 mmol), and methyl 2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]acetate (301 mg, 1.09 mmol) in a reaction vial with 1,4-dioxane (9.05 mL) and H₂O (1.81mL) is sparged with nitrogen and heated to 80°C for 90 min. The reaction is partitioned between DCM and H₂O and extracted through a phase separator with DCM (3x). Organic are combined and concentrated in vacuo. The residue is purified by silica chromatography eluting with 0% to 100% EtOAc in hexanes to give the title compound (172 mg, 55.5%). ES/MS (m/z) 286.1 (M+H).

Preparation 317

10 Methyl 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]acetate



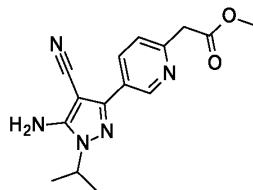
Methyl 2-(6-chloropyridin-3-yl)acetate (2.00 g, 10.78 mmol), hexabutylstannane (9.38 g, 16.16 mmol), and Pd(PPh₃)₄ (7.47 g, 6.46 mmol) are combined in 1,4-dioxane (40 mL) under N₂ and the reaction is stirred for three days at 65 °C.

15 5-amino-3-bromo-1-isopropylpyrazole-4-carbonitrile (0.75 g, 3.30 mmol) is added to a portion (25%) of the above reaction mixture under N₂ and the reaction is stirred for 12 hr at 75 °C. The solvent is removed under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 2:1 to 1:1 PE:EtOAc to afford crude product. The product is further purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 20% to 50% ACN in H₂O (0.1% FA) to give the title compound (0.12 g, 15%) as a yellow solid. ES/MS (m/z) 300.2 (M+H).

Preparation 318

20 Methyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetate

-132-

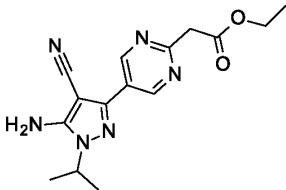
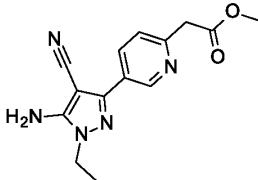


Methyl 2-(5-bromopyridin-2-yl)acetate (1.00 g, 4.35 mmol), bis(pinacolato)diboron (1.33 g, 5.22 mmol), KOAc (0.85 g, 8.70 mmol), Pd(dppf)Cl₂ (0.32 g, 0.43 mmol) and 1,4-dioxane (30 mL) are added together. The reaction mixture is stirred under N₂ at 100 °C for 2
5 hr. The reaction is filtered, and the filtrate is concentrated under vacuum to give an intermediate residue.

The residue, 5-amino-3-bromo-1-isopropylpyrazole-4-carbonitrile (0.99 g, 4.33 mmol), potassium carbonate (1.19 g, 8.60 mmol), Pd(dppf)Cl₂ (0.32 g, 0.43 mmol), 1,4-dioxane (30 mL), and H₂O (7 mL) are added together. The reaction mixture is stirred under
10 N₂ at 100 °C for 2 hr. The reaction is diluted with H₂O (50 mL) is extracted with EtOAc (3x100 mL). The combined organic extracts are washed with brine (2x100 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue is purified by silica gel chromatography, eluting with a gradient of 6:1 to 2:1 PE:EtOAc to give the title compound (0.65 g, 50%) as a yellow solid. ES/MS (m/z) 300.1 (M+H).

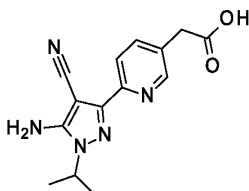
15 The following compounds in Table 24 are prepared essentially as described for methyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetate and adjusting reaction time to determine completion of the reaction.

Table 24

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
319	Ethyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrimidin-2-yl]acetate		315.2
320	Methyl 2-[5-(5-amino-4-cyano-1-ethyl-pyrazol-3-yl)-2-pyridyl]acetate		286.1

Preparation 321

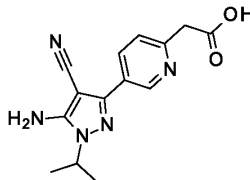
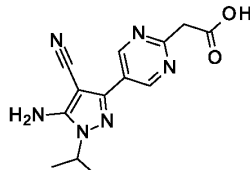
5 2-[6-(5-Amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]acetic acid



To methyl 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]acetate (0.10 g, 0.33 mmol) in methanol (2 mL) and H₂O (2 mL) is added LiOH (0.024 g, 1.00 mmol). The mixture is stirred at 60 °C for 2 hr. The reaction mixture is acidified with 1 M aq. HCl to pH 5 then extracted with EtOAc (2x30 mL). The combined organic extracts are washed with brine (2x20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 5% to 60% ACN in H₂O (0.1% FA) to give the title compound (0.080 g, 80%) as a yellow solid. ES/MS (m/z) 286.4 (M+H).

The following compounds in Table 25 are prepared essentially as described for 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]acetic acid and adjusting reaction time to determine completion of the reaction.

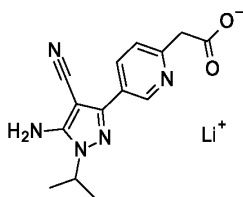
Table 25

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
322	2-[5-(5-Amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetic acid		286.1
323	2-[5-(5-Amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrimidin-2-yl]acetic acid		287.1

5

Preparation 324

Lithium 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetate



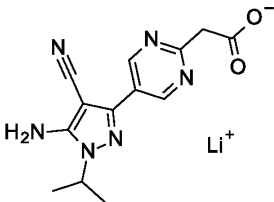
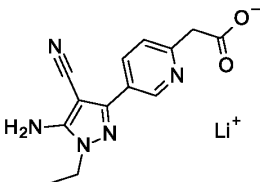
To methyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetate (2.40 g, 8.00 mmol) in THF (20 mL) and H₂O (4 mL) is added LiOH (0.17 g, 7.20 mmol). The mixture is stirred at RT for 2 hr. The reaction mixture is diluted with H₂O (20 mL) then washed with EtOAc (3x50 mL). The aqueous layer is concentrated under reduced pressure to give the title compound (1.50 g, 65%) as a yellow solid. ES/MS (m/z) 286.1 (M+H).

10

-135-

The following compounds in Table 26 are prepared essentially as described for lithium 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-2-pyridyl]acetate and adjusting reaction time to determine completion of the reaction.

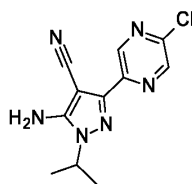
Table 26

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
325	Lithium 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrimidin-2-yl]acetate		287.1
326	Lithium 2-[5-(5-amino-4-cyano-1-ethyl-pyrazol-3-yl)-2-pyridyl]acetate		272.0

5

Preparation 327

5-Amino-3-(5-chloropyrazin-2-yl)-1-isopropyl-pyrazole-4-carbonitrile



To a stirred solution of 5-chloropyrazine-2-carbaldehyde (0.30 g, 2.11 mmol) and isopropylhydrazinehydrochloride (0.26 g, 2.32 mmol) in DMF (4 mL) is added DIPEA (0.30 g, 2.32 mmol) in portions at RT under N₂. The mixture is stirred for 1 hr at 80 °C then is cooled to RT. To the mixture is added a solution of N-bromosuccinimide (0.41 g, 2.32 mmol) in DMF (4 mL) in portions over 5 min. The mixture is stirred for 2 hr at RT.

10

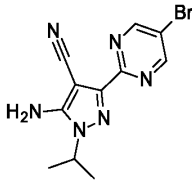
-136-

At the same time, to a stirred solution of malonitrile (0.15 g, 2.32 mmol) in EtOH (2 mL) is added sodium ethoxide (0.39 g, 5.80 mmol) at 0 °C under N₂. The mixture is stirred for 30 min at RT.

To the second mixture at 0 °C under N₂ is added the first mixture dropwise over 30 min. The reaction is stirred for 2 hr at 80 °C. The mixture is diluted with EtOAc and washed with H₂O. The organic layer is concentrated under vacuum. The residue is purified by silica gel chromatography, eluting with a gradient of 3:1 to 2:1 PE:EtOAc to give the title compound (0.26 g, 47%) as a white solid. ¹H NMR(d₆-DMSO, 300 MHz) δ (ppm) 8.88 (d, 1H), 8.82 (d, 1H), 6.80 (s, 2H), 4.56 (m, 1H), 1.37 (d, 6H).

The following compounds in Table 27 are prepared essentially as described for 5-amino-3-(5-chloropyrazin-2-yl)-1-isopropyl-pyrazole-4-carbonitrile and adjusting reaction time to determine completion of the reaction.

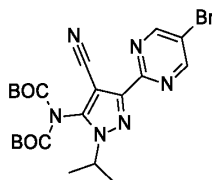
Table 27

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
328	5-Amino-3-(5-bromopyrimidin-2-yl)-1-isopropyl-pyrazole-4-carbonitrile		307.1 309.1

15

Preparation 329

tert-Butyl N-[5-(5-bromopyrimidin-2-yl)-4-cyano-2-isopropyl-pyrazol-3-yl]-N-*tert*-butoxycarbonyl-carbamate

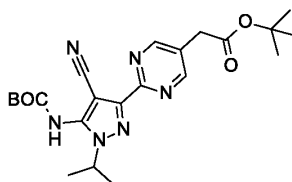


-137-

A mixture of 5-amino-3-(5-bromopyrimidin-2-yl)-1-isopropyl-pyrazole-4-carbonitrile (0.35 g, 1.14 mmol), di-*tert*-butyl dicarbonate (0.50 g, 2.28 mmol), and DMAP (0.029 g, 0.23 mmol) in THF (10 mL) is stirred for 4 hr at RT. The mixture is concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 10:1 to 1:1 PE:EtOAc to give the title compound (0.40 g, 69%) as a yellow solid. ES/MS (m/z) 507.0, 509.1 (M+H).

Preparation 330

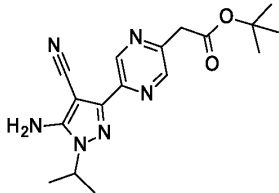
tert-Butyl 2-[2-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]pyrimidin-5-yl]acetate



A solution of *tert*-butyl N-[5-(5-bromopyrimidin-2-yl)-4-cyano-2-isopropyl-pyrazol-3-yl]-N-*tert*-butoxycarbonyl-carbamate (0.39 g, 0.77 mmol), *tert*-butyl 2-(bromozincio)acetate (0.40 g, 1.54 mmol) and Pd(*t*-Bu₃P)₂ (0.079 g, 0.15 mmol) in THF (20 mL) is stirred for 4 hr at 80 °C under N₂ and allowed to cool to RT. The solution is concentrated under reduced pressure and the residue is purified by silica gel chromatography, eluting with EtOAc to afford crude product. The product is further purified by reversed-phase chromatography (C18 column), eluting with a gradient of 30% to 50% ACN in H₂O (0.1% FA) to give the title compound (0.24 g, 71%) as a yellow solid. ES/MS (m/z) 443.2 (M+H).

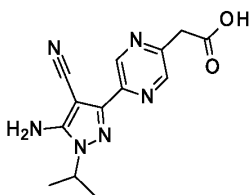
The following compounds in Table 28 are prepared essentially as described for *tert*-butyl 2-[2-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]pyrimidin-5-yl]acetate and adjusting reaction time to determine completion of the reaction.

Table 28

Prep No.	Chemical Name	Structure	ES/MS m/z (M+H)
331	<i>tert</i> -Butyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrazin-2-yl]acetate		343.3

Preparation 332

5 2-[5-(5-Amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrazin-2-yl]acetic acid

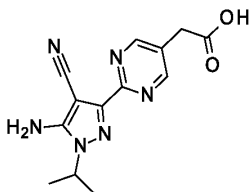


To *tert*-butyl 2-[5-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrazin-2-yl]acetate (0.26 g, 0.76 mmol) is added TFA (10 mL). The mixture is stirred for 30 min at RT and concentrated under reduced pressure to give the title compound as a yellow solid (0.20 g, 91%) which is used without further purification.

10

Preparation 333

2-[2-(5-Amino-4-cyano-1-isopropyl-pyrazol-3-yl)pyrimidin-5-yl]acetic acid



-139-

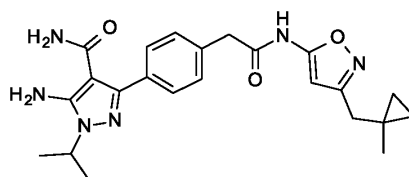
To *tert*-butyl 2-[2-[5-(*tert*-butoxycarbonylamino)-4-cyano-1-isopropyl-pyrazol-3-yl]pyrimidin-5-yl]acetate (0.22 g, 0.50 mmol) is added 4M HCl in 1,4-dioxane (10 mL). The mixture is stirred for 1 hr at RT and concentrated under reduced pressure. The reaction is adjusted to pH 6 with saturated aqueous NaHCO₃, then extracted with EtOAc (3x50 mL).

- 5 The combined organic extracts are concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 30% to 40% ACN in H₂O (0.1% FA) to give the title compound (0.075 g, 53%) as a yellow solid. ES/MS (m/z) 287.1 (M+H).

10

Example 1

5-Amino-1-isopropyl-3-(4-(2-((3-((1-methylcyclopropyl)methyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide

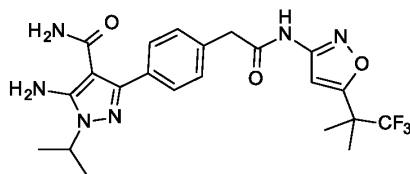


- 3-[(1-Methylcyclopropyl)methyl]isoxazol-5-amine (62 mg, 0.407 mmol) and 2-(4-(5-
15 amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.10 g, 0.331 mmol) are combined in EtOAc (0.38 mL), pyridine (0.64 mL) and ACN (0.64 mL). The mixture is stirred for 5 min and a cloudy suspension is observed. The mixture is cooled to -20 °C and T3P[®] (0.58 mL, 0.99 mmol, 50% in DMF) is added dropwise. The solution is stirred at -20 °C for 45 min. The mixture is diluted with H₂O (50 mL) and extracted with EtOAc (2x50
20 mL). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 10% to 100% EtOAc in hexanes to give the title compound (28 mg, 19%). ES/MS (m/z) 437.2 (M+H).

Example 2

- 25 5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide

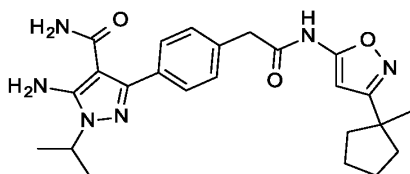
-140-



5-(2,2,2-Trifluoro-1,1-dimethyl-ethyl)isoxazol-3-amine (0.394 g, 2.03 mmol) and 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.500 g, 1.65 mmol) are combined in ACN (20 mL), EtOAc (16 mL) and pyridine (2 mL). The mixture is stirred for 2 min until a clear and colorless solution results. The solution is cooled to -20 °C and T3P® (1.89 mL, 3.23 mmol, 50% in DMF) is added dropwise. The solution is stirred at -20 °C for 30 min. The reaction is diluted with H₂O (8 mL) and extracted with EtOAc (2x10 mL). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 0% to 100% EtOAc in hexanes followed by 0% to 10% MeOH (with 0.1% NH₄OH) in EtOAc to give the title compound (0.363 g, 46%). ES/MS (m/z) 478.8 (M+H).

Example 3

5-Amino-1-isopropyl-3-(4-(2-((3-(1-methylcyclopentyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide



15

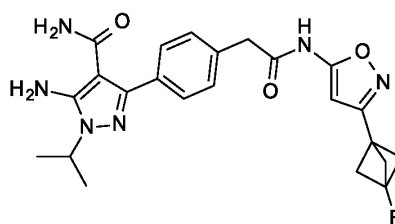
To a mixture of 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (20 mg, 0.066 mmol), 3-(1-methylcyclopentyl)isoxazol-5-amine (11 mg, 0.066 mmol) and [[(E)-(1-cyano-2-ethoxy-2-oxo-ethylidene)amino]oxy-morpholino-methylene]-dimethyl-ammonium hexafluorophosphate (34 mg, 0.079 mmol) in DMF (3 mL) is added DIPEA (0.034 mL, 0.195 mmol) and the mixture is stirred at RT for 6 hr. The mixture is diluted with H₂O (20 mL) and extracted with EtOAc (2x20 mL). The combined organic extracts are washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography,

-141-

eluting with a gradient of 0% to 100% EtOAc in hexanes to give the title compound (3.4 mg, 11%). ES/MS (m/z) 451.2 (M+H).

Example 4

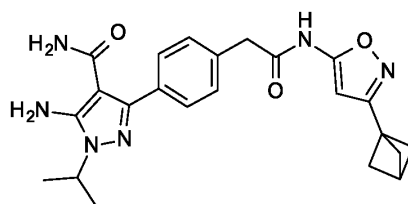
5-Amino-3-(4-(2-((3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide



2-(4-(5-Amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.100 g, 0.331 mmol), 3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine (61 mg, 0.363 mmol), T3P® (0.28 mL, 0.470 mmol, 50% in EtOAc) and DIPEA (0.17 mL, 0.976 mmol) are added together in DCM (5 mL) in a sealed tube and stirred for 10 hr at RT under N₂. The mixture is concentrated under reduced pressure and the residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 20% to 50% ACN in H₂O (0.1% NH₄HCO₃), to give the title compound (67 mg, 45%) as a white solid. ES/MS (m/z) 453.1 (M+H).

Example 5

5-Amino-3-(4-(((3-[bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)carbamoyl)methyl)phenyl)-1-isopropylpyrazole-4-carboxamide



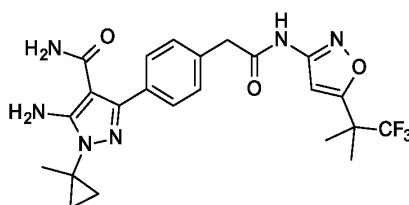
2-(4-(5-Amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.100 g, 0.331 mmol), 3-[bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-amine (60 mg, 0.400 mmol) and DIPEA (0.17 mL, 0.976 mmol) are added together in DCM (10 mL). T3P® (0.30 mL, 0.504

-142-

mmol, 50% in EtOAc) is added and the mixture is stirred for 2 hr at RT under N₂. The solution is concentrated under reduced pressure and re-dissolved in ACN (5 mL). The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 20% to 60% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (24 mg, 17%) as white solid. ES/MS (m/z) 435.3 (M+H).

Example 6

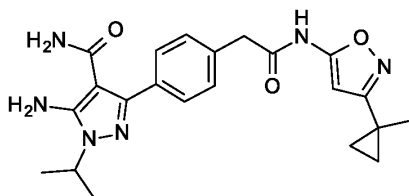
5-Amino-1-(1-methylcyclopropyl)-3-[4-([5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide



To a stirred mixture of 2-(4-(5-Amino-4-carbamoyl-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)acetic acid (70 mg, 0.223 mmol) and NMI (55 mg, 0.670 mmol) in ACN (5 mL) is added 5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-3-amine (65 mg, 0.335 mmol) and TCFH (94 mg, 0.335 mmol) in portions at RT under N₂. The mixture is stirred for 2 hr at 50 °C under N₂. The mixture is cooled to RT and concentrated under reduced pressure to a residue. The residue is purified by preparative TLC, eluting with 100% EtOAc and further purified by reversed-phase chromatography (C18 column), eluting with a gradient of 40% to 50% ACN in H₂O to give the title compound (20 mg, 18%) as a white solid. ES/MS (m/z) 491.2 (M+H).

Example 7

5-Amino-1-isopropyl-3-[4-([3-(1-methylcyclopropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide

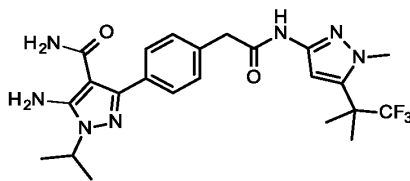


-143-

To a stirred mixture of 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.300 g, 0.992 mmol) and 3-(1-methylcyclopropyl)-1,2-oxazol-5-amine (0.151 g, 1.09 mmol) in DCM (10 mL) is added DIPEA (0.26 mL, 1.49 mmol) and T3P® (0.71 mL, 1.19 mmol, 50% in EtOAc) in portions at RT under N₂. The mixture is stirred for 3 hr at RT under N₂ and concentrated to dryness. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 30% to 40% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (69 mg, 16%) as a white solid. ES/MS (m/z) 423.3 (M+H).

Example 8

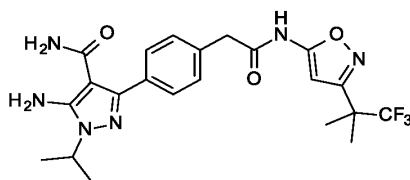
5-Amino-3-[4-([1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-yl]carbamoyl)methyl]phenyl]-1-(propan-2-yl)-1H-pyrazole-4-carboxamide



A solution of 1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-amine (35 mg, 0.169 mmol), 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (56 mg, 0.185 mmol), HATU (96 mg, 0.252 mmol) and DIPEA (0.088 mL, 0.505 mmol) in DMF (2 mL) is stirred for 2 hr at RT under N₂. The mixture is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 50% to 70% ACN in H₂O (0.1% FA) to give the title compound (28 mg, 34%) as a white solid. ES/MS (m/z) 492.3 (M+H).

