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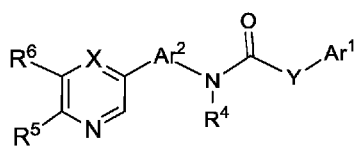
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(54) Title: PERK INHIBITING COMPOUNDS



(I)

(57) Abstract: Provided herein are compounds of formula (I), compositions, and methods useful for inhibiting PERK and for treating related conditions, diseases, and disorders.



PERK INHIBITING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Application No. 62/893,512, filed August 29, 2019, which is incorporated herein by reference in its entirety.

5

BACKGROUND OF THE INVENTION

[0002] Embodiments of the present invention relate to novel pyridinyl and pyrazinyl carboxamide compounds, to pharmaceutical compositions comprising the compounds, to methods of using the compounds to treat physiological disorders, and to intermediates and processes useful in the synthesis of the compounds. The present invention is in the field of treatment of cancer and, other diseases and disorders involving protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK).

[0003] PERK, an eIF2 kinase involved in the unfolded protein response (UPR) regulates protein synthesis, aids cells to alleviate the impact of endoplasmic reticulum stress and has been implicated in tumor genesis and cancer cell survival.

[0004] Tumor cells thrive in a hostile microenvironment caused mainly by nutrient and oxygen limitation, high metabolic demand, and oxidative stress. These stresses are known to disrupt the protein folding capacity of the endoplasmic reticulum (ER) eliciting a cellular remediation response known as the UPR. The UPR serves as a mechanism for cellular survival whereby cells are able to adapt to cope with ER stress, but under extreme stress the UPR switches the cellular machinery toward apoptosis, contributing to greater tumorigenic potential of cancer cells, tumor metastasis, tumor drug resistance, and the ability of cancer cells to avoid effective immune responses. Tumors are believed to utilize the UPR for survival under stressed conditions such as nutrient deprivation or treatment with chemotherapy. Other stress stimuli that activate UPR include hypoxia, disruption of protein glycosylation, depletion of luminal ER calcium, or changes in ER redox status.

[0005] There are three major ER transmembrane sensors of the UPR: 1) inositol requiring enzyme (IRE1a/IRE1p, encoded by ERN1 and ERN2, respectively); 2) PKR-like ER kinase (PERK, also known as PEK, encoded by EIF2AK3); and 3) the activating transcription factor 6a (encoded by ATF6). Each of these three sensors is regulated similarly through binding of the ER luminal chaperone protein GRP78 or BiP (encoded by HSPA5). When protein folding demands of the ER exceed capacity, reduced BiP binding results in activation of these ER

sensor proteins resulting in the induction of coordinated signaling pathways to increase the folding capacity of the ER and alleviate the underlying stress. Effective responses lead to cell adaptation and survival while irreparable ER stress triggers cell death and apoptosis.

[0006] PERK is a type I transmembrane serine/threonine kinase and a member of a family of kinases that phosphorylate the eukaryotic translation initiation factor 2 α (eIF2- α) and regulate translation initiation. Other family members include HRI (EIF2AK1), PKR (EIF2AK2), and GCN2 (EIF2AK4). Each eIF2 kinase responds to different cellular stress signals to regulate general translation and gene specific translational control.

[0007] PERK is an ER transmembrane protein with a stress-sensing domain inside the ER lumen and a cytosolic kinase domain. Upon sensing misfolded proteins, PERK is activated by autophosphorylation and oligomerization through release of BiP/Grp78 from the stress-sensing domain. Activated PERK phosphorylates and activates its downstream substrate, eukaryotic initiation factor 2 α (eIF2 α), which inhibits the ribosome translation initiation complex in order to attenuate protein synthesis. This serves to prevent exacerbation of ER stress by preventing the accumulation of additional misfolded proteins. Although it inhibits general protein synthesis, activated eIF2 α causes the translation of specific mRNAs involved in restoring ER homeostasis including activating transcription factor 4 (ATF4). ATF4 mediates the transcription of certain UPR target genes including those for the endoplasmic-reticulum-associated protein degradation (ERAD) pathway proteins which target misfolded proteins for ubiquitination and degradation by the proteasome. ATF4 also causes the expression of the transcription factor C/EBP homologous protein (CHoP), which sensitizes cells to ER stress-mediated apoptosis, providing a pathway for regulated removal of severely stressed cells by the organism.