Example 9

5-Amino-1-isopropyl-3-[4-([3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide

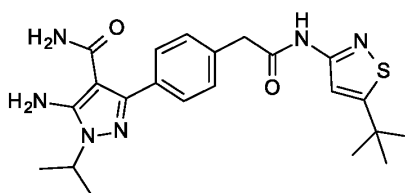


-144-

A solution of 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.150 g, 0.496 mmol), 3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-amine (0.106 g, 0.546 mmol), DIPEA (0.35 mL, 2.01 mmol) and T3P[®] (0.59 mL, 0.991 mmol, 50% in EtOAc) in DCM (5 mL) is stirred for 2 hr at RT under N₂. The mixture is concentrated and the residue is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 30% to 50% ACN in H₂O (0.1% FA). The product is further purified by reversed-phase preparative HPLC (Phenomenex Gemini C6-Phenyl column), eluting with a gradient of 37% to 45% ACN in H₂O (0.05% FA) to give the title compound (81 mg, 34%) as a white solid. ES/MS (m/z) 479.3 (M+H).

Example 10

5-Amino-3-(4-(2-((5-(*tert*-butyl)isothiazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide

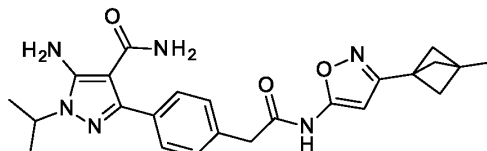


5-*tert*-Butylisothiazol-3-amine (47 mg, 0.301 mmol) and 2-[4-(5-amino-4-carbamoyl-1-isopropyl-pyrazol-3-yl)phenyl]acetic acid (60 mg, 0.198 mmol) are combined in ACN (1.05 mL), EtOAc (0.65 mL) and pyridine (0.31 mL). The mixture is stirred for 2 min until a clear and colorless solution results. The solution is cooled to -20 °C and T3P[®] (0.26 mL, 0.437 mmol, 50% in EtOAc) is added dropwise. The solution is stirred at -20 °C for 30 mins. The reaction is diluted with H₂O (8 mL) and extracted with DCM (2x10 mL). The combined organic extracts are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 0% to 100% EtOAc in hexanes followed by 0% to 20% MeOH (with 1% NH₄OH) in EtOAc to give the title compound (21 mg, 24%) as a pale yellow solid. ES/MS (m/z) 441.2 (M+H).

Example 11

-145-

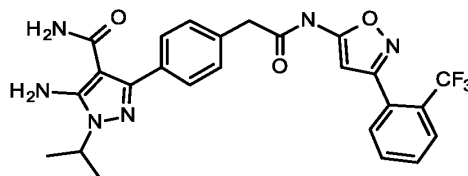
5-Amino-1-isopropyl-3-(4-[[3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)pyrazole-4-carboxamide



To a stirred mixture of 2-(4-(5-amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (0.300 g, 0.992 mmol) and 3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-amine (0.163 g, 0.993 mmol) in DCM (20 mL) is added DIPEA (0.52 mL, 2.99 mmol) and T3P® (0.89 mL, 1.50 mmol, 50% in EtOAc) at RT. The mixture is stirred for 1 hr at 50 °C under N₂ in a sealed tube. The mixture is concentrated under reduced pressure and purified by reversed-phase chromatography (C18 column), eluting with a gradient of 30% to 40% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (90 mg, 20%) as a white solid. ES/MS (m/z) 449.2 (M+H).

Example 12

5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(2-(trifluoromethyl)phenyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide



15

2-(4-(5-Amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (75 mg, 0.248 mmol) and 3-[2-(trifluoromethyl)phenyl]isoxazol-5-amine (53 mg, 0.232 mmol) in EtOAc (0.14 mL) and ACN (0.14 mL) is treated with pyridine (0.14 mL) and T3P® (0.28 mL, 0.470 mmol, 50% in EtOAc). The mixture is stirred at 0 °C for 20 min under N₂, then partitioned between H₂O and EtOAc. The organic layer is concentrated and purified by reversed-phase preparative HPLC, eluting with a gradient of 5% to 95% ACN in H₂O (0.2% TFA) to give the title compound (4.1 mg, 3.4%). ES/MS (m/z) 513.1 (M+H).

20

The following compounds in Table 29 are prepared essentially as described for 5-amino-1-isopropyl-3-(4-(2-oxo-2-((3-(2-(trifluoromethyl)phenyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide using the appropriate amine and carboxylic acid with a coupling reagent, about 1-6 equivalents, base, about 1-4 equiv and solvent, about 0.3-20 mL, adjusting the reaction time to determine completion of the reaction, and purification conditions as appropriate. The reaction temperature can range from -20 °C to 50 °C, T3P® can be added in 50% EtOAc, 50% DMF and TCFH can be added in portions.

*Coupling reagents: 1 T3P®, 2 TCFH, 3 BTFFH, 4 COMU®, 5 TBTU, 6 TFFH, 7 HATU, 8

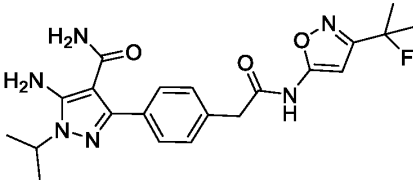
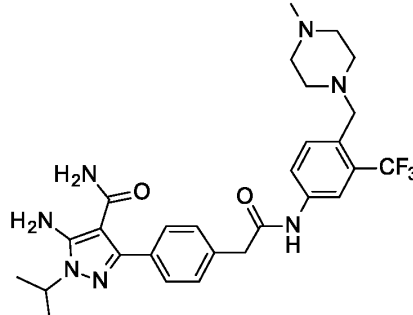
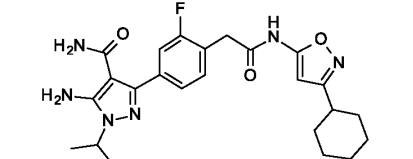
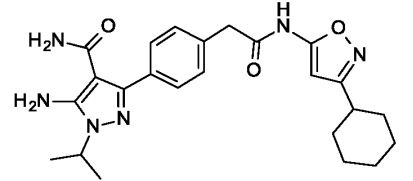
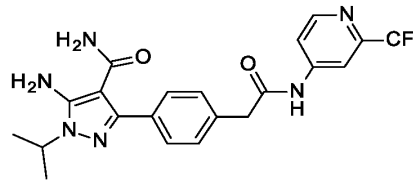
10 EDCI/HOBT

Bases: a NMI, b pyridine, c DIPEA

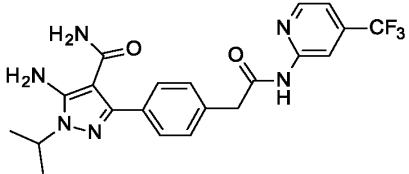
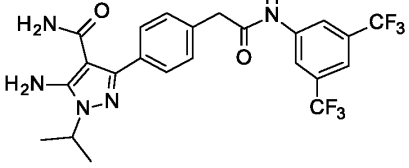
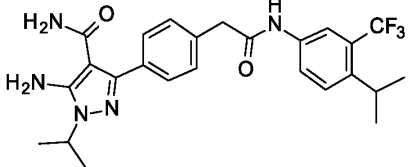
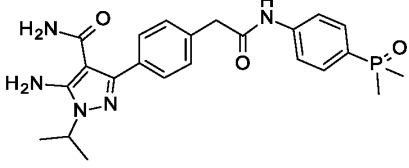
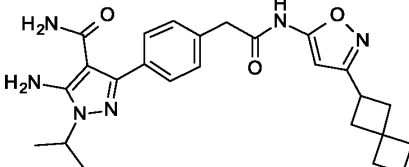
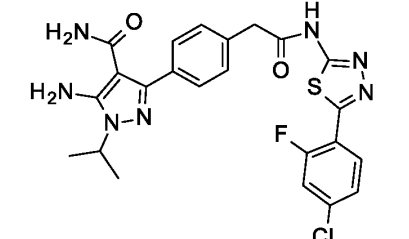
Solvents: I EtOAc, II ACN, III DMF, IV DCM, V THF

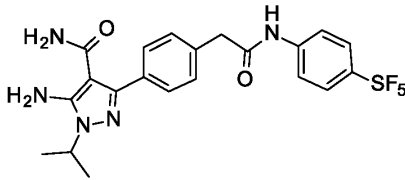
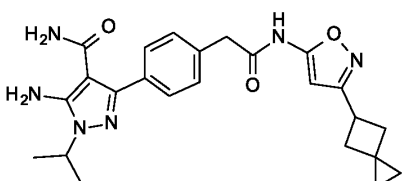
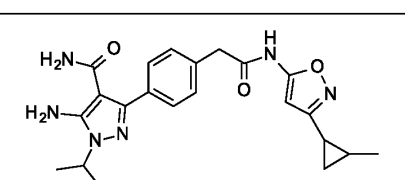
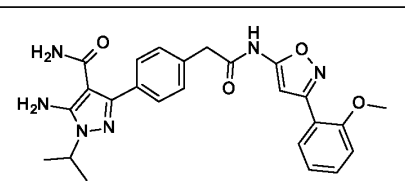
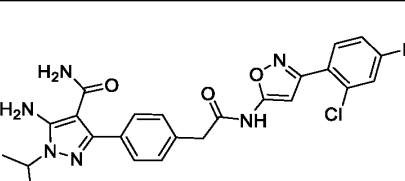
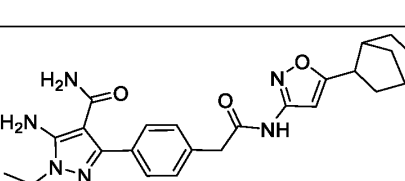
Table 29

Ex. No.	Chemical name	Structure	ES/MS m/z (M+H)	*
13	5-Amino-1-isopropyl-3-(4-(2-((5-(1-methylcyclohexyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		465	3, a, II
14	5-Amino-3-(4-(2-((3-(2-chlorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		479.2	1, b, II

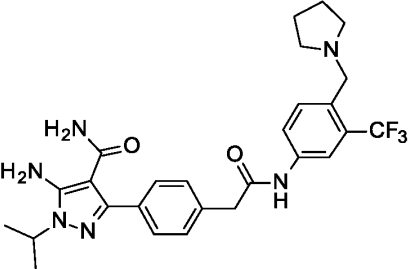
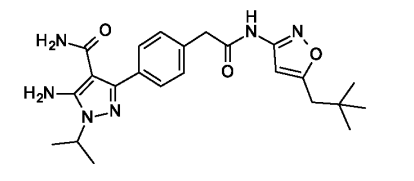
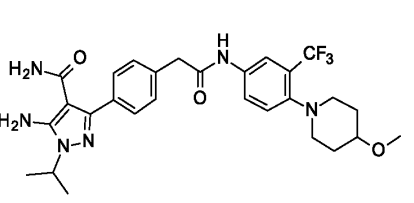
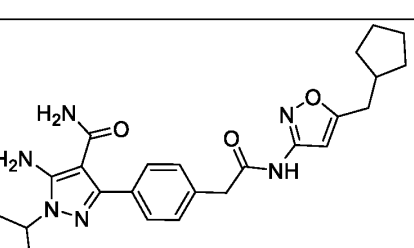
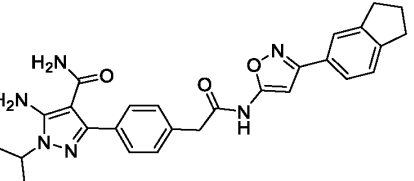
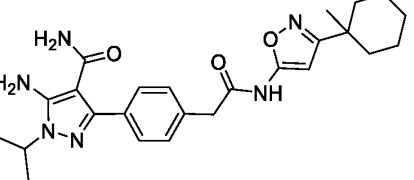
15	5-Amino-3-(4-(2-((3-(2-fluoropropan-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		429.1	2, a, III
16	5-Amino-1-isopropyl-3-(4-(2-(((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		558.3	2, a, III
17	5-Amino-3-(4-(2-((3-cyclohexylisoxazol-5-yl)amino)-2-oxoethyl)-3-fluorophenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		469.2	4, c, III
18	5-Amino-3-(4-(2-((3-cyclohexylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		450.8	2, a, III
19	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((2-(trifluoromethyl)pyridin-4-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		447.2	3, a, I & II

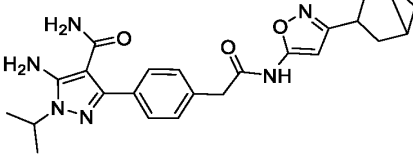
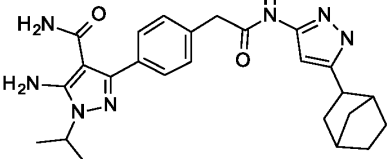
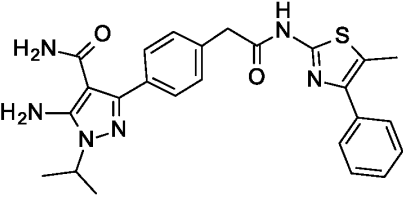
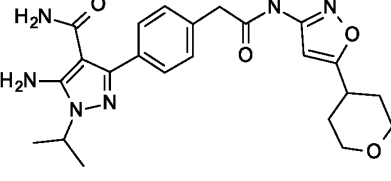
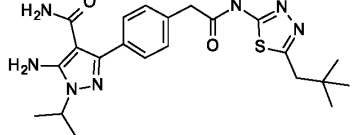
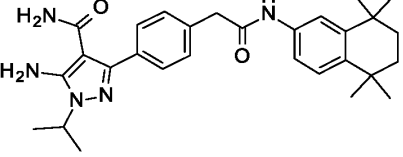
-148-

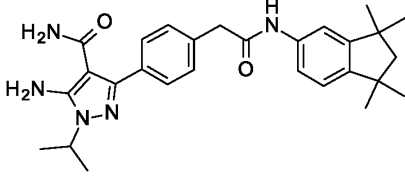
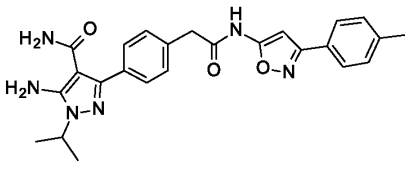
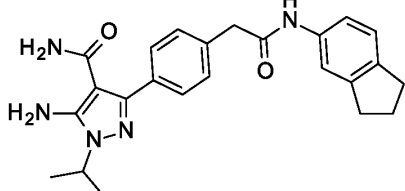
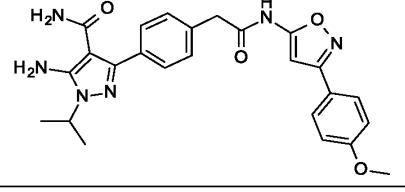
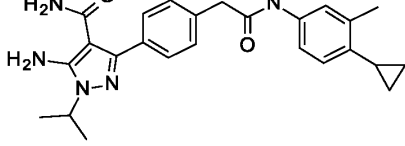
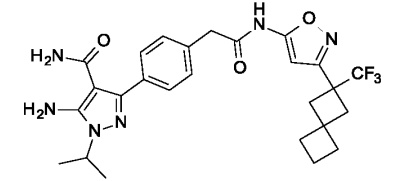
20	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((4-(trifluoromethyl)pyridin-2-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		447.2	3, a, I & II
21	5-Amino-3-(4-(2-((3,5-bis(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		513.7	2, a, III
22	5-Amino-1-isopropyl-3-(4-(2-((4-isopropyl-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		488.2	6, a, I & II
23	5-Amino-3-(4-(2-((4-(dimethylphosphoryl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		454.2	5, c, IV
24	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(spiro[3.3]heptan-2-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		463.2	2, a, I & II
25	5-Amino-3-(4-(2-((5-(4-chloro-2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		514.2	2, a, I & II

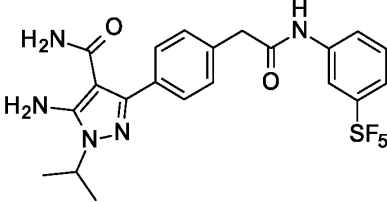
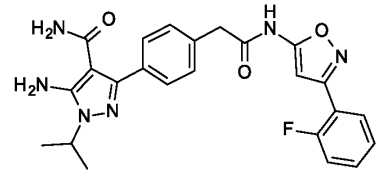
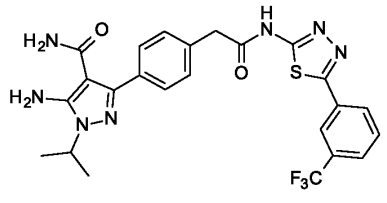
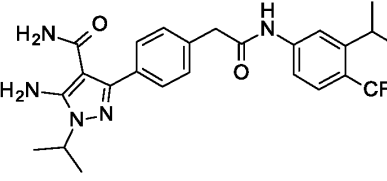
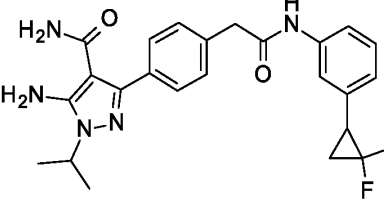
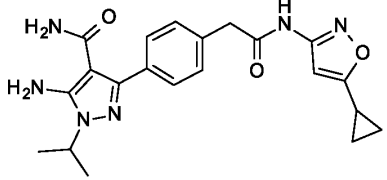
26	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((4-(pentafluoro-λ 6-sulfanyl)phenyl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		504.2	5, c, IV
27	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(spiro[2.3]hexan-5-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		449.2	2, a, I & II
28	5-Amino-1-isopropyl-3-(4-(2-((3-(2-methylcyclopropyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		423.8	2, a, III
29	5-Amino-1-isopropyl-3-(4-(2-((3-(2-methoxyphenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		475.2	1, b, I & II
30	5-Amino-3-(4-(2-((3-(2-chloro-4-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		497.1	2, a, III
31	5-Amino-3-(4-(2-((5-(bicyclo[2.2.1]heptan-2-yl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.2	2, a, III

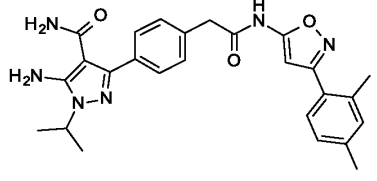
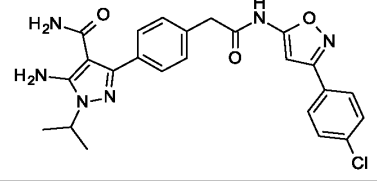
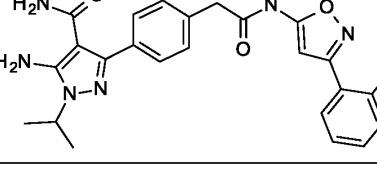
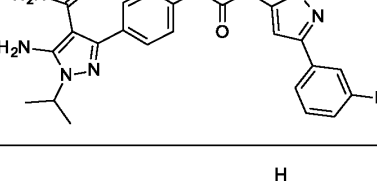
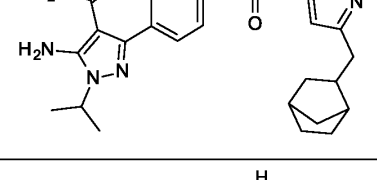
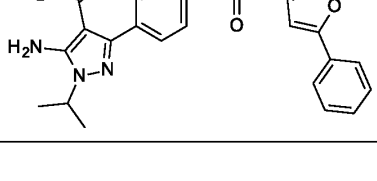
-150-

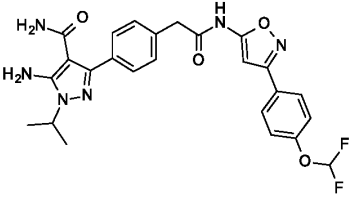
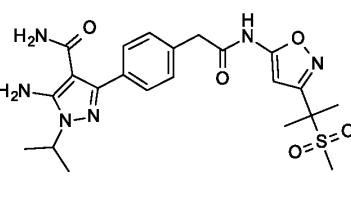
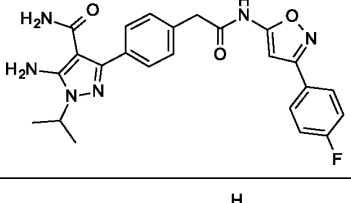
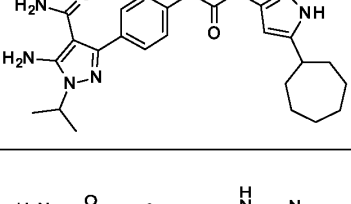
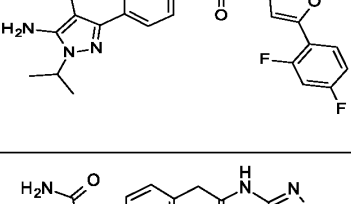
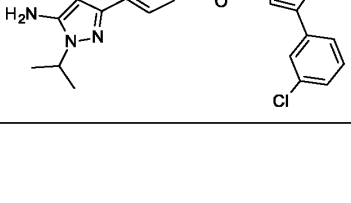
32	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((4-(pyrrolidin-1-ylmethyl)-3-(trifluoromethyl)phenyl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		529.2	2, a, I & II
33	5-Amino-1-isopropyl-3-(4-(2-((5-neopentylisoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		439.3	3, a, I & II
34	5-Amino-1-isopropyl-3-(4-(2-((4-(4-methoxypiperidin-1-yl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		559.2	6, a, I & II
35	5-Amino-3-(4-(2-((5-(cyclopentylmethyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		451.2	6, a, III
36	5-Amino-3-(4-(2-((3-(2,3-dihydro-1H-inden-5-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		485.2	2, a, III
37	5-Amino-1-isopropyl-3-(4-(2-((3-(1-methylcyclohexyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		465.2	2, a, III

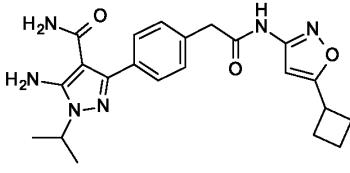
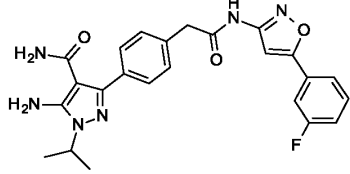
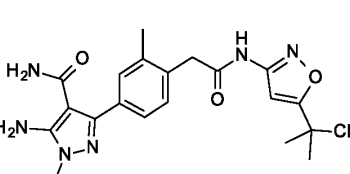
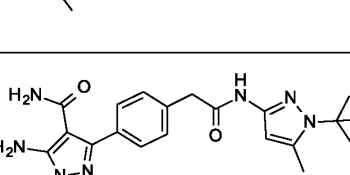
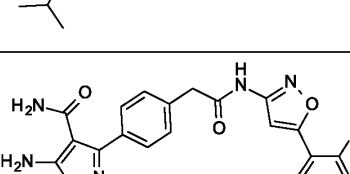
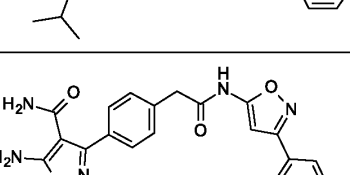
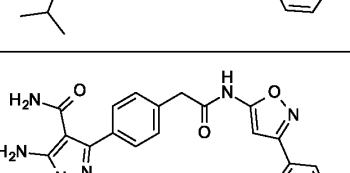
38	5-Amino-3-(4-(2-((3-(bicyclo[2.2.1]heptan-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		462.8	2, a, III
39	5-Amino-3-(4-(2-((5-(bicyclo[2.2.1]heptan-2-yl)-1H-pyrazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		462.2	1, b, I & II
40	5-Amino-1-isopropyl-3-(4-(2-((5-methyl-4-phenylthiazol-2-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		474.8	2, a, III
41	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-(tetrahydro-2H-pyran-4-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		452.8	2, a, III
42	5-Amino-1-isopropyl-3-(4-(2-((5-neopentyl-1,3,4-thiadiazol-2-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		455.8	2, a, III
43	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		488.2	5, c, IV

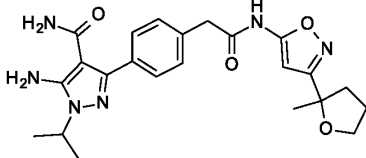
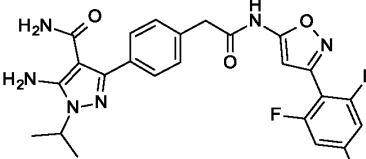
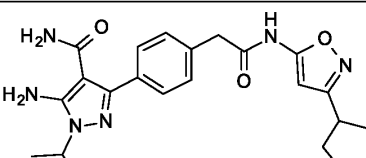
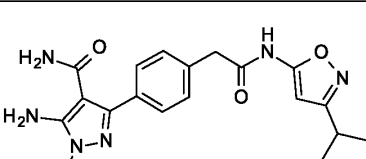
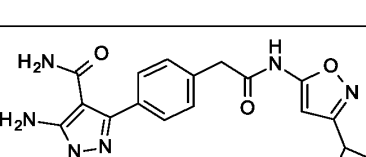
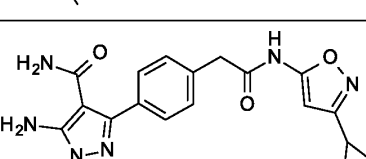
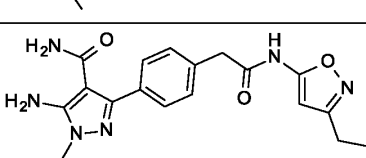
44	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((1,1,3,3-tetramethyl-2,3-dihydro-1H-inden-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		474.2	5, c, IV
45	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(p-tolyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		459.2	1, b, I & II
46	5-Amino-3-(4-(2-((2,3-dihydro-1H-inden-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		418.2	5, c, IV
47	5-Amino-1-isopropyl-3-(4-(2-((3-(4-methoxyphenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		474.2	1, b, I & II
48	5-Amino-3-(4-(2-((4-cyclopropyl-3-methylphenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		432.2	5, c, IV
49	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(2-(trifluoromethyl)spiro[3.3]heptan-2-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		531.2	2, a, I & II

50	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(pentafluoro- λ^6 -sulfaneyl)phenyl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		503.2	5, c, IV
51	5-Amino-3-(4-(2-((3-(2-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.2	1, b, I & II
52	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-(3-(trifluoromethyl)phenyl)-1,3,4-thiadiazol-2-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		530.2	2, a, I & II
53	5-Amino-1-isopropyl-3-(4-(2-((3-isopropyl-4-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		488.2	5, c, IV
54	5-Amino-3-(4-(2-((3-(2,2-difluorocyclopropyl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		453.2	5, c, IV
55	5-Amino-3-(4-(2-((5-cyclopropylisoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		409.2	1, b, I & II

56	5-Amino-3-(4-(2-((3-(2,4-dimethylphenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		473.2	1, b, I & II
57	5-Amino-3-(4-(2-((3-(4-chlorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		479.1	1, b, I & II
58	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(o-tolyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		459.2	1, b, I & II
59	5-Amino-3-(4-(2-((3-(3-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.2	1, b, I & II
60	5-Amino-3-(4-(2-((3-(3-(bicyclo[2.2.1]heptan-2-ylmethyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		477.2	1, b, I & II
61	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-phenylisoxazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		445.1	1, b, I & II

62	5-Amino-3-(4-(2-((3-(4-(difluoromethoxy)phenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		511.1	1, b, I & II
63	5-Amino-1-isopropyl-3-(4-(2-((3-(2-(methylsulfonyl)propan-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		489.2	1, b, I & II
64	5-Amino-3-(4-(2-((3-(4-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.1	1, b, I & II
65	5-Amino-3-(4-(2-((5-cycloheptyl-1H-pyrazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		464.1	1, b, I & II
66	5-Amino-3-(4-(2-((5-(2,4-difluorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		481.1	1, b, I & II
67	5-Amino-3-(4-(2-((5-(3-chlorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		479.1	4, c, III

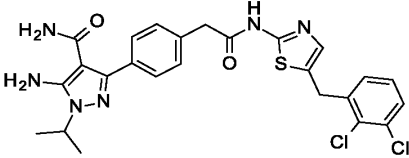
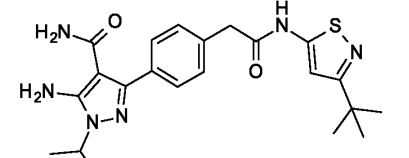
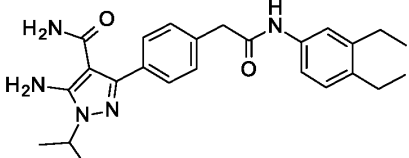
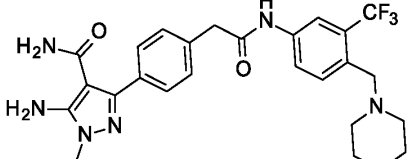
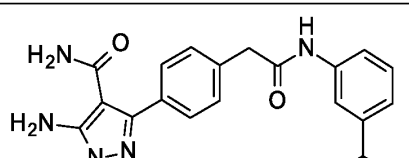
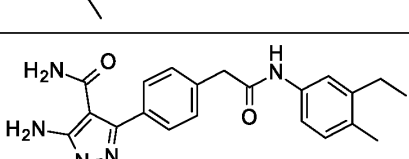
68	5-Amino-3-(4-(2-((5-cyclobutylisoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		423.2	1, b, I & II
69	5-Amino-3-(4-(2-((5-(3-fluorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.1	1, b, I & II
70	5-Amino-1-isopropyl-3-(3-methyl-4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		493.2	1, b, I & II
71	5-Amino-3-(4-(2-((1-(tert-butyl)-5-methyl-1H-pyrazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		438.2	1, b, I & II
72	5-Amino-3-(4-(2-((5-(2-fluorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.1	1, b, I & II
73	5-Amino-1-isopropyl-3-(4-(2-((3-(3-methoxyphenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		475.1	1, b, I & II
74	5-Amino-3-(4-(2-((3-(3-bromophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		525.1	1, b, I & II

75	5-Amino-1-isopropyl-3-(4-(2-((3-(2-methyltetrahydrofuran-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		453.2	1, b, I & II
76	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(2,4,6-trifluorophenyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		499.1	1, b, I & II
77	5-Amino-3-(4-(2-((3-(bicyclo[3.1.0]hexan-3-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		449.2	1, b, I & II
78	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(tetrahydrofuran-3-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		438.8	1, b, I & II
79	5-Amino-3-(4-(2-((3-(cyclobutylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		423.1	1, b, I & II
80	5-Amino-3-(4-(2-((3-(cyclopropylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		408.5	1, b, I & II
81	5-Amino-3-(4-(2-((3-(cyclopropylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-		396.8	1, b, I & II

-158-

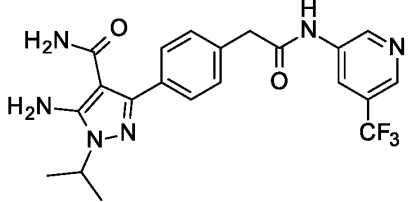
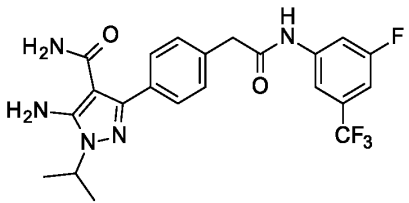
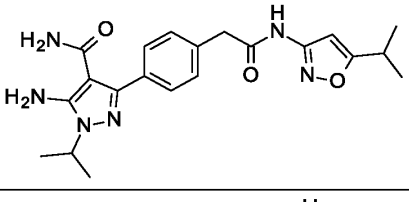
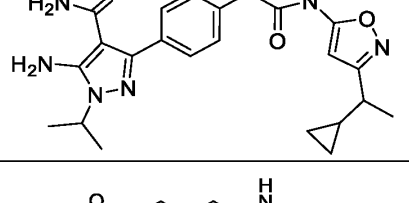
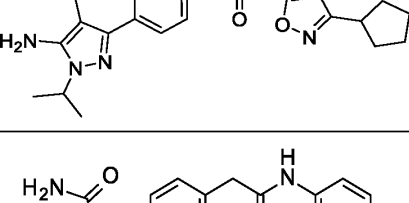
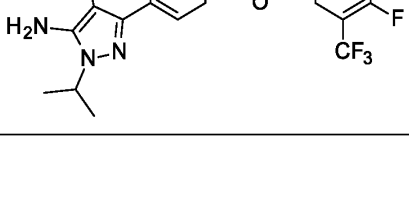
	isopropyl-1H-pyrazole-4-carboxamide			
82	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-((1-(trifluoromethyl)cyclopropyl)methyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		491.2	1, b, I & II
83	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(<i>tert</i> -pentyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		438.8	1, b, I & II
84	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		531.2	1, c, III
85	5-Amino-3-(3-chloro-4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		513.1	1, b, I & II
86	5-Amino-3-(4-(2-((3-(cyclopropylmethyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		423.1	1, b, I & II
87	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-phenylisoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		445.2	1, b, I & II

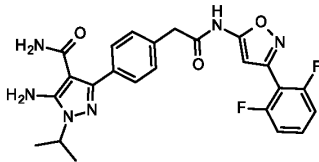
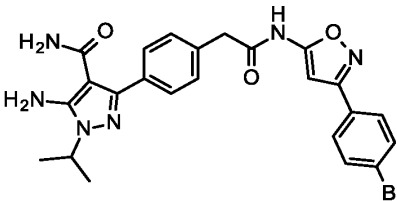
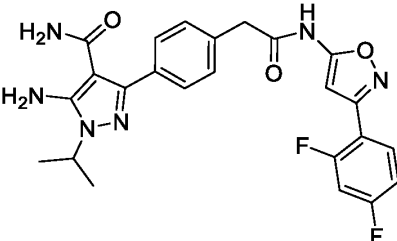
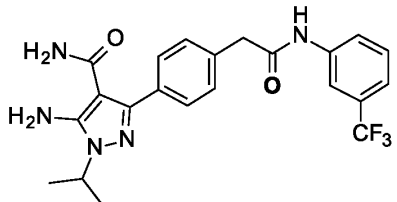
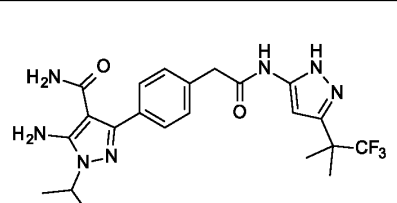
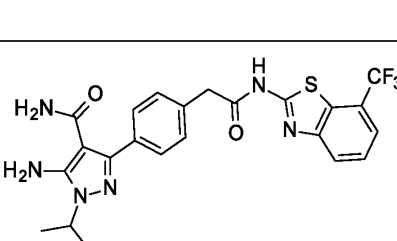
88	5-Amino-3-(4-(2-((3-(3,3-dimethylcyclobutyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		451.2	2, a, III
89	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(3-(trifluoromethyl)phenyl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		513.2	1, b, I & II
90	5-Amino-3-(4-(2-((5-(tert-butyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		425.2	1, b, I & II
91	5-Amino-3-(4-(2-((3-((difluoromethyl)thio)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		459.2	5, c, IV
92	5-Amino-3-(4-(2-((5-(2,4-dichlorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		514.2	2, a, I & II
93	5-Amino-3-(4-(2-((3-(2,4-dichlorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		512.2	2, a, I & II

94	5-Amino-3-(4-(2-((5-(2,3-dichlorobenzyl)thiazol-2-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		543.2	2, a, I & II
95	5-Amino-3-(4-(2-((3-(<i>tert</i> -butyl)isothiazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		441.2	1, b, I & II
96	5-Amino-3-(4-(2-((3,4-diethylphenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		434.2	5, c, IV
97	5-Amino-1-isopropyl-3-(4-(2-((4-(morpholinomethyl)-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		545.2	5, c, IV
98	5-Amino-3-(4-(2-((3-(<i>tert</i> -butyl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		434.2	5, c, IV
99	5-Amino-3-(4-(2-((3-ethyl-4-methylphenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		420.2	5, c, IV

100	5-Amino-3-(4-(2-((3-(6,6-difluorospiro[3.3]heptan-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		499.2	2, a, I & II
101	5-Amino-3-(4-(2-((4-ethyl-3-methylphenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		420.2	5, c, IV
102	5-Amino-3-(4-(2-((3-(3,3-difluorocyclobutyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		459.2	2, a, I & II
103	5-Amino-3-(4-(2-((5-(2,4-dichlorophenyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		514.2	2, a, II & III
104	5-Amino-1-isopropyl-3-(4-(2-((3-(1-methylcyclopropyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		432.2	3, a, III
105	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-(2,2,2-trifluoroethyl)-1,3,4-thiadiazol-2-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		468.1	2, a, II

106	5-Amino-1-isopropyl-3-(4-(2-((3-methyl-5-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		460.2	2, a, III
107	5-Amino-3-(4-(2-((3-(cyclohexylmethyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		465.2	2, a, II
108	5-Amino-3-(4-(2-((3-(3-chlorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		479.1	1, b, I
109	5-Amino-1-isopropyl-3-(4-(2-((4-methyl-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		460.7	2, a, III
110	5-Amino-3-(4-(2-((5-(1,1-difluoroethyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		433.1	3, a, III
111	5-Amino-1-isopropyl-3-(4-(2-((5-(1-methylcyclopentyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		451.2	4, c, III

112	5-Amino-1-isopropyl-3-(4-(2-oxo-2-((5-(trifluoromethyl)pyridin-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		447.3	3, a, III
113	5-Amino-3-(4-(2-((3-fluoro-5-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		464.7	2, a, III
114	5-Amino-1-isopropyl-3-(4-(2-((5-isopropylisoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		410.8	2, a, I & II
115	5-Amino-3-(4-(2-((3-(1-cyclopropylethyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		437.2	2, a, II
116	5-Amino-3-(4-(2-((3-cyclopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		437.1	6, a, II
117	5-Amino-3-(4-(2-((4-fluoro-3-(trifluoromethyl)phenyl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		463.7	2, a, III

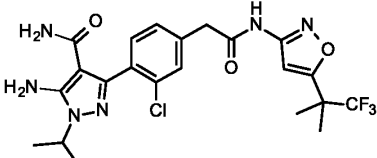
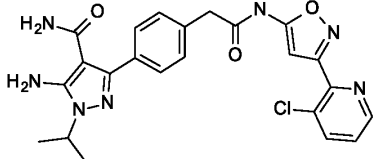
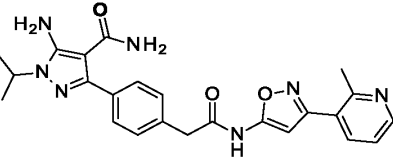
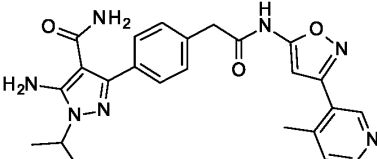
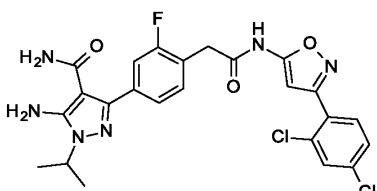
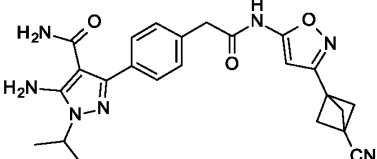
118	5-Amino-3-(4-(2-((3-(2,6-difluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		481.1	2, a, I & II
119	5-Amino-3-(4-(2-((3-(4-bromophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		524.6	2, a, I & II
120	5-Amino-3-(4-(2-((3-(2,4-difluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		481.2	2, a, II
121	5-Amino-1-(propan-2-yl)-3-[4-([3-(trifluoromethyl)phenyl]carbamoyl)methyl]phenyl]-1H-pyrazole-4-carboxamide		446.3	7, c, III
122	5-Amino-1-(propan-2-yl)-3-[4-([3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-5-yl]carbamoyl)methyl]phenyl]-1H-pyrazole-4-carboxamide		478.2	7, c, III
123	5-Amino-1-(propan-2-yl)-3-[4-([7-(trifluoromethyl)-1,3-benzothiazol-2-yl]carbamoyl)methyl]phenyl]-1H-pyrazole-4-carboxamide		503.1	8, V

124	5-Amino-1- <i>tert</i> -butyl-3-[4-([5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		493.3	7, c, III
125	5-Amino-1-cyclopentyl-3-(4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		505.2	1, c, III
126	5-Amino-3-(4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazole-4-carboxamide, Isomer 1		533.1	1, c, III
127	5-Amino-3-(4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)isoxazol-3-yl)amino)ethyl)phenyl)-1-(1,1,1-trifluoropropan-2-yl)-1H-pyrazole-4-carboxamide, Isomer 2		533.1	1, c, III
128	5-Amino-3-[3-fluoro-4-([3-(trifluoromethyl)phenyl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		464.1	7, c, III
129	5-Amino-3-[3-fluoro-4-([5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		497.3	1, c, III

-166-

	nyl]-1-isopropylpyrazole-4-carboxamide			
130	5-Amino-3-(3-fluoro-4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-yl)amino)ethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		496.2	1, c, 125
131	5-Amino-3-[3-fluoro-4-((1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazol-3-yl)carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		510.3	7, c, III
132	5-Amino-3-[3-fluoro-4-((3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl)carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		497.3	1, c, IV
133	5-Amino-3-(3-fluoro-4-(2-oxo-2-((7-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)ethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		521.2	8, V
134	5-Amino-1-cyclopentyl-3-(4-(2-oxo-2-((5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		504.2	1, c, III

135	5-Amino-1-cyclopentyl-3-(4-(2-(1-methyl-5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1H-pyrazol-3-ylamino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		518.3	7, c, III
136	5-Amino-1-cyclopentyl-3-[4-([3-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		505.2	1, c, III
137	5-Amino-1-cyclopentyl-3-(4-(2-oxo-2-((7-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide		529.3	8, V
138	5-Amino-1-isopropyl-3-(4-(2-((5-(1-methylcyclopropyl)isoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		423.3	1, c, III
139	5-Amino-3-(3-fluoro-4-[[[(5-phenyl-1H-pyrazol-3-yl)carbamoyl]methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		462.2	1, c, III
140	5-Amino-3-(3-fluoro-4-[[[(1-methyl-5-phenylpyrazol-3-yl)carbamoyl]methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		476.2	7, c, III

141	5-Amino-3-[2-chloro-4-([5-(1,1,1-trifluoro-2-methylpropan-2-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		513.3	1, c, III
142	5-Amino-3-(4-(2-((3-(3-chloropyridin-2-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		480.2	1, c, IV
143	5-Amino-1-isopropyl-3-[4-([3-(2-methylpyridin-3-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		230.6 (M+2H))/2	1, c, IV
144	5-Amino-1-isopropyl-3-[4-([3-(4-methylpyridin-3-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		460.1	1, c, IV
145	5-Amino-3-[4-([3-(2,4-dichlorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]-3-fluorophenyl]-1-isopropylpyrazole-4-carboxamide		531.1	1, c, IV
146	5-Amino-3-(4-([3-(3-cyanobicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)carbamoyl)methyl]phenyl)-1-isopropylpyrazole-4-carboxamide		460.2	1, c, IV

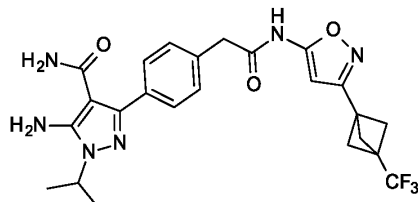
-169-

147	5-Amino-3-[3-fluoro-4- [[3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		521.2	1, c, IV
148	5-Amino-3-(3-fluoro-4- [[3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl)-1-isopropylpyrazole-4-carboxamide		467.3	1, c, IV
149	5-Amino-1-isopropyl-3-[4- [[5-(pyridin-3-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		446.2	1, c, IV
150	5-Amino-1-isopropyl-3-[4- [[5-(pyridin-4-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		446.3	1, c, IV
151	5-Amino-3-[4- [[3-(1-cyano-1-methylethyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		436.2	1, c, IV
152	5-Amino-1-isopropyl-3-[4- [[3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		449.2	1, c, IV

Example 153

-170-

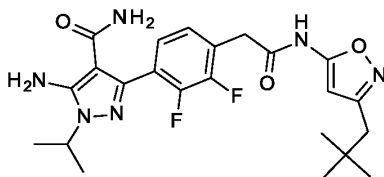
5-Amino-1-isopropyl-3-(4-(2-oxo-2-((3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1H-pyrazole-4-carboxamide



2-(4-(5-Amino-4-carbamoyl-1-isopropyl-1H-pyrazol-3-yl)phenyl)acetic acid (196
 5 mg, 0.65 mmol) and 3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-amine
 (140.00 mg, 0.65 mmol) are combined in DCM. DIPEA (251.36 mg, 1.95 mmol) and
 T3P® (536.32 mg, 0.84 mmol, 50 wt% in EtOAc) are added dropwise at RT and under N₂
 and the reaction is stirred for 1 hr at 50 °C in a sealed tube. The reaction is concentrated
 under reduced pressure and the residue is purified by reversed phase flash
 10 chromatography (C18 column), eluting with a gradient of 40% to 50% ACN in H₂O
 (0.1% NH₄HCO₃) to give the title compound (120 mg). The material is titrated with
 hexanes (3 mL). The precipitated solids are collected by filtration and washed with
 hexanes (3x3 mL) to give the title product (85.1 mg, 34%) as a white solid ES/MS (m/z)
 503.2 (M+H).