[0008] Phosphorylation of eIF2 results in reduced initiation of general translation due to a reduction in eIF2B exchange factor activity decreasing the amount of protein entering the ER (and thus the protein folding burden) and translational demand for ATP.

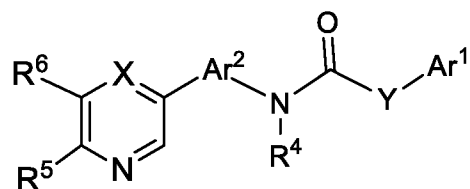
[0009] Phosphorylation of eIF2 also increases translation of some mRNAs in a gene specific manner including the transcription factor ATF4. ATF4 transcriptional targets include numerous genes involved in cell adaptation and survival including several involved in protein folding, nutrient uptake, amino acid metabolism, redox homeostasis, and autophagy.

Selective inhibition of the PERK arm of the UPR is expected to profoundly affect tumor cell

growth and survival. As such, compounds which inhibit PERK are believed to be useful in treating cancer.

SUMMARY OF THE INVENTION

[0010] Embodiments of the present invention provide a compound having the structure (I):



(I)

wherein:

Ar¹ is aryl, heteroaryl, or cycloalkyl, optionally substituted by one or more independent R¹ substituents;

Ar² is aryl or heteroaryl, optionally substituted by one or more independent R² substituents;

Y is C(R^{3a})(R^{3b})C₀₋₆alkyl, NR^{3a}, -O-, C(O), CF₂, CNOR^{3bb}, or a direct bond to Ar¹;

R^{3a} is H, alkyl, or cycloalkyl;

R^{3b} is H, alkyl, OR^{3c}, or NR^{3d}R^{3e};

R^{3bb} is H or alkyl;

R⁴ is H, alkyl, or OH;

X is CR⁷ or N;

R¹ is one or more independent H, deuterium, halo, CN, NO₂, alkyl, cycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, or C₀₋₆alkyl-O-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G¹ substituents;

R² is one or more independent H, deuterium, halo, CN, NO₂, alkyl, C₀₋₆alkylcycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, or C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H, alkyl, or cycloalkyl, optionally substituted by one or more independent G³ substituents;

R⁵ is H, CH₃, NHR⁹, or OR⁹;

R⁶ is H, alkyl, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H, CN, or alkyl, optionally substituted by one or more independent deuterium or halo;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, or C_{0-12} alkyl C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4 substituents; or

R^{8a} and R^{8b} taken together with the nitrogen to which they are attached form 5-10 membered heterocyclyl;

R^9 is H, alkyl, cycloalkyl, or heterocycloalkyl;

G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, C_{0-12} alkyl C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

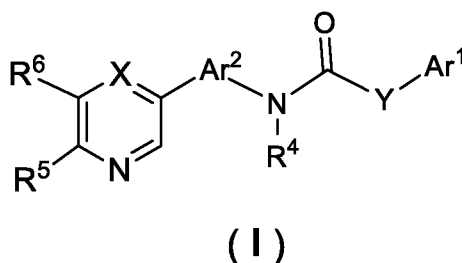
n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0011] With the current state of medical treatment, patients developing cancer often have a poor prognosis even if the disease is detected early. As such, there remains a significant need for new and effective therapies to treat cancer. The compounds of the present invention are inhibitors of PERK, and are believed to be useful in treating cancer.