15 Example 154

5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluoro-
 phenyl]-1-isopropyl-pyrazole-4-carboxamide



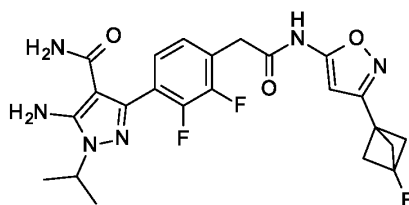
To *tert*-butyl N-[4-carbamoyl-5-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-
 20 2-oxo-ethyl]-2,3-difluoro-phenyl]-2-isopropyl-pyrazol-3-yl]carbamate (45 mg, 0.078 mmol)
 in DCM (0.55 mL) is added TFA (0.23 mL, 3.12 mmol) at RT. The mixture is stirred for 3
 hr. The reaction mixture is concentrated under reduced pressure, the pH of the residue is

-171-

made basic with saturated aq. NaHCO_3 and extracted with EtOAc. The organic extract is washed with brine and concentrated under reduced pressure. The residue is purified by silica gel chromatography, eluting with a gradient of 1% to 10% MeOH in DCM to give a white solid. This solid is triturated in $i\text{Pr}_2\text{O}$ at RT, filtered, washed with $i\text{Pr}_2\text{O}$, and dried under vacuum at 80 °C overnight to give the title compound (26 mg, 70%) as a white solid. ES/MS (m/z) 475 (M+H).

Example 155

5-Amino-3-(2,3-difluoro-4-(2-((3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide



To *tert*-butyl (4-carbamoyl-3-(2,3-difluoro-4-(2-((3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazol-5-yl)carbamate (30 mg, 0.051 mmol) in DCM (2 mL) is added TFA (0.39 mL, 5.10 mmol). The reaction mixture is stirred at RT for 2 hr. The reaction mixture is quenched with cold saturated aq. NaHCO_3 and the aqueous layer is extracted with EtOAc. The organic extract is washed with brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material is purified by silica gel chromatography, eluting with a gradient of 10% to 100% EtOAc in heptane to give the title compound (10 mg, 40%). ES/MS (m/z) 489.4 (M+H).

The following compounds in Table 30 are prepared essentially as described for 5-amino-3-(2,3-difluoro-4-(2-((3-(3-fluorobicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide adjusting reaction time to determine completion of the reaction, using appropriate chromatography conditions for purification, and/or titration in an appropriate solvent if needed. TFA can also be added dropwise to the reaction. THF can be substituted for DCM if appropriate for solubility.

Table 30

-172-

Pre p. No.	Chemical name	Structure	ES/MS m/z (M+H)
156	5-Amino-3-(2,3-difluoro-4-(2-oxo-2-((3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		539.4
157	5-Amino-3-[3-chloro-4-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		547.1
158	5-Amino-3-[4-[2-[[3-[2,4-dichloro-5-[(dimethylamino)methyl]phenyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		570.8

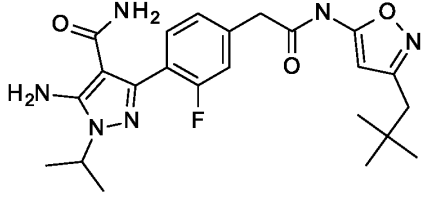
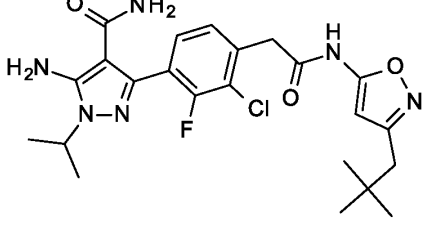
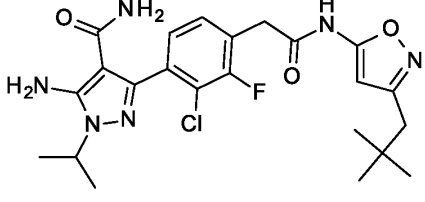
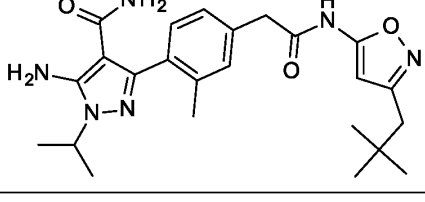
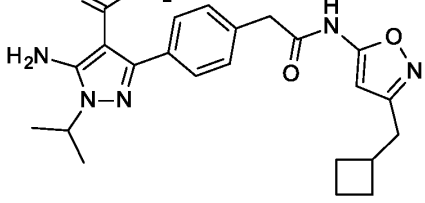
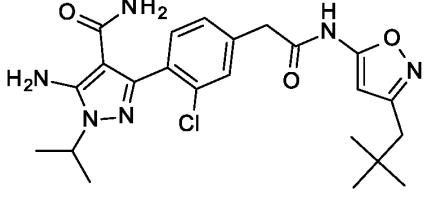
-173-

159	5-Amino-1-(azetidin-3-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		452.2
160	5-Amino-3-[4-[2-[[3-(2,2-dimethylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		437
161	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[(3-spiro[2.2]pentan-2-yl)isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide		435.1
162	5-Amino-3-[4-[2-[[3-[(2,2-difluorocyclopropyl)methyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		459
163	5-Amino-3-[4-[2-[[3-(3,3-difluorocyclopentyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		473
164	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[(3-spiro[2.3]hexan-2-yl)isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide		449.3

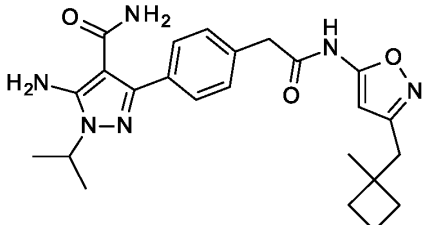
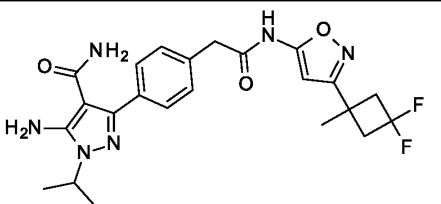
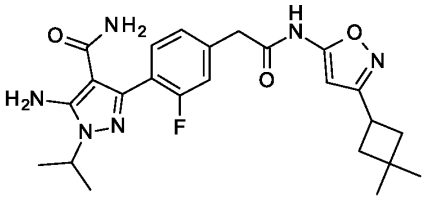
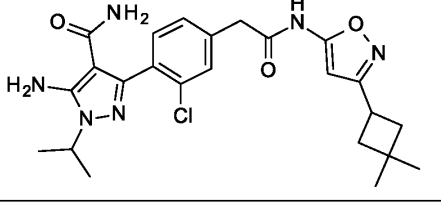
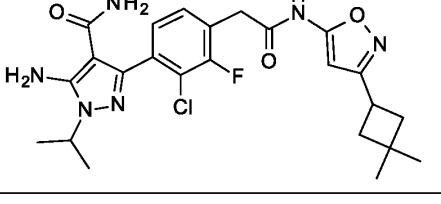
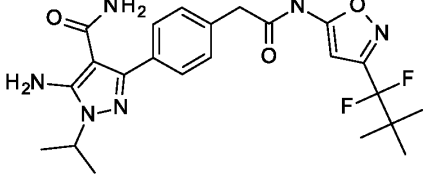
-174-

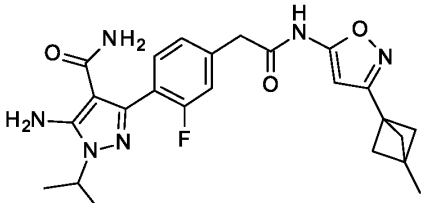
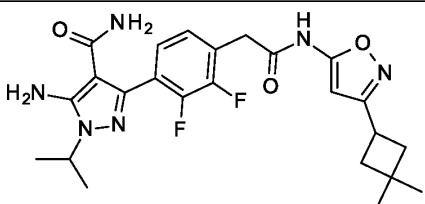
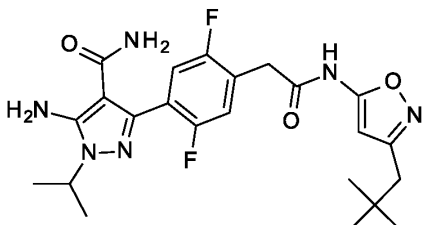
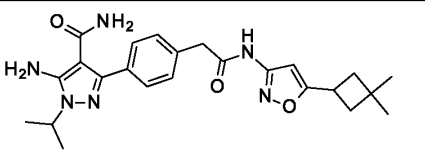
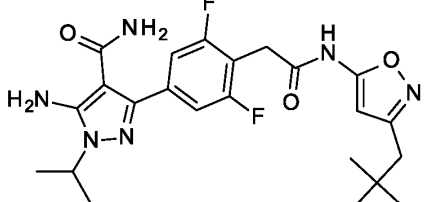
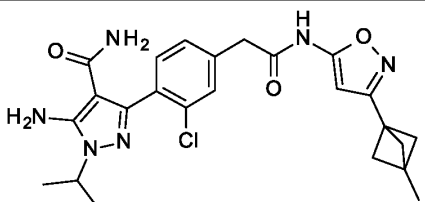
165	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[(5-spiro[2.3]hexan-2-yl)isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide		449
166	5-Amino-3-[4-[2-[[5-(2,2-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		451.1
167	5-Amino-3-[4-[2-[[3-(2,2-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		451.1
168	5-Amino-1-isopropyl-3-[3-methoxy-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]pyrazole-4-carboxamide		481
169	5-Amino-3-[3,5-difluoro-4-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		515.4
170	5-Amino-3-[2-(hydroxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		481
171	5-Amino-3-[4-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-methoxy-phenyl]-1-isopropyl-pyrazole-4-carboxamide		543.2

-175-

172	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluorophenyl]-1-isopropyl-pyrazole-4-carboxamide		457.2
173	5-Amino-3-[3-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluorophenyl]-1-isopropyl-pyrazole-4-carboxamide		491.1
174	5-Amino-3-[2-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-fluorophenyl]-1-isopropyl-pyrazole-4-carboxamide		491.1
175	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-methylphenyl]-1-isopropyl-pyrazole-4-carboxamide		453.1
176	5-Amino-3-[4-[2-[[3-(cyclobutylmethyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		437
177	5-Amino-3-[2-chloro-4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		473

-176-

178	5-Amino-1-isopropyl-3-[4-[2-[[3-(1-methylcyclobutyl)methyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]pyrazole-4-carboxamide		451.2
179	5-Amino-3-[4-[2-[[3-(3,3-difluoro-1-methylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		473.1
180	5-Amino-3-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-fluoro-phenyl]-1-isopropyl-pyrazole-4-carboxamide		469.2
181	5-Amino-3-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		485.1
182	5-Amino-3-[2-chloro-4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-fluoro-phenyl]-1-isopropyl-pyrazole-4-carboxamide		503.1
183	5-Amino-3-[4-[2-[[3-(1,1-difluoro-2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		475

184	5-Amino-3-[2-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		467
185	5-Amino-3-[4-[2-[[3-(3,3-dimethylcyclobutyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,3-difluoro-phenyl]-1-isopropyl-pyrazole-4-carboxamide		487
186	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2,5-difluoro-phenyl]-1-isopropyl-pyrazole-4-carboxamide		475.1
187	5-Amino-3-[4-[2-[[5-(3,3-dimethylcyclobutyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		451
188	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3,5-difluoro-phenyl]-1-isopropyl-pyrazole-4-carboxamide		475.1
189	5-Amino-3-[2-chloro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		483.1

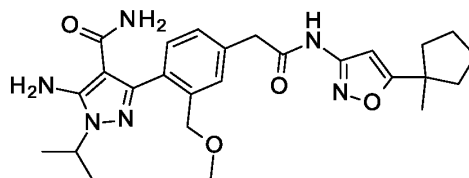
-178-

190	5-Amino-3-[2-chloro-3-fluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		501
191	5-Amino-3-[4-[2-[[3-(3,3-dimethylcyclobutyl)-4-fluoroisoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		469.1
192	5-Amino-3-[3,5-difluoro-4-[2-[[3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		485
193	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)-4-fluoroisoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		457.1
194	5-Amino-3-[4-[2-[[4-fluoro-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		467
195	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[5-[1-(trifluoromethyl)cyclopropyl]isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide		477.4

Example 196

-179-

5-Amino-1-isopropyl-3-[2-(methoxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]pyrazole-4-carboxamide



To 2-[4-bromo-3-(methoxymethyl)phenyl]-N-[5-(1-methylcyclopentyl)isoxazol-3-yl]acetamide (0.130 g, 0.319 mmol) in THF (3 mL) is added bis(pinacolato)diboron (89 mg, 0.350 mmol) and KOAc (95 mg, 0.968 mmol). The reaction mixture is degassed with Ar for 10 min, Pd(dppf)Cl₂·CH₂Cl₂ (27 mg, 0.032 mmol) is added, the mixture is stirred at 50 °C overnight, and cooled to RT. 5-Amino-3-bromo-1-isopropyl-pyrazole-4-carboxamide (95 mg, 0.384 mmol) in THF (1.2 mL) is added followed by K₃PO₄ (0.206 g, 0.970 mmol) in H₂O (1.2 mL). The mixture is degassed with Ar for 10 min and XantPhos Pd G3 (95%, 16 mg, 0.016 mmol) is added. The mixture is heated to 50 °C for 20 hr, cooled to RT, and filtered through talcum powder. The filtrate is diluted with EtOAc/H₂O and the aqueous layer is extracted with EtOAc (2x). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material is purified by silica gel chromatography, eluting with a gradient of 1% to 10% MeOH in DCM, followed by a second chromatography, eluting with a gradient of 90% to 100% EtOAc in DCM and by reversed-phase chromatography (C18Aq column), eluting with a gradient of 0% to 100% ACN (0.1% HOAc) in H₂O to give the title compound. The residue is dissolved in DCM and added dropwise to pentane. The suspension is stirred at RT for 2 hr and filtered. The solid is dried under vacuum at 38 °C for 3 days to give the title compound (35 mg, 22%). ES/MS (m/z) 495 (M+H).

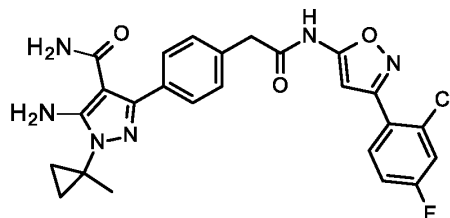
The following compounds in Table 31 are prepared essentially as described for , 5-amino-1-isopropyl-3-[2-(methoxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]pyrazole-4-carboxamide adjusting reaction time to determine completion of the reaction and using appropriate chromatography conditions for purification. The reaction temperature can range from about 50-55 °C.

Table 31

Ex No.	Chemical name	Structure	ES/MS m/z (M+H)
197	5-Amino-1-isopropyl-3-[3-(methoxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]pyrazole-4-carboxamide		495
198	5-Amino-3-[3-(hydroxymethyl)-4-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		481

Example 199

5-Amino-3-(4-(2-((3-(2-chloro-4-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(1-methylcyclopropyl)-1H-pyrazole-4-carboxamide



5

2-(4-(5-Amino-4-cyano-1-(1-methylcyclopropyl)-1H-pyrazol-3-yl)phenyl)-N-(3-(2-chloro-4-fluorophenyl)isoxazol-5-yl)acetamide (66 mg, 0.134 mmol) and Parkins catalyst (69.2 mg, 0.161 mmol) are stirred in EtOH (1.0 mL) and H₂O (1.0 mL) at 60 °C for 4 hr, then 50 °C for 4 hrs and RT overnight. The reaction mixture and extracted with EtOAc and washed with H₂O (3x). The combined organic extracts are concentrated, and purified by silica gel chromatography, eluting with a gradient of 0% to 100% EtOAc in hexanes followed by 0% to 20% MeOH (with 1% NH₄OH) in EtOAc to give the title compound (35 mg, 51%). ES/MS (m/z) 509.1

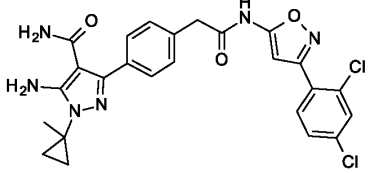
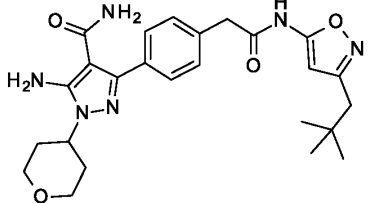
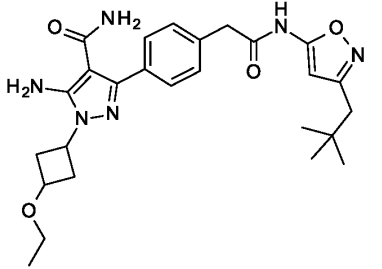
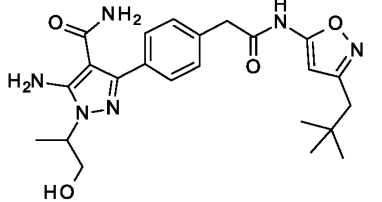
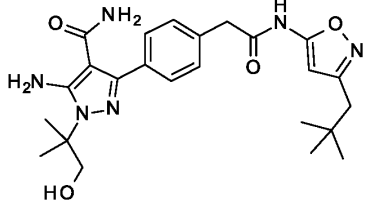
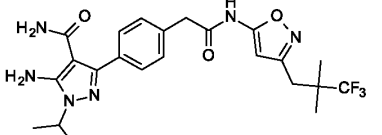
The following compounds in Table 32 are prepared essentially as described for 5-amino-3-(4-(2-((3-(2-chloro-4-fluorophenyl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(1-

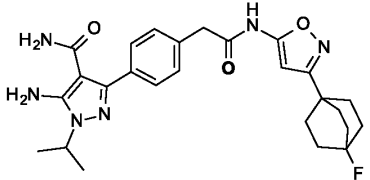
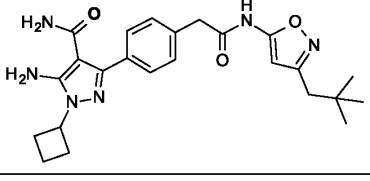
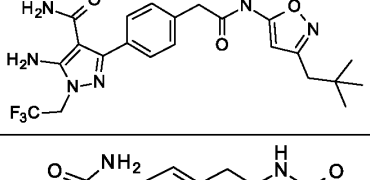
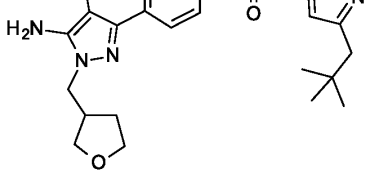
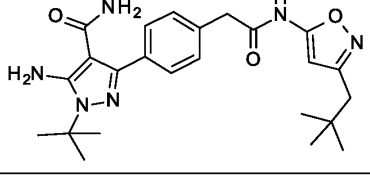
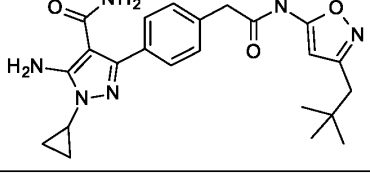
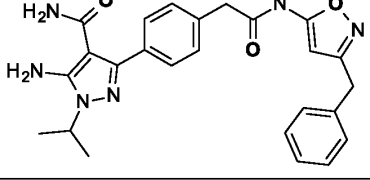
15

methylcyclopropyl)-1H-pyrazole-4-carboxamide adjusting reaction time to determine completion of the reaction and using appropriate chromatography conditions for purification.

Table 32

Ex. No.	Chemical name	Structure	ES/MS m/z (M+H)
200	5-Amino-1-(1-cyclopropylethyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		465.2
201	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazole-4-carboxamide,		467.2
202	5-Amino-1-cyclopentyl-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		465.2
203	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazole-4-carboxamide,		481.4

204	5-Amino-3-[4-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-(1-methylcyclopropyl)pyrazole-4-carboxamide		525.1
205	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide		481.2
206	5-Amino-1-(3-ethoxycyclobutyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		495.2
207	5-Amino-1-(1-hydroxypropan-2-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide,		455.2
208	5-Amino-1-(1-hydroxy-2-methylpropan-2-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		469.2
209	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-(3,3,3-trifluoro-2,2-dimethylpropyl)isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide		492.2

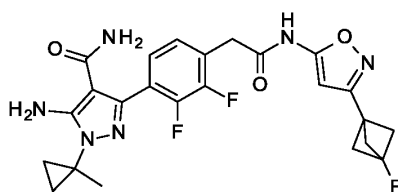
210	5-Amino-3-(4-(2-((3-(4-fluorobicyclo[2.2.2]octan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-isopropyl-1H-pyrazole-4-carboxamide		495.4
211	5-Amino-1-cyclobutyl-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		451.2
212	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide		479.2
213	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazole-4-carboxamide		481.4
214	5-Amino-1-(tert-butyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		453.2
215	5-Amino-1-cyclopropyl-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]pyrazole-4-carboxamide		437.2
216	5-Amino-3-[4-[2-[(3-benzylisoxazol-5-yl)amino]-2-oxoethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide		459.2

-184-

217	5-Amino-1-(bicyclo[1.1.1]pentan-1-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		463.2
218	5-Amino-3-[4-[2-[[3-(3-bicyclo[1.1.1]pentanylmethyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-1-isopropylpyrazole-4-carboxamide		449.2
219	5-Amino-3-[4-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-1-(1-methylcyclopropyl)pyrazole-4-carboxamide		451.2
220	5-Amino-1-(3-hydroxypropyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		455.2

Example 221

5-Amino-3-[2,3-difluoro-4-[2-[[3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)isoxazol-5-yl]amino]-2-oxoethyl]phenyl]-1-(1-methylcyclopropyl)pyrazole-4-carboxamide



- 5 2-[4-[5-Amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-(3-[3-fluorobicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide (60 mg, 0.124 mmol), NaOH (25 mg, 0.625 mmol) in EtOH:DMSO (6 mL, 5:1), and H₂O₂ (0.38 mL, 3.72 mmol, 30% in H₂O) are added together and stirred for 1 hr at 50 °C. The solution is allowed to cool to RT, quenched with saturated aq. Na₂SO₃ (10 mL) and extracted with EtOAc (3x20 mL).

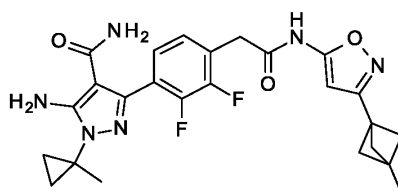
-185-

The organic extracts are dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 40% to 60% ACN in H₂O (0.1% FA) to give the title compound (45 mg, 73%). ES/MS (m/z) 501.2 (M+H).

5

Example 222

5-Amino-3-(2,3-difluoro-4-[[3-(3-methylbicyclo[1.1.1]pentan-1-yl)-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)-1-(1-methylcyclopropyl)pyrazole-4-carboxamide

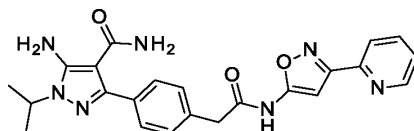


To a solution of 2-[4-[5-amino-4-cyano-1-(1-methylcyclopropyl)pyrazol-3-yl]-2,3-difluorophenyl]-N-(3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)acetamide (70 mg, 0.146 mmol) and NaOH (29 mg, 0.725 mmol) in EtOH (3 mL) and DMSO (0.60 mL) is added H₂O₂ (0.22 mL, 2.15 mmol, 30% in H₂O). The reaction is stirred for 1 hr at 50 °C. The mixture is allowed to cool to RT and quenched with saturated aq. Na₂SO₃ (10 mL) at 0 °C. The aqueous layer is extracted with EtOAc (2x30 mL). The combined organic extracts are washed with brine (2x20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 column), eluting with a gradient of 40% to 60% ACN in H₂O (0.1% NH₄HCO₃) to give the title compound (36 mg, 50%) as a white solid. ES/MS (m/z) 497.3 (M+H).

20

Example 223

5-Amino-1-isopropyl-3-[4-([3-(pyridin-2-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide



-186-

To a stirred solution of 2-[4-(5-amino-4-cyano-1-isopropylpyrazol-3-yl)phenyl]-N-[3-(pyridin-2-yl)-1,2-oxazol-5-yl]acetamide (60 mg, 0.140 mmol) and NaOH (28 mg, 0.700 mmol) in EtOH (1.5 mL), DMSO (0.30 mL), and H₂O (0.60 mL) is added H₂O₂ (0.22 mL, 2.15 mmol, 30% in H₂O) at RT. The mixture is stirred for 3 hr at 40 °C. The reaction is

5 quenched with saturated aq. Na₂SO₃ (10 mL). The mixture is extracted with EtOAc (3x100 mL). The combined organic extracts are washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate is concentrated under reduced pressure. The residue is purified by reversed-phase chromatography, eluting with a gradient of 10% to 30% ACN in H₂O (0.1% NH₃H₂O) to give the title compound (26 mg, 40%) as a white solid. ES/MS (m/z)

10 446.2 (M+H).

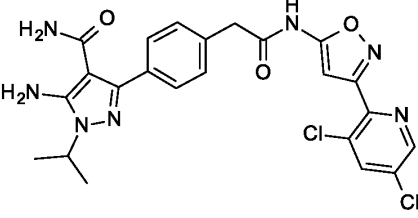
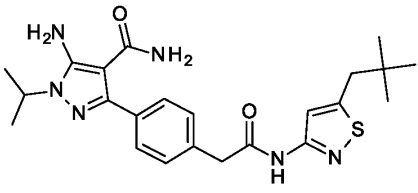
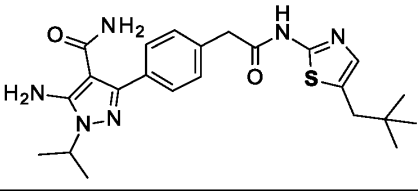
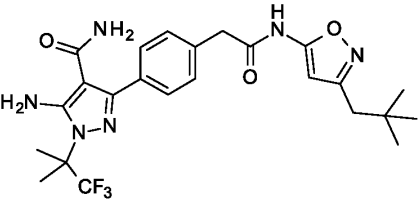
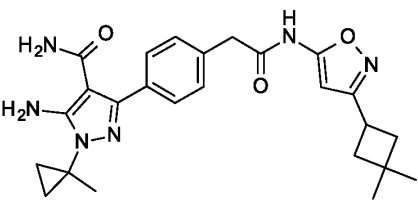
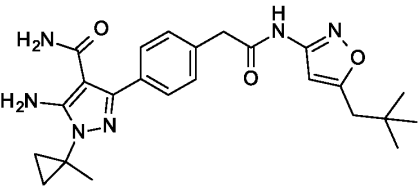
The following compounds in Table 33 are prepared essentially as described 5-amino-1-isopropyl-3-[4-([3-(pyridin-2-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide, 0.3 formic acid, using the appropriate reagents, adjusting reaction time to

15 determine completion of the reaction and using appropriate chromatography conditions for purification. The salt formation depends on purification conditions. H₂O₂ (about 15-30 equiv) can be added dropwise or portionwise, H₂O can be added if necessary, and temperature can range from about RT to 50 °.

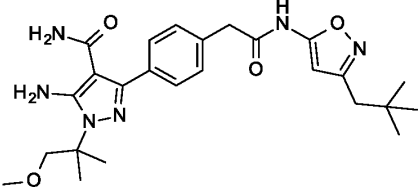
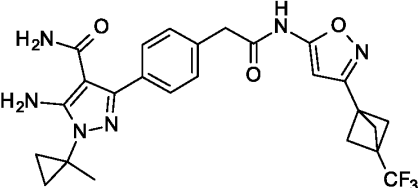
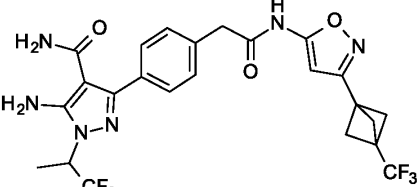
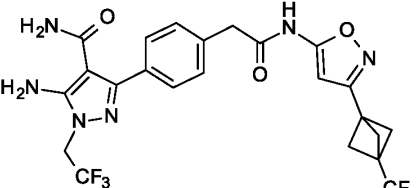
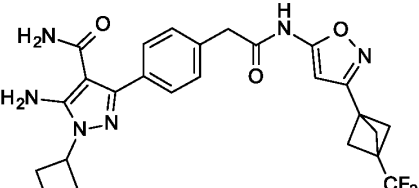
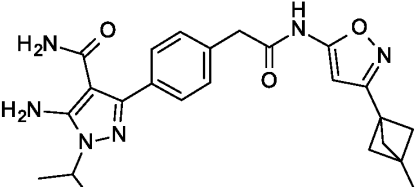
Table 33

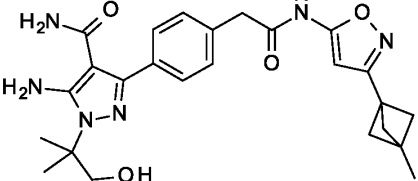
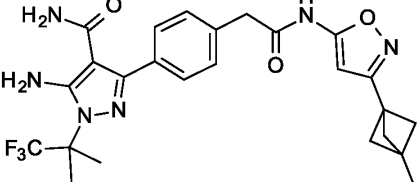
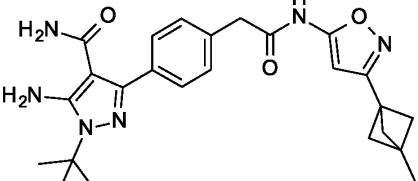
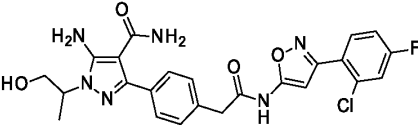
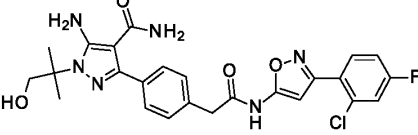
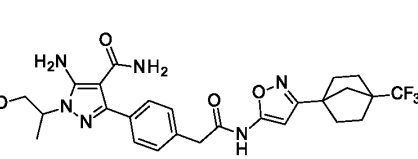
Ex. No.	Chemical name	Structure	ES/MS m/z (M+H)
224	5-Amino-1-isopropyl-3-[4-([5-(2-methylbutan-2-yl)-1,2-oxazol-3-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		439.4

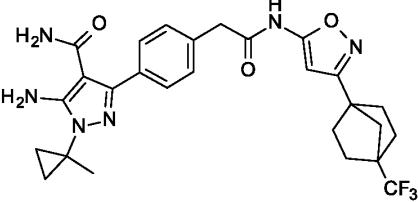
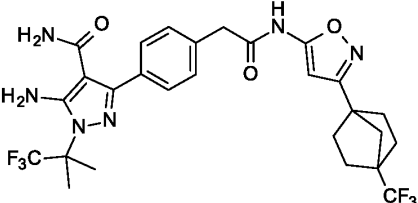
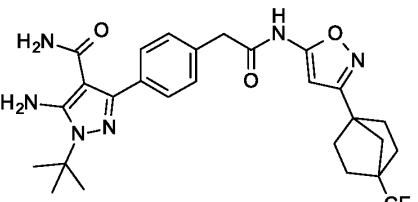
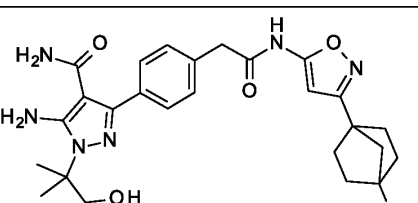
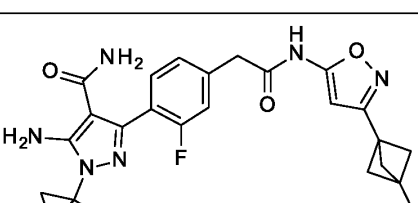
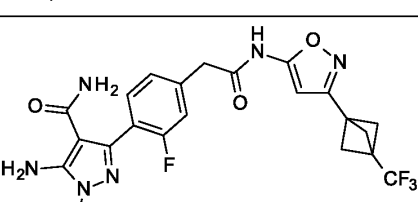
-187-

225	5-Amino-3-[4-([3-(3,5-dichloropyridin-2-yl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		514.1
226	5-Amino-3-[4-([5-(2,2-dimethylpropyl)-1,2-thiazol-3-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		455.3
227	5-Amino-3-[4-([5-(2,2-dimethylpropyl)-1,3-thiazol-2-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		455.4
228	5-Amino-3-[4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazole-4-carboxamide		507.3
229	5-Amino-3-[4-([3-(3,3-dimethylcyclobutyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-methylcyclopropyl)pyrazole-4-carboxamide		485.4 M+Na
230	5-Amino-1-(1-methylcyclopropyl)-3-(4-(2-((5-neopentylisoxazol-3-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide		451.4

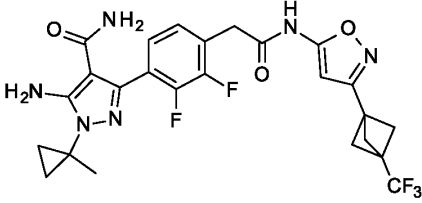
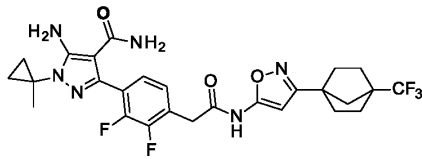
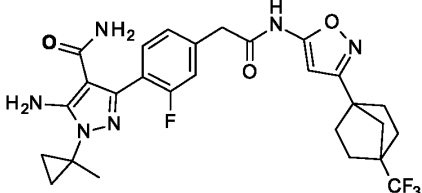
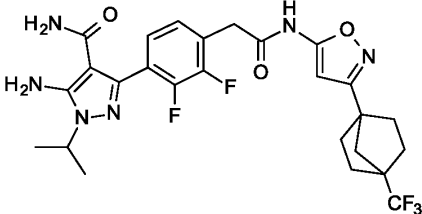
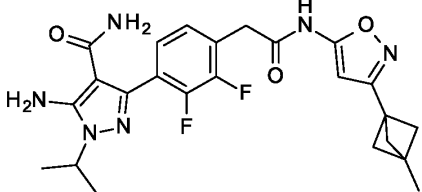
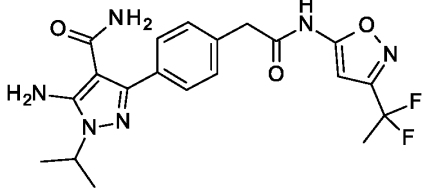
-188-

231	5-Amino-3-[4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-methoxy-2-methylpropan-2-yl)pyrazole-4-carboxamide		483.2
232	5-Amino-1-(1-methylcyclopropyl)-3-[4-([3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		515.5
233	5-Amino-3-[4-([3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-[1,1,1-trifluoropropan-2-yl]pyrazole-4-carboxamide		557.2
234	5-Amino-3-(4-(2-oxo-2-((3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide		543.3
235	5-Amino-1-cyclobutyl-3-[4-([3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		515.3
236	5-Amino-1-[1-hydroxypropan-2-yl]-3-[4-([3-(3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		465.2

237	5-Amino-1-(1-hydroxy-2-methylpropan-2-yl)-3-(4-[[[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)pyrazole-4-carboxamide		479.2
238	5-Amino-3-(4-[[[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)-1-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazole-4-carboxamide		517.3
239	5-Amino-1-tert-butyl-3-(4-[[[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)pyrazole-4-carboxamide		463.3
240	5-Amino-3-[4-([3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-hydroxypropan-2-yl)pyrazole-4-carboxamide		513.1
241	5-Amino-3-[4-([3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-hydroxy-2-methylpropan-2-yl)pyrazole-4-carboxamide		527.2
242	5-Amino-1-(1-hydroxypropan-2-yl)-3-[4-([3-(4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		547.3

243	5-Amino-1-(1-methylcyclopropyl)-3-[4-[[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		543.2
244	5-Amino-1-(1,1,1-trifluoro-2-methylpropan-2-yl)-3-[4-[[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		599.1
245	5-Amino-1-tert-butyl-3-[4-[[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		545.0
246	5-Amino-1-(1-hydroxy-2-methylpropan-2-yl)-3-[4-[[3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide		561.1
247	5-Amino-3-(2-fluoro-4-(2-((3-(3-methylbicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(1-methylcyclopropyl)-1H-pyrazole-4-carboxamide		479.1
248	5-Amino-3-(2-fluoro-4-(2-oxo-2-((3-(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)isoxazol-5-yl)amino)ethyl)phenyl)-1-(1-methylcyclopropyl)-1H-pyrazole-4-carboxamide		533

-191-

249	5-Amino-3-[2,3-difluoro-4- [[3-[3-(trifluoromethyl)bicyclo[1.1.1]]pentan-1-yl]-1,2-oxazol-5- yl]carbamoyl)methyl]phenyl] -1-(1-methylcyclopropyl)pyrazole- 4-carboxamide		551.1
250	5-Amino-3-[2,3-difluoro-4- [[3-[4-(trifluoromethyl)bicyclo[2.2.1]]heptan-1-yl]-1,2-oxazol-5- yl]carbamoyl)methyl]phenyl] -1-(1-methylcyclopropyl)pyrazole- 4-carboxamide		579.2
251	5-Amino-3-(2-fluoro-4-(2- oxo-2-((3-(4-(trifluoromethyl)bicyclo[2.2.1]]heptan-1-yl)isoxazol-5- yl)amino)ethyl)phenyl)-1-(1- methylcyclopropyl)-1H- pyrazole-4-carboxamide		561.2
252	5-Amino-3-[2,3-difluoro-4- [[3-[4-(trifluoromethyl)bicyclo[2.2.1]]heptan-1-yl]-1,2-oxazol-5- yl]carbamoyl)methyl]phenyl] -1-isopropylpyrazole-4- carboxamide		567.3
253	5-Amino-3-[2,3-difluoro-4- [[3-[4-(trifluoromethyl)bicyclo[2.2.1]]heptan-1-yl]-1,2-oxazol-5- yl]carbamoyl)methyl]phenyl] -1-isopropylpyrazole-4- carboxamide		485.2
254	5-Amino-3-(4-(2-((3-(1,1- difluoroethyl)isoxazol-5- yl)amino)-2-oxoethyl)phenyl)-1- isopropyl-1H-pyrazole-4- carboxamide		433.5

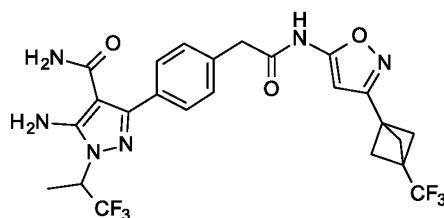
-192-

255	5-Amino-3-[4-([5-(2,2-dimethylpropyl)-4-methyl-1,3-thiazol-2-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		491.4 M+Na
256	5-Amino-3-[4-([3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-methylcyclopropyl)pyrazole-4-carboxamide		461.2
257	5-Amino-3-[4-([3-(2,2-dimethylpropyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-isopropylpyrazole-4-carboxamide		439.4

Example 258

5-Amino-3-[4-([3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-[1,1,1-trifluoropropan-2-yl]pyrazole-4-carboxamide, Isomer

1



5

Example 259

5-Amino-3-[4-([3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-[1,1,1-trifluoropropan-2-yl]pyrazole-4-carboxamide, Isomer

2

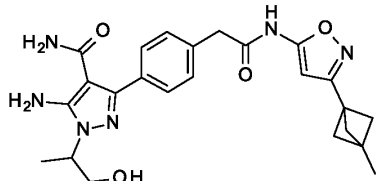
10 5-Amino-3-[4-([3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-[1,1,1-trifluoropropan-2-yl]pyrazole-4-carboxamide (70 mg) is purified by Prep-CHIRAL-HPLC with the following conditions: Column: Lux 5 μ

-193-

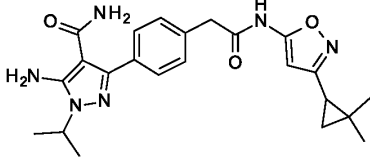
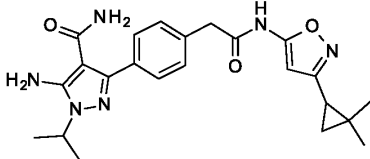
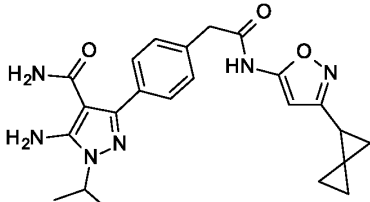
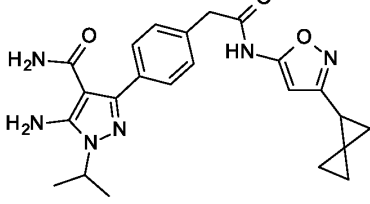
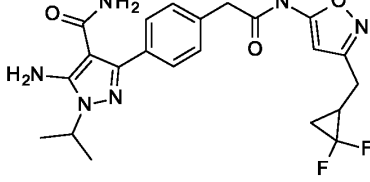
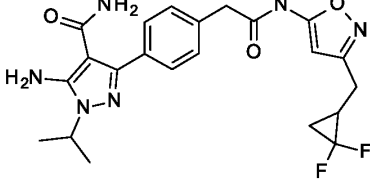
Cellulose-4, AXIA Packed, 2.12*25 cm, 5 μ m eluting with 80% hexanes (0.1%TFA) and 20% IPA; flow rate 20 mL/min in 37 min 205/250 nm to give the title compound of Isomer 1 $t_{(R)}$ 18.6 min (15.4 mg, 22.0%, ee=100%) as a light brown solid, ES/MS (m/z) 557.2 (M+H) and the title compound of Isomer 2 $t_{(R)}$ 29.8 min (14.9 mg, 21.2%, ee=99.5%) as a light brown solid, ES/MS (m/z) 557.2 (M+H).