[0012] The present invention provides a compound having the structure (I):



wherein:

Ar¹ is aryl, heteroaryl, or cycloalkyl, optionally substituted by one or more independent R¹ substituents;

Ar² is aryl or heteroaryl, optionally substituted by one or more independent R² substituents;

5 Y is C(R^{3a})(R^{3b})C₀₋₆alkyl, NR^{3a}, -O-, C(O), CF₂, CNOR^{3bb}, or a direct bond to Ar¹;

R^{3a} is H, alkyl, or cycloalkyl;

R^{3b} is H, alkyl, OR^{3c}, or NR^{3d}R^{3e};

R^{3bb} is H or alkyl;

R⁴ is H, alkyl, or OH;

10 X is CR⁷ or N;

R¹ is one or more independent H, deuterium, halo, CN, NO₂, alkyl, cycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, or C₀₋₆alkyl-O-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G¹ substituents;

15 R² is one or more independent H, deuterium, halo, CN, NO₂, alkyl, C₀₋₆alkylcycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, or C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H, alkyl, or cycloalkyl, optionally substituted by one or more independent G³ substituents;

R⁵ is H, CH₃, NHR⁹, or OR⁹;

20 R⁶ is H, alkyl, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H, CN, or alkyl, optionally substituted by one or more independent deuterium or halo;

R^{8a} and R^{8b} are each independently H, C₁₋₁₂alkyl, C₀₋₁₂alkylC₃₋₁₂cycloalkyl, or C₀₋₁₂alkylC₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G⁴

25 substituents; or

R^{8a} and R^{8b} taken together with the nitrogen to which they are attached form 5-10 membered heterocyclyl;

R⁹ is H, alkyl, cycloalkyl, or heterocycloalkyl;

G¹, G², G³, or G⁴ are each independently H, deuterium, halo, CN, NO₂, C₁₋₁₂alkyl, C₀₋

$_{12}\text{alkylC}_{3-12}\text{cycloalkyl}$, $\text{C}_{0-12}\text{alkylC}_{3-12}\text{heterocycloalkyl}$, OR^{10} , $\text{NR}^{10}\text{R}^{11}$, C(O)R^{10} , C(O)OR^{10} , $\text{C(O)NR}^{10}\text{R}^{11}$, OC(O)R^{10} , OC(O)OR^{10} , $\text{OC(O)NR}^{10}\text{R}^{11}$, $\text{N(R}^{12})\text{C(O)R}^{10}$, $\text{N(R}^{12})\text{C(O)OR}^{10}$, $\text{N(R}^{12})\text{C(O)NR}^{10}\text{R}^{11}$, $\text{S(O)}_n\text{R}^{10}$, $\text{S(O)}_n\text{OR}^{10}$, $\text{S(O)}_n\text{NR}^{10}\text{R}^{11}$, $\text{N(R}^{12})\text{S(O)}_n\text{R}^{10}$, $\text{N(R}^{12})\text{S(O)}_n\text{OR}^{10}$, or $\text{N(R}^{12})\text{S(O)}_n\text{NR}^{10}\text{R}^{11}$, optionally substituted by one or more independent

5 H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

10 or a pharmaceutically acceptable salt thereof.

[0013] In some embodiments, a pharmaceutical composition comprising the compound of the present invention and a pharmaceutically acceptable carrier.

[0014] In some embodiments, a pharmaceutical composition comprising the compound of the present invention, an anti-cancer agent and a pharmaceutically acceptable carrier.

15 **[0015]** The present invention provides a method of inhibiting the growth of a tumor comprising contacting a tumor cell with an effective amount of the compound of the present invention or a pharmaceutically acceptable salt, so as to thereby inhibit the growth of the tumor.

[0016] The present invention further provides a method of inhibiting the growth of a tumor comprising contacting a tumor cell with an effective amount of the compound of the present invention or a pharmaceutically acceptable salt thereof, in combination with an anti-cancer agent, so as to thereby inhibit the growth and/or metastasis of the tumor.