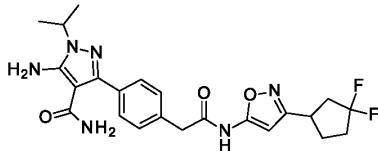
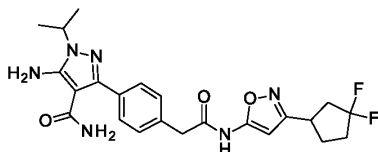
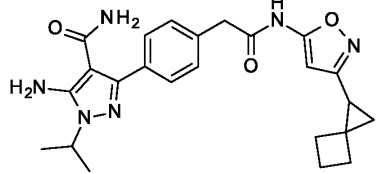
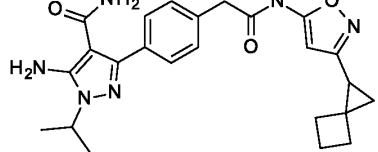
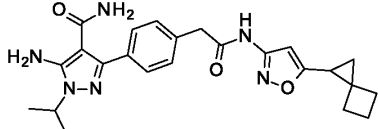
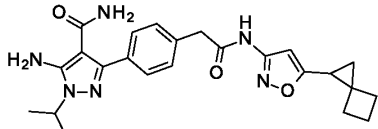
The following compounds in Table 34 are prepared essentially as described 5-amino-3-[4-[(3-[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)carbamoyl)methyl]phenyl]-1-[1,1,1-trifluoropropan-2-yl]pyrazole-4-carboxamide, Isomer 1 and Isomer 2 and adjusting the purification system as appropriate.

10 Table 34

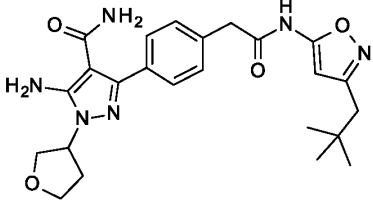
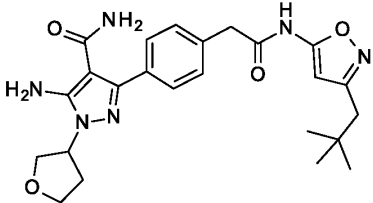
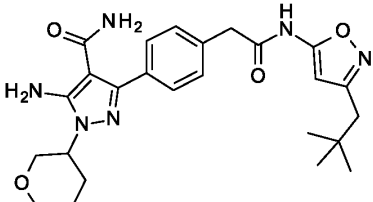
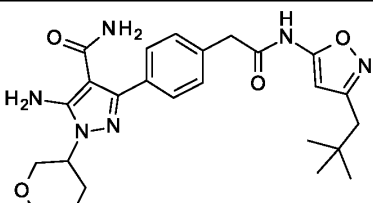
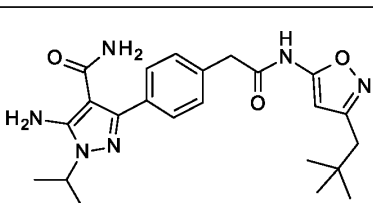
Ex. No.	Chemical name	Structure	ES/MS m/z (M+H)	$t_{(R)}$ min
1260	5-Amino-1-[1-hydroxypropan-2-yl]-3-(4-[[3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl)carbamoyl)methyl]phenyl)pyrazole-4-carboxamide, Isomer 1		465.1	5.25

¹ 261	5-Amino-1-[1-hydroxypropan-2-yl]-3-(4-[[[3-[3-methylbicyclo[1.1.1]pentan-1-yl]-1,2-oxazol-5-yl]carbamoyl]methyl]phenyl)pyrazole-4-carboxamide, Isomer 2		465.1	11.5
¹ 262	5-Amino-3-[4-([3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-hydroxypropan-2-yl)pyrazole-4-carboxamide, Isomer 1			8.12
¹ 263	5-Amino-3-[4-([3-(2-chloro-4-fluorophenyl)-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]-1-(1-hydroxypropan-2-yl)pyrazole-4-carboxamide, Isomer 2			16.3
² 264	5-Amino-1-[1-hydroxypropan-2-yl]-3-[4-([3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide, Isomer 1		547.2	11.4 3
² 265	5-Amino-1-[1-hydroxypropan-2-yl]-3-[4-([3-[4-(trifluoromethyl)bicyclo[2.2.1]heptan-1-yl]-1,2-oxazol-5-yl]carbamoyl)methyl]phenyl]pyrazole-4-carboxamide, Isomer 2		547.3	18.0 5

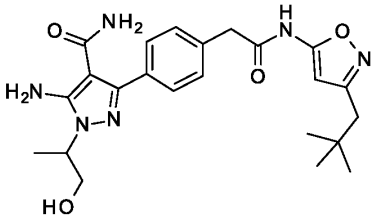
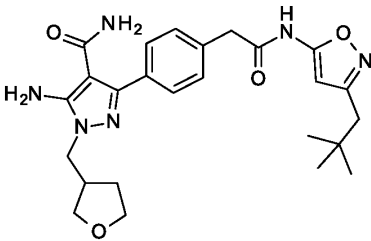
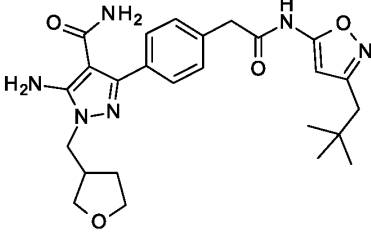
³ 266	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-dimethylcyclopropyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		437	8.70
³ 267	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-dimethylcyclopropyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		437	12.8
⁴ 268	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[spiro[2.2]pentan-2-yl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		435.1	8.29
⁴ 269	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[spiro[2.2]pentan-2-yl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		435.1	10.15
⁵ 270	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-difluorocyclopropyl]methyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		459	5.35
⁵ 271	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-difluorocyclopropyl]methyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		459.1	6.35

272	5-Amino-3-[4-[2-[[3-[3,3-difluorocyclopentyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide, Isomer 1		473	28.5
273	5-Amino-3-[4-[2-[[3-[3,3-difluorocyclopentyl]isoxazol-5-yl]amino]-2-oxo-ethyl]phenyl]-1-isopropyl-pyrazole-4-carboxamide, Isomer 2		473	32.8 4
⁴ 274	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[spiro[2.3]hexan-2-yl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		449	10.6
⁴ 275	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[spiro[2.3]hexan-2-yl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		449	13.5 4
⁶ 276	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[5-[spiro[2.3]hexan-2-yl]isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		449.1	2.22
277	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[5-[spiro[2.3]hexan-2-yl]isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		449.1	3.79

278	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[5-[2,2-dimethylcyclobutyl]isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		451.1	20.95
279	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[5-[2,2-dimethylcyclobutyl]isoxazol-3-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		451	21.94
280	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-dimethylcyclobutyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 1		451.1	5.27
⁷ 281	5-Amino-1-isopropyl-3-[4-[2-oxo-2-[[3-[2,2-dimethylcyclobutyl]isoxazol-5-yl]amino]ethyl]phenyl]pyrazole-4-carboxamide, Isomer 2		451.4	5.76
⁸ 282	5-Amino-1-(1-cyclopropylethyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide, Isomer 1		465.2	2.37
⁸ 283	5-Amino-1-(1-cyclopropylethyl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide, Isomer 2		465.2	2.96

⁹ 284	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazole-4-carboxamide, Isomer 1		467.2	1.7
⁹ 285	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydrofuran-3-yl)-1H-pyrazole-4-carboxamide, Isomer 2		467.2	2.2
286	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazole-4-carboxamide, Isomer 1		481.4	4.9
287	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazole-4-carboxamide, Isomer 2		481.4	7.1
¹⁰ 288	5-Amino-1-(1-hydroxypropan-2-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide, Isomer 1		455.2	1.11

-199-

10 ²⁸⁹	5-Amino-1-(1-hydroxypropan-2-yl)-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1H-pyrazole-4-carboxamide, Isomer 2		455.2	1.46
11 ²⁹⁰	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazole-4-carboxamide, Isomer 1		481.4	1.71
11 ²⁹¹	5-Amino-3-(4-(2-((3-neopentylisoxazol-5-yl)amino)-2-oxoethyl)phenyl)-1-((tetrahydrofuran-3-yl)methyl)-1H-pyrazole-4-carboxamide, Isomer 2		481.4	2.38

¹CHIRAL ART Amylose-SA, 2*25 cm, 5 μm, 70% hexanes (10 mM NH₃ in MeOH and 30% EtOH).

²CHIRALPAK IA 2*25 cm, 5 μm, 70% hexanes (10 mM NH₃ in MeOH) and 30% EtOH.

³CHIRALPAK AD 250 mm x 4.6, 5 μm, 70% to 30% CO₂ with EtOH (0.5% IPAm).

5 ⁴ Waters Prep SFC200 Chiralpak AD-H 5μm, 250 x 30 mm 70 30 CO₂ / EtOH (0.5% IPAm).

⁵CHIRALPAK AD-H 5 μm, 250x30 mm, 78% CO₂/MeOH (0.5% IPAm).

⁶Chiralcel OD 500x76.5 mm, 20 μm, 100% ACN (0.05% IPA).

⁷Waters Prep SFC80 (Pirkle (R,R) Whelk-01 5 μm, 250x21.1 mm, 70% CO₂/MeOH (0.5% IPAm).

10 ⁸ChiralPak IC, 4.6x150 mm, 30% MeOH/CO₂.

⁹ChiralPak AD-H, 4.6x150 mm, 35% EtOH/CO₂.

¹⁰ChiralCel OJ-H, 4.6x150 mm, 15% MeOH/CO₂.

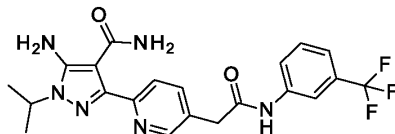
¹¹ChiralPak IA, 4.6x150 mm, 30% EtOH/CO₂.

15

Example 292

5-Amino-1-isopropyl-3-[5-[2-oxo-2-[3-(trifluoromethyl)anilino]ethyl]-2-pyridyl]pyrazole-4-carboxamide

-200-



To a stirred solution of 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]acetic acid (0.070 g, 0.24 mmol), 3-(trifluoromethyl)aniline (0.047 g, 0.29 mmol), and DIPEA (0.16 g, 1.22 mmol) in DMF (2 mL) is added T3P[®] (0.46 g, 0.73 mmol, 50% in DMF). The mixture is stirred for 2 hr at RT under N₂ then concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 40% to 60% ACN in H₂O (0.1% FA) to give 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]-N-[3-(trifluoromethyl)phenyl]acetamide (0.050 g, 45%) as a white solid. ES/MS (m/z) 429.1 (M+H).

To a stirred solution of 2-[6-(5-amino-4-cyano-1-isopropyl-pyrazol-3-yl)-3-pyridyl]-N-[3-(trifluoromethyl)phenyl]acetamide (0.050 g, 0.11 mmol) and NaOH (0.13 g, 0.58 mmol) in EtOH:DMSO (1.2 mL, 5:1) at 0 °C is added H₂O₂ (0.13 g, 1.16 mmol, 30% in H₂O). The mixture is stirred for 4 hr at 40 °C. The solution is cooled to 0 °C, quenched with saturated aq. Na₂SO₃, and extracted with EtOAc (2x10 mL). The combined organic extracts are washed with brine (2x30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by reversed-phase chromatography (C18 gel column), eluting with a gradient of 35% to 45% ACN in H₂O (0.1% NH₃H₂O) to give the title compound (0.021 g, 40%) as a white solid. ES/MS (m/z) 447.1 (M+H).

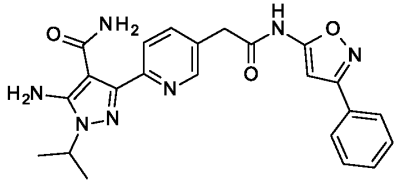
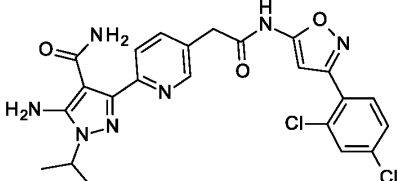
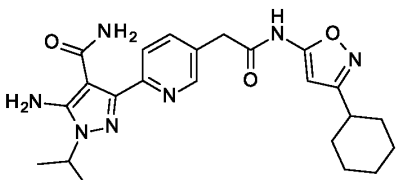
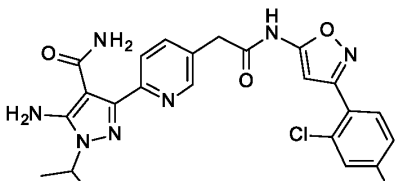
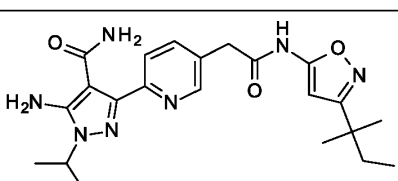
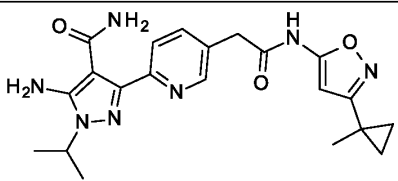
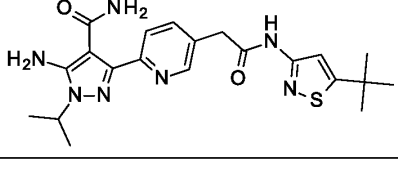
The compounds in Table 35 are prepared essentially as described for 5-amino-1-isopropyl-3-[5-[2-oxo-2-[3-(trifluoromethyl)anilino]ethyl]-2-pyridyl]pyrazole-4-carboxamide, using the appropriate amine and carboxylic acid (or lithium salt) and adjusting the reaction time as needed to complete the reaction.

-201-

Table 35

Ex. No.	Chemical Name	Structure	ES/MS m/z (M+H)
293	5-Amino-1-isopropyl-3-[5-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]-2-pyridyl]pyrazole-4-carboxamide		480.2
294	5-Amino-1-isopropyl-3-[5-[2-[[3-(1-methylcyclopentyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]pyrazole-4-carboxamide		452
295	5-Amino-1-isopropyl-3-[5-[2-[[3-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]-2-pyridyl]pyrazole-4-carboxamide		452.2
296	5-Amino-3-[5-[2-[[3-(2-chlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		480
297	5-Amino-3-[5-[2-[(5-tert-butylisoxazol-3-yl)amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		426
298	5-Amino-1-isopropyl-3-[5-[2-oxo-2-[(5-phenylisoxazol-3-yl)amino]ethyl]-2-pyridyl]pyrazole-4-carboxamide		446

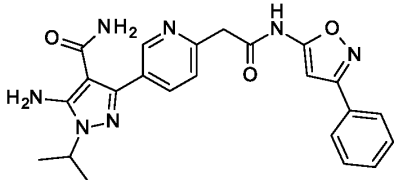
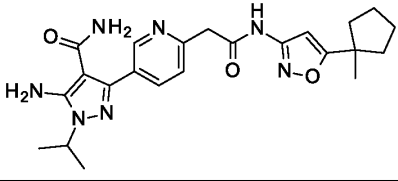
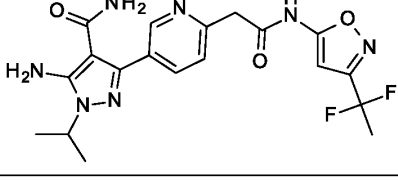
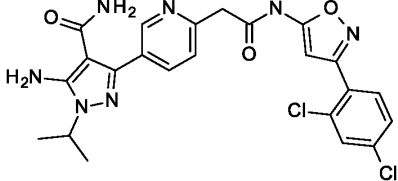
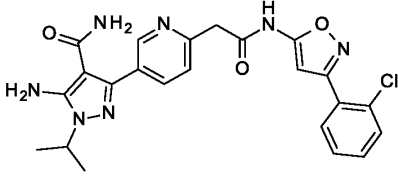
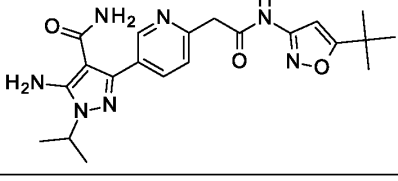
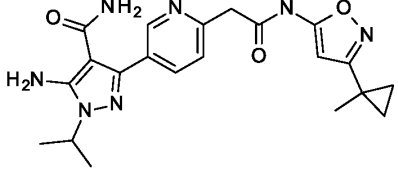
-202-

299	5-Amino-1-isopropyl-3-[5-[2-oxo-2-[(3-phenylisoxazol-5-yl)amino]ethyl]-2-pyridyl]pyrazole-4-carboxamide		446
300	5-Amino-3-[5-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		514.1
301	5-Amino-3-[5-[2-[(3-cyclohexylisoxazol-5-yl)amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		452.4
302	5-Amino-3-[5-[2-[[3-(2-chloro-4-fluoro-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		498
303	5-Amino-3-[5-[2-[[3-(1,1-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		440
304	5-Amino-1-isopropyl-3-[5-[2-[[3-(1-methylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]pyrazole-4-carboxamide		424
305	5-Amino-3-[5-[2-[(5-tert-butylisothiazol-3-yl)amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		442

-203-

306	5-Amino-3-[5-[2-[[3-(1,1-difluoroethyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-2-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		434
307	5-Amino-1-isopropyl-3-[5-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]pyrazin-2-yl]pyrazole-4-carboxamide		481.1
308	5-Amino-3-[5-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]pyrazin-2-yl]-1-isopropyl-pyrazole-4-carboxamide		515.1
309	5-Amino-1-isopropyl-3-[5-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]pyrazin-2-yl]pyrazole-4-carboxamide		453.2
310	5-Amino-3-[5-[2-[[3-(1,1-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]pyrazin-2-yl]-1-isopropyl-pyrazole-4-carboxamide		441.3
311	5-Amino-3-[5-[2-[(5-tert-butylisoxazol-3-yl)amino]-2-oxo-ethyl]pyrazin-2-yl]-1-isopropyl-pyrazole-4-carboxamide		425.3 (M-H)
312	5-Amino-1-isopropyl-3-[6-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]-3-pyridyl]pyrazole-4-carboxamide		480.3

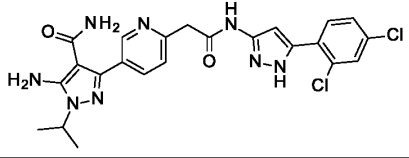
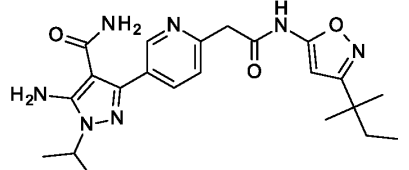
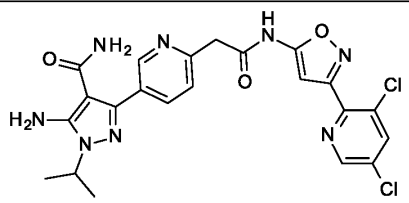
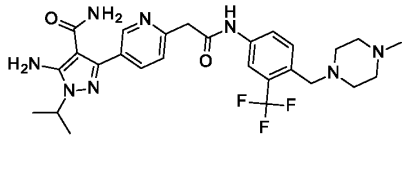
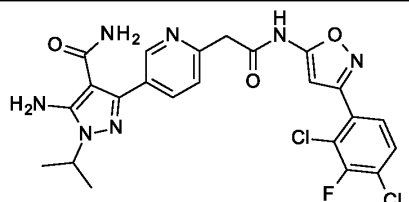
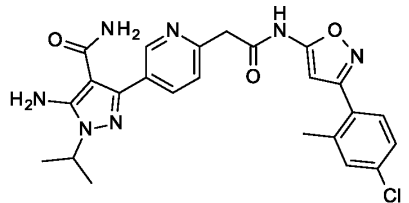
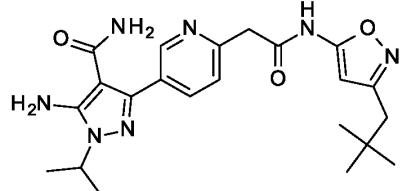
-204-

313	5-Amino-1-isopropyl-3-[6-[2-oxo-2-[(3-phenylisoxazol-5-yl)amino]ethyl]-3-pyridyl]pyrazole-4-carboxamide		446
314	5-Amino-1-isopropyl-3-[6-[2-[[5-(1-methylcyclopentyl)isoxazol-3-yl]amino]-2-oxo-ethyl]-3-pyridyl]pyrazole-4-carboxamide		452
315	5-Amino-3-[6-[2-[[3-(1,1-difluoroethyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		434
316	5-Amino-3-[6-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		514
317	5-Amino-3-[6-[2-[[3-(2-chlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		480.2
318	5-Amino-3-[6-[2-[(5-tert-butylisoxazol-3-yl)amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		426.4
319	5-Amino-1-isopropyl-3-[6-[2-[[3-(1-methylcyclopropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]pyrazole-4-carboxamide		424

-205-

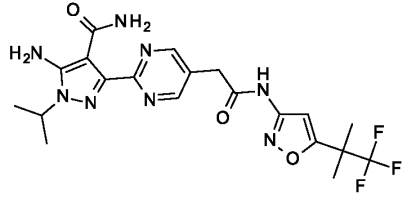
320	5-Amino-3-[6-[2-[[3-(4-chloro-3-fluoro-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		498.2
321	5-Amino-3-[6-[2-[[3-(4-chloro-2-fluoro-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		498.2
322	5-Amino-3-[6-[2-[[3-(4-chloro-2-methoxy-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		510.2
323	5-Amino-3-[6-[2-[[3-(2-chloro-4-fluoro-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		498
324	5-Amino-3-[6-[2-[[3-(2-chloro-4-methyl-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		494.2
325	5-Amino-3-[6-[2-[[3-[2-chloro-4-(trifluoromethyl)phenyl]isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		548.1

-206-

326	5-Amino-3-[6-[2-[[5-(2,4-dichlorophenyl)-1H-pyrazol-3-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		513.2
327	5-Amino-3-[6-[2-[[3-(1,1-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		440.4
328	5-Amino-3-[6-[2-[[3-(3,5-dichloro-2-pyridyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		515.0
329	5-Amino-1-isopropyl-3-[6-[2-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)anilino]-2-oxo-ethyl]-3-pyridyl]pyrazole-4-carboxamide		559.3
330	5-Amino-3-[6-[2-[[3-(2,4-dichloro-3-fluorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		532.1
331	5-Amino-3-[6-[2-[[3-(4-chloro-2-methylphenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		494.1
332	5-Amino-3-[6-[2-[[3-(2,2-dimethylpropyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		440.2

333	5-Amino-3-[6-[2-[[5-(2,4-dichlorophenyl)-1-methyl-pyrazol-3-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		527.1
334	5-Amino-3-[6-[2-[[3-(2-chloro-4-methoxy-phenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		510.1
335	5-Amino-1-isopropyl-3-[6-[2-oxo-2-[[5-(3,3,3-trifluoro-1,1-dimethyl-propyl)isoxazol-3-yl]amino]ethyl]-3-pyridyl]pyrazole-4-carboxamide		494.2
336	5-Amino-3-[6-[2-[[5-(2,2-dimethylpropyl)isoxazol-3-yl]amino]-2-oxo-ethyl]-3-pyridyl]-1-isopropyl-pyrazole-4-carboxamide		440.1
337	5-Amino-1-ethyl-3-[6-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]-3-pyridyl]pyrazole-4-carboxamide		466.1
338	5-Amino-1-isopropyl-3-[2-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]pyrimidin-5-yl]pyrazole-4-carboxamide		481.3
339	5-Amino-3-[2-[2-[[3-(2,4-dichlorophenyl)isoxazol-5-yl]amino]-2-oxo-ethyl]pyrimidin-5-yl]-1-isopropyl-pyrazole-4-carboxamide		515.1

-208-

340	5-Amino-1-isopropyl-3-[5-[2-oxo-2-[[5-(2,2,2-trifluoro-1,1-dimethyl-ethyl)isoxazol-3-yl]amino]ethyl]pyrimidin-2-yl]pyrazole-4-carboxamide		481.1
-----	---	--	-------

Biological Assays

The following assays demonstrate that the compounds described herein are RET kinase inhibitors

5

Assay A: RET Enzyme Assay

Compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx are screened for their ability to inhibit wildtype, V804M, and G810S mutant RET kinase using CisBio's HTRF® KinEASE™-TK assay technology. N-terminal GST tagged recombinant human RET cytoplasmic domain (aa 658-end) from Eurofins (1.25 nM RET; Catalog No. 14-570M) or N-terminal GST tagged recombinant human V804M mutant RET cytoplasmic domain (aa 658-end) from Millipore (1.25 nM enzyme; Catalog No. 14-760) or N-Terminal GST-tagged recombinant human G810S (aa-658-end) (1.25 nM Enzyme; produced in insect cells) is incubated with 62.5 nM TK-substrate biotin (CisBio, part of Catalog No. 62TK0PEC) and 1 mM ATP along with test compound (0.4% final DMSO in the assay) in a 1X Cisbio enzymatic buffer consisting of 1 nM DTT, 5 mM MgCl₂, 0.04% BSA and 0.05% Tween20 in a volume of 10 µL. Compounds are typically prepared in a threefold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 40-60 min (40 min for V804M, 60 min for WT and G810S) incubation at 22 °C, the reaction is quenched by adding quench solution (10 µL) containing 7.8 nM Streptavidine-XL665 and 0.5X TK-ab-Cryptate in HTRF detection buffer (all from CisBio, part of Cat. No. 62TK0PEC). After a 60-80 min incubation (60 minutes for WT, 80 minutes for V804M and G810S) at 22 °C, the extent of reaction is determined using a PHERastar plate reader via HTRF detection at excitation/emission 337/665 nm. Percent of inhibition is calculated with 0% inhibition referring to control conditions containing no compound (0.4% DMSO only)

-209-

and 100% inhibition represented by conditions containing no enzyme. The % inhibition values are fit to a 4 parameter logistic curve, and the determined IC₅₀ value is defined as the estimated concentration of inhibitor at the inflexion point of the fitted curve. The compounds of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 153, 154, 199, 221, 222, 292, 293, 294, 299, 300, 301, 302, 303, 306, 308, 310, 311, 316, 317, 318, 321, 324, 329, 330, and 335 all exhibited IC₅₀ values of less than 150 nM in at least one of wildtype, V804M, and G810S mutant RET kinases in these assays. This data demonstrates these compounds are RET inhibitors, as are the other compounds disclosed herein.

10

Assay B: RET cell assay

Compounds of formulas I, Ia to Ix, IIa to IIx, and/or IIIa to IIIx are screened for their ability to inhibit the intracellular autophosphorylation of RET at tyrosine 1062 as detected by In-Cell Western. HEK293 cells containing a doxycycline-inducible plasmid for inducible expression of KIF5B-RET WT and RET mutant forms V804M and G810S are seeded at 25,000 cells/ well into black poly-D-lysine pre-coated 384-well plates (Corning, Catalog No. 356697). Expression of KIF5B-RET is induced with doxycycline at 1 µg/mL and cells are incubated at 37 °C overnight. Compounds are prepared in a threefold serial dilution in DMSO before further diluting 1:100 in media prior to the addition to the cells (0.1% final DMSO concentration). Compound treatment is performed for 1 hr at 37 °C followed by fixation of cells with 4% formaldehyde for 20 min at RT and cell permeabilisation with ice-cold MeOH for 10 min at RT. Cells are incubated with Intercept® blocking buffer (Li-COR, Catalogue No. 927-70010) for 1 hr at RT. Incubation with primary antibodies against human phospho-RET (Y1062) (R&D, Catalogue No. AF5009, 1/250 dilution) and human glyceraldehyde-3-phosphate dehydrogenase (clone 6C5, Merck, Catalog No. MAB374, 1/1000 dilution) are performed overnight at 4 °C. Incubation with secondary antibodies IRDye® 800CW goat anti-rabbit IgG (Li-COR, Catalogue No. 926-32211, 1/1000 dilution) and IRDye® 680CW goat anti-mouse IgG (Li-COR, Catalogue No. 926-68070, 1/1000 dilution) are performed for 1 hr at RT. All antibody dilutions are done in Intercept® blocking buffer containing 0.05% Tween20. After washing cells with PBS-T (Cell Signaling

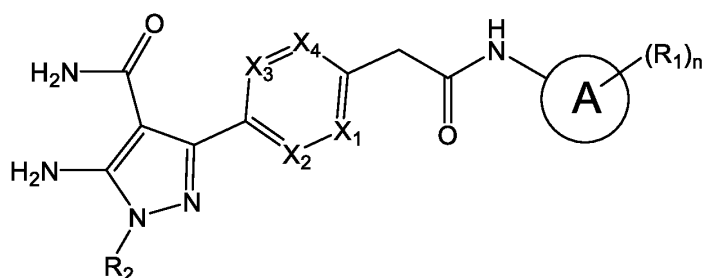
-210-

technology, Catalogue No. 9809), the images are acquired on a Li-COR Odyssey LCx at 700 and 800 nm. Percent of DMSO control is calculated with 100% signal referring to control conditions containing no compound (0.4% DMSO only) and 0% signal represented by conditions containing control compound. The % of DMSO control values are fit to a 4
5 parameter logistic curve, and the determined EC₅₀ value is defined as the estimated concentration of inhibitor at the inflexion point of the fitted curve. The compounds of Examples 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 153, 154, 199, 221, 222, 292, 293, 294, 299, 300, 301, 302, 303, 306, 308, 310, 311, 316, 317, 318, 321, 324, 329, 330, and 335 all inhibited the intracellular autophosphorylation of RET at tyrosine 1062 with EC₅₀ values of less than 150
10 nM in at least one of wildtype, V804M, and G810S RET mutant cell assays. This data demonstrates these compounds are RET inhibitors, as are the other compounds disclosed herein.

-211-

CLAIMS

1. A compound of the formula:



5 wherein

A is C₆-C₁₀ aryl or C₅-C₆ heteroaryl;

each R₁ is independently hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ heteroalkyl, -(C₁-C₄ alkyl)(C₅-C₆ heteroalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ heteroalkyl)(C₃-C₇ cycloheteroalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicycyl), -(C₀-C₄ alkyl)(C₅-C₆ aryl), -(C₀-C₄ alkyl)(C₅-C₆ heteroaryl), -(C₀-C₄ alkyl)(C₄-C₁₀ heterobicycyl), C₅-C₁₂ spiranyl, C₅-C₁₂ heterospiranyl, dimethylphosphoryl, adamantyl, C₁-C₆ alkoxy, -(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl), difluoromethylsulfanyl, or pentafluorosulfanyl, wherein each R₁ is unsubstituted or when it is capable of being substituted, it is substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, mono-, di-, or trihalomethoxy, mono-, di-, or tri-halomethyl, and C₀-C₃ alkyl-pyrrolidinyl, where the pyrrolidinyl group is unsubstituted or substituted with one, two or 3 independently selected halogen atoms, and wherein two R₁ groups can fuse to form a ring structure that includes a portion of A and is optionally aromatic, and n is 1, 2, 3, 4, 5, or 6;

X₁, X₂, X₃, and X₄ are each independently N, CH, C-CH₃, C-CH₂-OH, C-OCH₃, C-CH₂-OCH₃, or C-halogen; and

-212-

R₂ is C₁-C₆ alkyl, -(C₀-C₄ alkyl)(C₃-C₇ cycloalkyl), -(C₀-C₄ alkyl)(C₄-C₇ heterocycloalkyl), -(C₀-C₄ alkyl)(C₄-C₁₀ bicyclic) each optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl;

5 or a pharmaceutically acceptable salt thereof.

2. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein at least one of X₁, X₂, X₃, and X₄ is CH.

10 3. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein X₁, X₂, X₃, and X₄ are each CH.

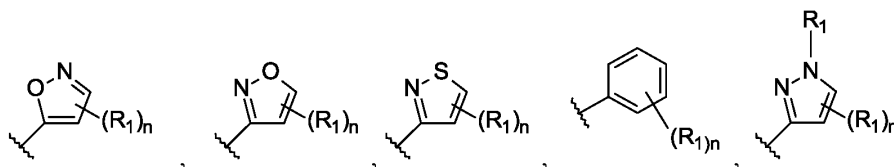
4. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein at least one of X₁, X₂, X₃, and X₄ is N.

15

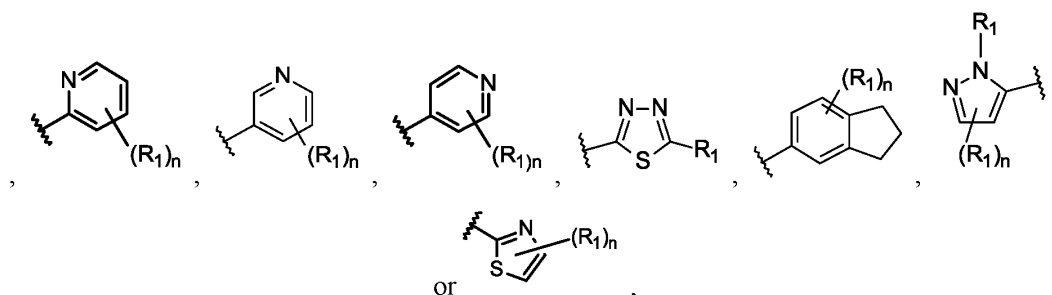
5. The compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein X₁ is N and each of X₂, X₃, and X₄ is CH.

6. The compound or a pharmaceutically acceptable salts thereof according to claim 1, 20 wherein X₂ is N and each of X₁, X₃, and X₄ is CH.

7. The compounds or a pharmaceutically acceptable salts thereof according to any one of claims 1 to 6, wherein A-(R₁)_n is



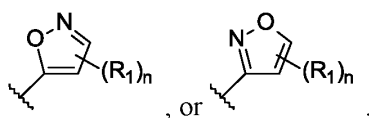
-213-



wherein a wavy line indicates connection to the backbone and the maximum value of n depends on the number of substitutable positions on the A-ring.

5

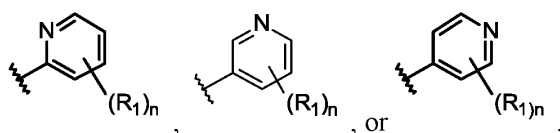
8. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-(R₁)_n is



and the maximum value of n depends on the number of substitutable positions on the A-ring.

10

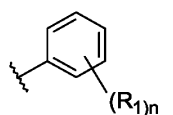
9. The compound or a pharmaceutically acceptable salts thereof according to any one of claims 1-7, wherein A-(R₁)_n is



and the maximum value of n depends on the number of substitutable positions on the A-ring.

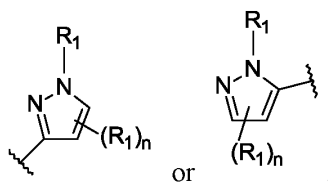
15

10. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-(R₁)_n is



-214-

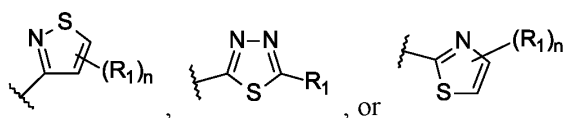
11. The compound or a pharmaceutically acceptable salts thereof according to any one of claims 1-7, wherein A-(R₁)_n is



and the maximum value of n depends on the number of substitutable positions on the A-ring.

5

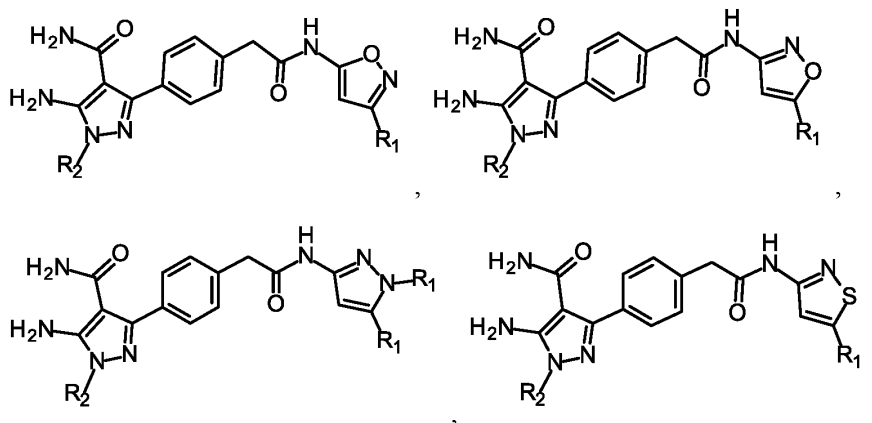
12. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein A-(R₁)_n is



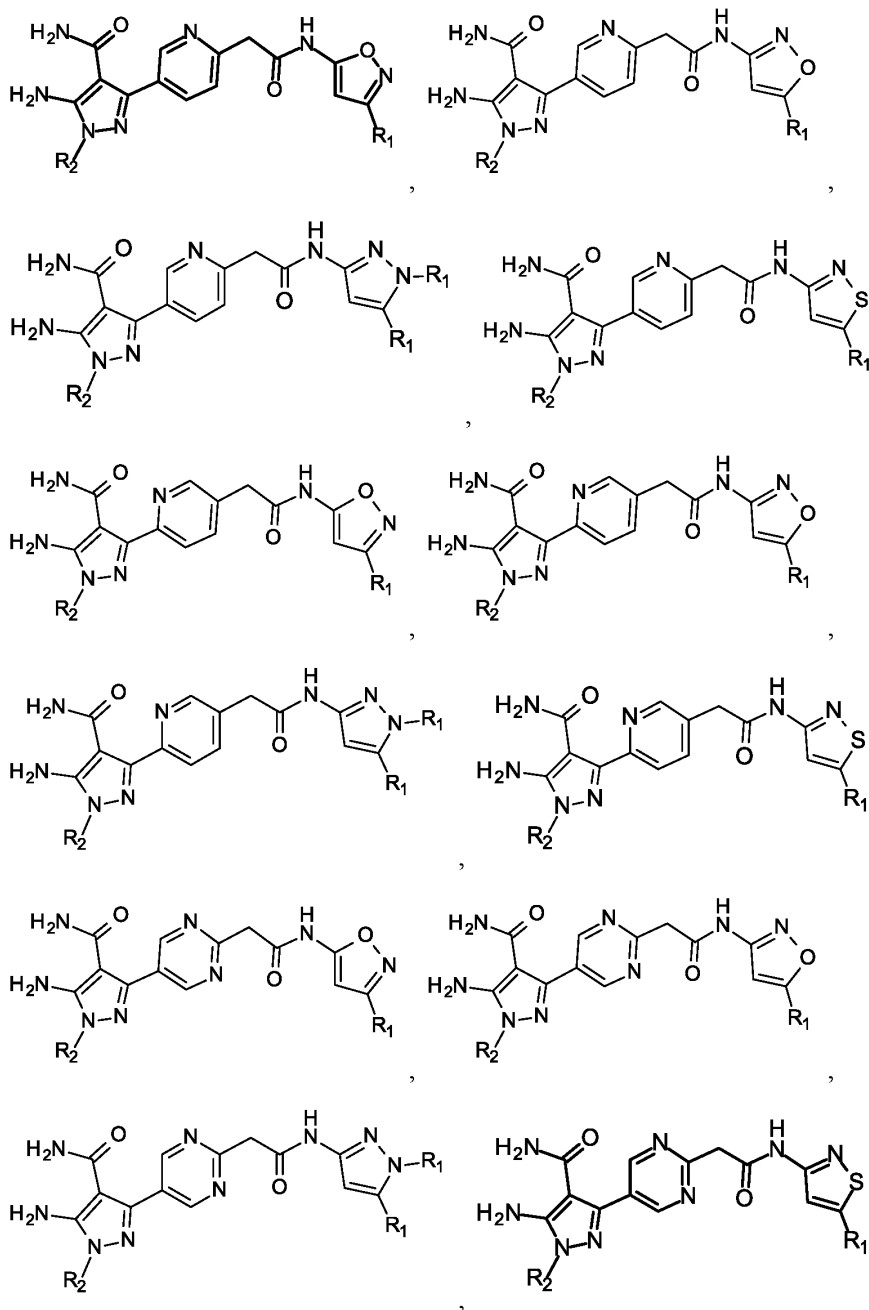
and the maximum value of n depends on the number of substitutable positions on the A-ring.

10

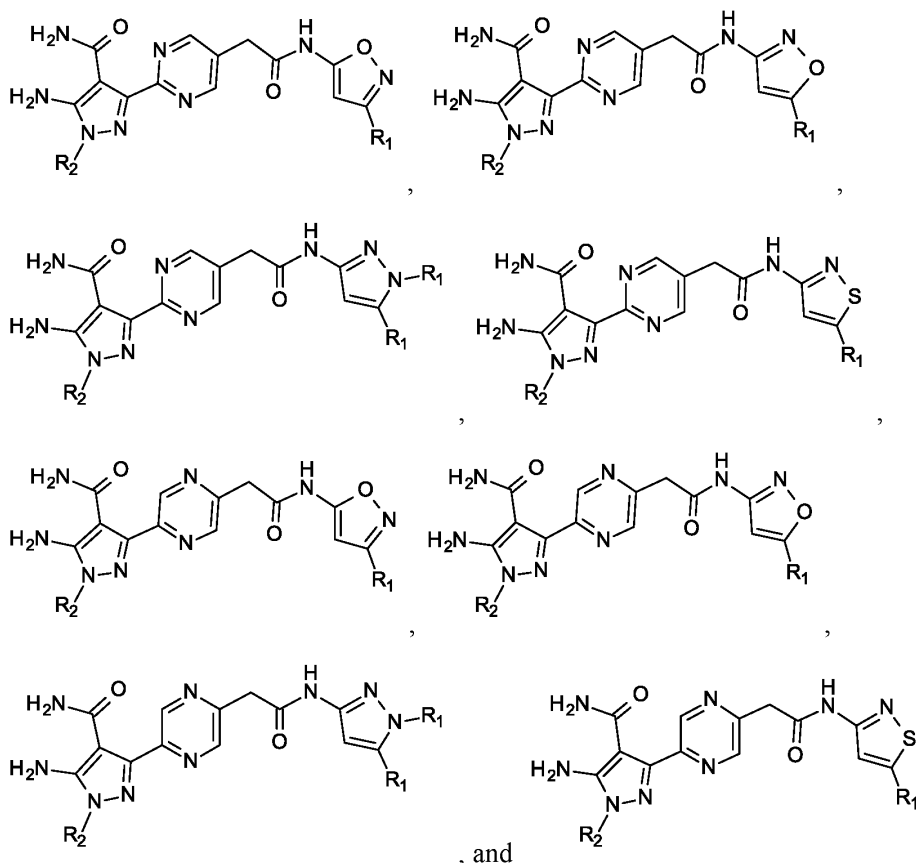
13. The compound or a pharmaceutically acceptable salt thereof according to any one of claim 1, wherein the compound is selected from the group consisting of



-215-



-216-

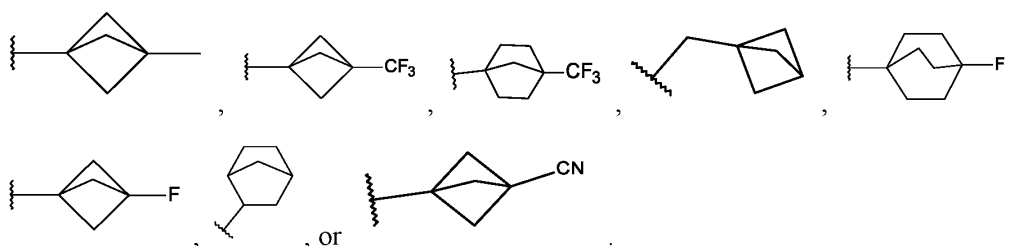


14. The compound according to any one of claims 1 to 13, wherein each R_1 is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_4 - C_{10} bicycyl and C_5 - C_{12} spiranyl, wherein the C_4 - C_{10} bicycyl is a C_4 - C_8 bridged bicycloalkyl, and wherein each R_1 is optionally substituted with one or more of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N -dimethylmethylamine, or mono-, di-, or tri-halomethyl.
15. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently 2,2-dimethylpropyl; 2-chloro-4-fluorophenyl; 2,4-dichlorophenyl; 1,1-dimethyl-2,2,2-trifluoroethyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; trifluoromethyl; 1,1-dimethyl-2,2-difluoropropyl; 1,1-dimethyl-3,3,3-

-217-

trifluoropropyl; 1-methylcyclopropyl; (1-methylcyclopropyl)methyl; 3-methylbicyclo[1.1.1]pentan-1-yl; 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl; or (3,3-dimethylcyclobutyl)methyl.

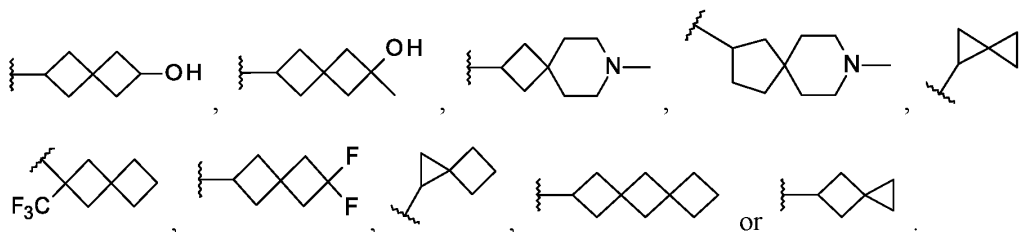
- 5 16. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is a C_4 - C_8 bridged bicycloalkyl that is unsubstituted or substituted with 1 or 2 groups independently selected from the group consisting of methyl, ethyl, CF_3 , halo, and CN.
- 10 17. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, or claim 16, wherein each R_1 is independently



- 15 18. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein n is 1 and R_1 is a C_5 - C_{12} spirane that is unsubstituted or substituted with 1 or 2 groups that are independently selected from the group consisting of $=O$, $-OH$, methyl, ethyl, CF_3 , and halo.

- 20 19. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently
-

-218-

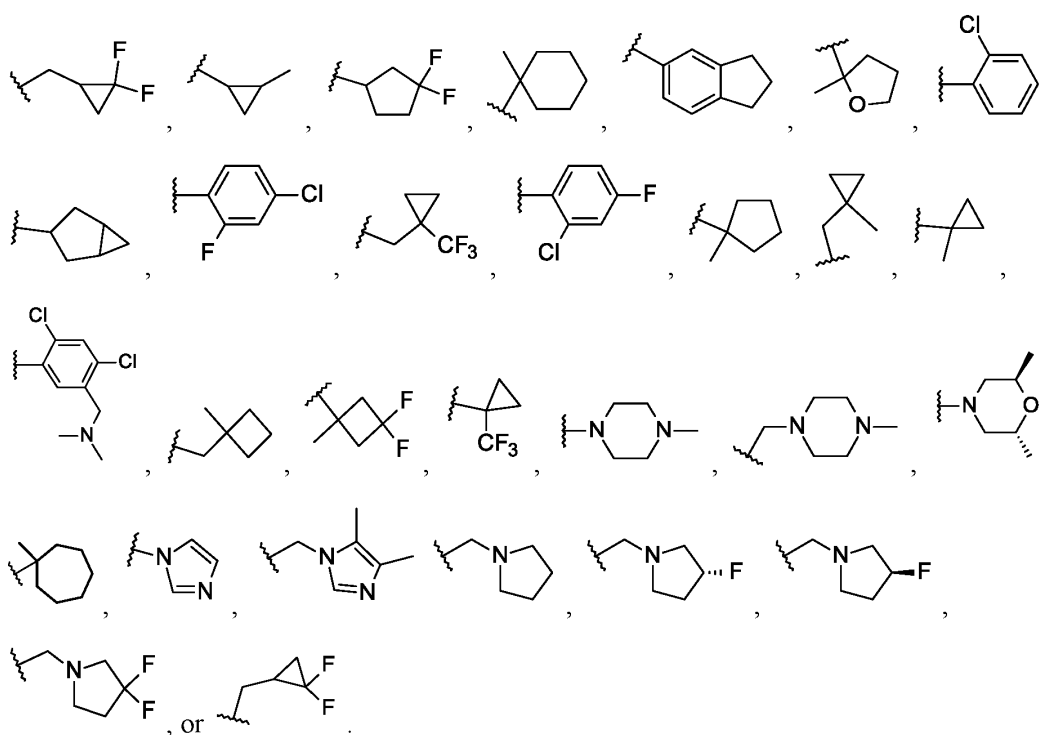


20. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently halogen, C_1 - C_6 alkyl, $-(C_0$ - C_4 alkyl)(C_3 - C_7 cycloalkyl), $-(C_0$ - C_4 alkyl)(phenyl), $-(C_1$ - C_4 alkyl)(C_5 - C_6 heteroalkyl), $-(C_0$ - C_4 heteroalkyl)(C_3 - C_7 cycloheteroalkyl), or $-(C_0$ - C_4 alkyl)(C_5 - C_6 heteroaryl), wherein each R_1 is optionally substituted with one or more substituents independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N -dimethylmethylamine, and mono-, di-, or tri-halomethyl.

21. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 13, wherein each R_1 is independently $-CH_2C(CH_3)_3$, $-CH(CH_2CH_3)_2$, $-CF_2CH_3$, $-CH_2CH_2CF_3$, $-C(CH_3)_2F$, $-C(CH_3)_2CF_3$, $-CH_2$ -cyclopentyl, $-CH_2$ -cyclohexyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -morpholinyl, $-CH_2$ -pyrrolidinyl, phenyl, naphthyl, pyran-4-yl, 4-methylphenyl, 4-methoxyphenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, 3-trifluoromethylphenyl, 3-fluoro-5-trifluoromethylphenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2,4-dimethylphenyl, 4-chlorophenyl, 2-methylphenyl, 3-fluorophenyl, 3-chlorophenyl, 2-methoxyphenyl, 4-difluoromethoxyphenyl, $-C(CH_3)_2SO_2CH_3$, 4-fluorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3-chlorophenyl, methyl, ethyl, *tert*-butyl, isopropyl, trifluoromethyl, 3-methoxyphenyl, 3-bromophenyl, 4-bromophenyl, 2,4,6-trifluoromethylphenyl, 3-tetrahydrofuranyl, $-C(CH_3)_2CH_2CH_3$, $-C(CH_3)_2OH$, 3,3-dimethylcyclobut-1-yl, 2,3-dichlorobenzyl, 3,3-difluoromethylcyclobutyl, 2,2-dimethylcycloprop-1-yl, 2,2-difluorocyclopropyl, N -methylimidazolyl, 2-methyl-4-chlorophenyl, 2,4-dichloro-3-fluorophenyl, $-CH_2OCH_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CF_2C(CH_3)_3$, $-CH(CH_3)$ cyclopropyl, 2,6-difluorophenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-chloropyrid-2-

yl, 2-methylpyrid-3-yl, 4-methylpyrid-3-yl, 3,5-dichloropyrid-2-yl, 3,3-difluorocyclopentyl, fluoro, chloro, bromo, 2-methoxy-4-chloro-phenyl, 2-fluoro-4-chlorophenyl, 3-fluoro-4-chlorophenyl, benzyl, piperidinyl, 4-methyl-piperidinyl, 4-methoxy-piperidinyl, N-methylpyrazol-3-yl, -C(O)-piperidinyl, -OCHF₂,

5

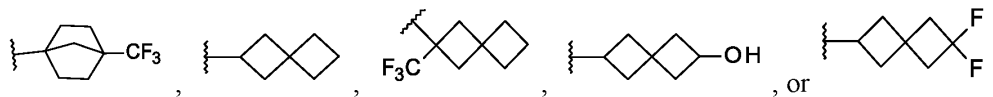


22. The compound or a pharmaceutically acceptable salt thereof according to any one of

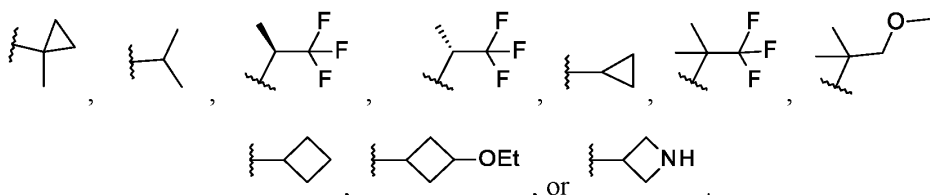


claims 1 to 13, wherein n is 1 and R₁ is 2,2-dimethylpropyl or

15 23. The compound or a pharmaceutically acceptable salt thereof according to any one of
claims 1 to 13, wherein R₁ is independently



24. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-13, wherein R₁ is C₁-C₆ alkyl, which is unsubstituted or substituted with one or more substituents that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, methylamine, N,N-dimethylmethylamine, and mono-, di-, and tri-halomethyl and n is 1 or 2.
25. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R₂ is -C₁-C₆ alkyl, -C₁-C₄ alkyl-tetrahydrofuranyl, C₃-C₆ cycloalkyl, tetrahydrofuranyl, pyranyl, -C₁-C₄ alkyl – tetrahydropyranyl, -C₁-C₄ alkyl – C₃-C₆ cycloalkyl, and azetidiny, wherein each is unsubstituted or substituted with one or two groups that are independently selected from the group consisting of halogen, cyano, hydroxyl, oxo, methyl, methoxy, hydroxymethyl, ethyl, ethoxy, hydroxyethyl, cyclopropyl, or mono-, di-, or tri-halomethyl.
26. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R₂ is of *tert*-butyl, -CH(CH₃)-cyclopropyl, -2-tetrahydrofuranyl, -3-tetrahydrofuranyl, -3-pyranyl, -4-pyranyl, -CH(CH₃)CH₂OH, -C(CH₃)₂CH₂OH, -CH₂-(2-tetrahydrofuranyl), -CH₂-(3-tetrahydrofuranyl), -(CH₂)₃OH, -C(CH₃)₂CH₂OCH₃, -CH(CH₃)CF₃, -CH₂CF₃, -C(CH₃)₂CH₂OCH₃, cyclopentyl,

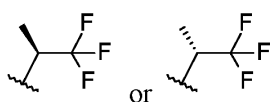


27. The compound or a pharmaceutically acceptable salt thereof according to any one of
25 claims 1-24, wherein R₂ is

-221-

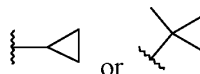


28. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R₂ is

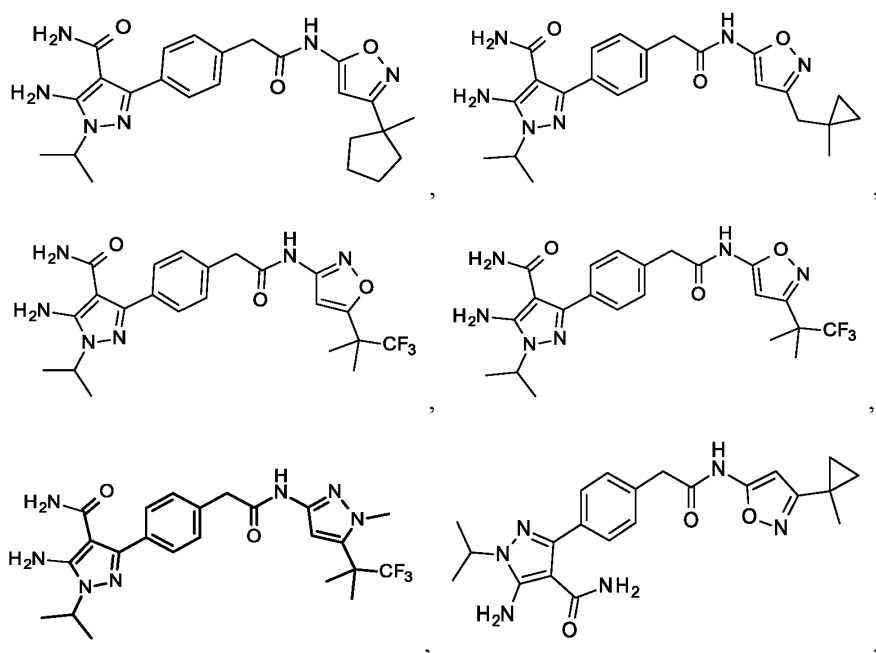


5

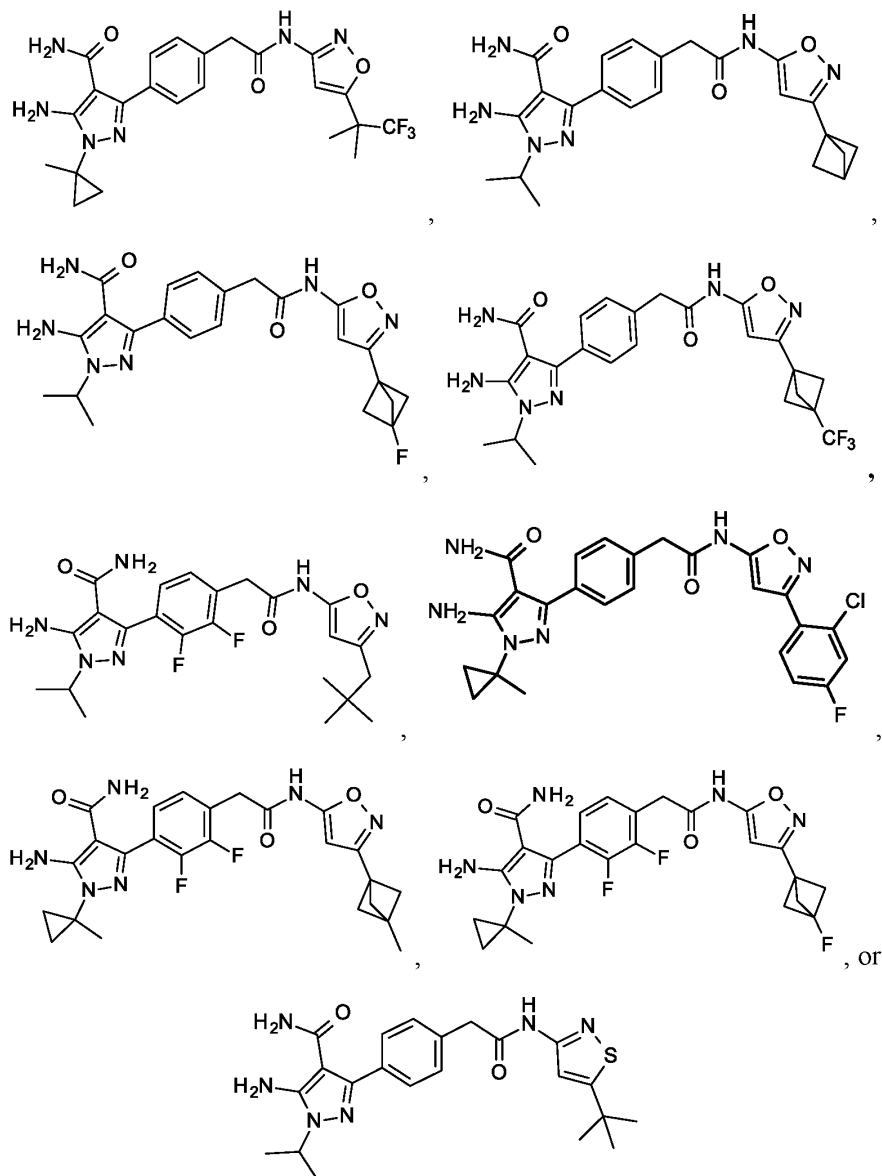
29. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-24, wherein R₂ is



30. The compound or a pharmaceutically acceptable salt thereof, according to claim 1
10 that is:

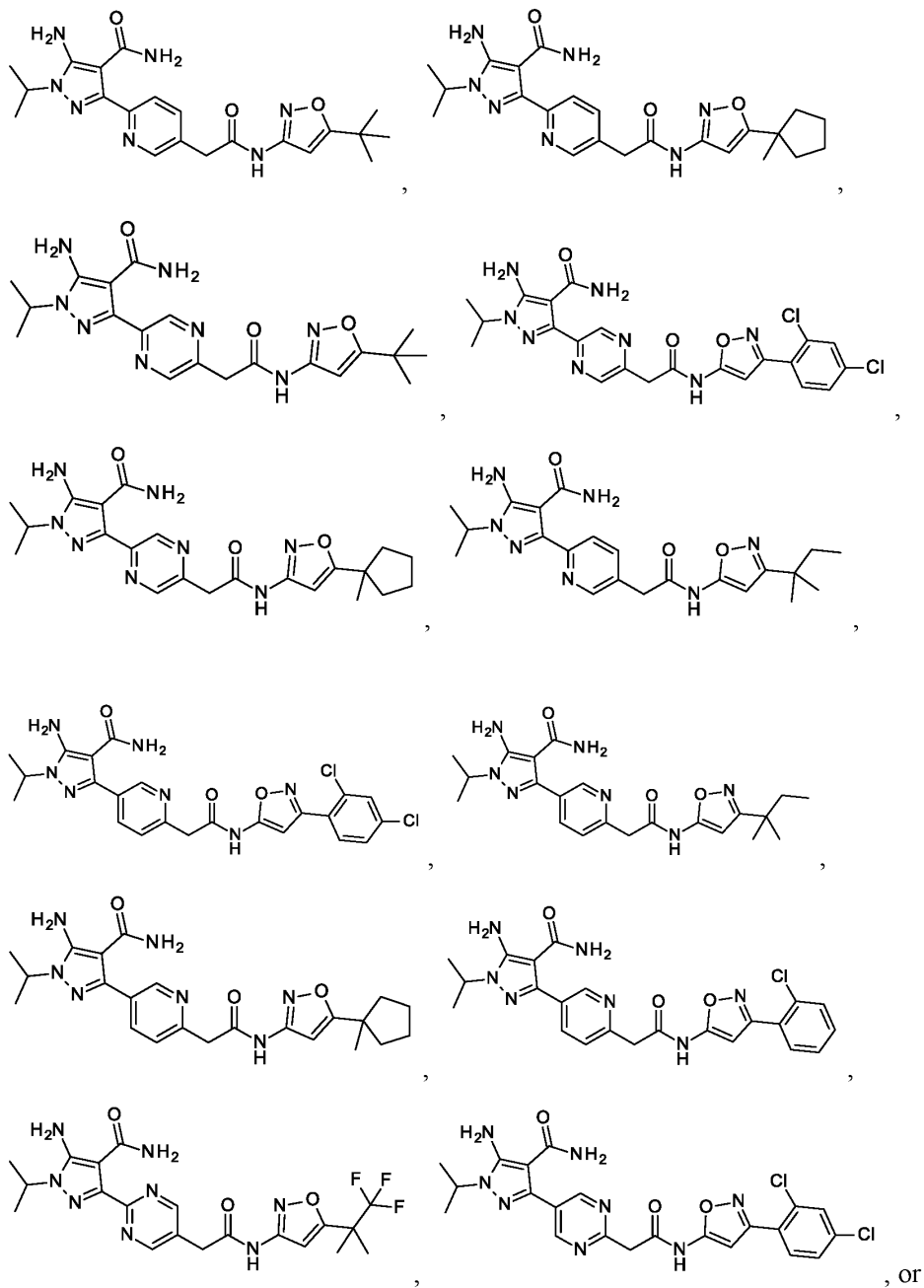


-222-

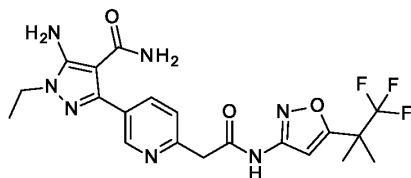


5

31. The compound or a pharmaceutically acceptable salt thereof, according to claim 1 that is



-224-



32. A method of treating cancer in a patient, comprising administering to a patient in need of such treatment an effective amount of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31.
33. The method of claim 32, wherein the cancer is a RET-associated cancer.
34. The method according to claim 32 or 33, wherein the cancer is selected from the group consisting of lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.
35. The method of claim 34, wherein the cancer is medullary thyroid cancer.
36. The method of claim 34, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, RET fusion lung cancer, or lung adenocarcinoma.
37. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for use in therapy.
38. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for use in the treatment of cancer.

-225-

39. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 38, wherein the cancer is a RET-associated cancer.

5 40. A compound, or a pharmaceutically acceptable salt thereof, for use according to claim 38 or 39, wherein the cancer is selected from the group consisting of: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast
10 cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

41. A compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 38-39, wherein the cancer is medullary thyroid cancer.

15

42. The compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 38-40, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, RET fusion lung cancer, or lung adenocarcinoma.

20

43. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 31 for the manufacture of a medicament for treating cancer.

44. A pharmaceutical composition comprising a compound, or a pharmaceutically
25 acceptable salt thereof, according to any one of claims 1 to 31 and at least one pharmaceutically acceptable carrier, diluent, or excipient.