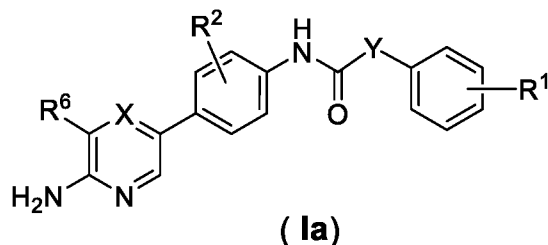
[0017] The present invention also provides a method of inhibiting PERK comprising contacting the tumor cell with an effective amount of the compound of the present invention or a pharmaceutically acceptable salt thereof.

[0018] In some embodiments of the method, further comprising contacting the tumor cell with an effective amount of an anti-cancer agent.

[0019] In some embodiments of the method, further comprising administering to the mammal an effective amount of an anti-cancer agent.

30

[0020] The present invention yet further provides a compound having the following structure (Ia):



wherein:

5 Y is CR^{3a}R^{3b};

R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or NR^{3d}R^{3e};

R¹ is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, or C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, optionally substituted by one or more
10 independent G¹ substituents;

R² is one or more independent H, deuterium, halo, alkyl, C₀₋₆alkylcycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, or C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H or alkyl, optionally substituted by one or
15 more independent G³ substituents;

X is CR⁷ or N;

R⁶ is H, alkyl, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H, CN, or alkyl, optionally substituted by one or more independent deuterium or
halo;

20 R^{8a} and R^{8b} are each independently H, C₁₋₁₂alkyl, C₀₋₁₂alkylC₃₋₁₂cycloalkyl, or C₀₋₁₂alkylC₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G⁴ substituents;

G¹, G², G³, or G⁴ are each independently H, deuterium, halo, CN, NO₂, C₁₋₁₂alkyl, C₀₋₁₂alkylC₃₋₁₂cycloalkyl, C₀₋₁₂alkylC₃₋₁₂heterocycloalkyl, OR¹⁰, NR¹⁰R¹¹, C(O)R¹⁰, C(O)OR¹⁰,
25 C(O)NR¹⁰R¹¹, OC(O)R¹⁰, OC(O)OR¹⁰, OC(O)NR¹⁰R¹¹, N(R¹²)C(O)R¹⁰, N(R¹²)C(O)OR¹⁰,
N(R¹²)C(O)NR¹⁰R¹¹, S(=O)_nR¹⁰, S(O)_nOR¹⁰, S(O)_nNR¹⁰R¹¹, N(R¹²)S(O)_nR¹⁰,

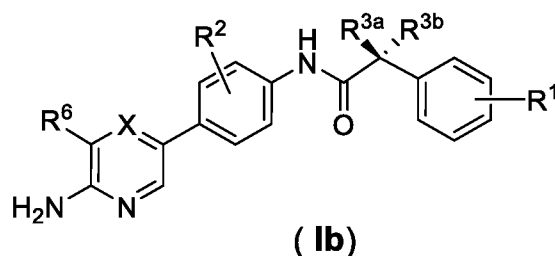
$N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H,
 5 deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

[0021] The present invention yet further provides a compound having the following structure **(Ib)**:



wherein:

X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C_{0-6} alkyl- $O-C_{1-12}$ alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl- $O-C_{3-12}$ cycloalkyl, optionally substituted by one or more
 15 independent G^1 substituents;

R^2 is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C_{0-6} alkyl- $O-C_{1-12}$ alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl- $O-C_{3-12}$ cycloalkyl, optionally substituted by one or more independent G^2 substituents;

R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or $NR^{3d}R^{3e}$;

R^{3c} , R^{3d} and R^{3e} are each independently H or alkyl, optionally substituted by one or more independent G^3 substituents;

R^6 is CO_2R^{8a} or $CO(NR^{8a}R^{8b})$;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{3-12} cycloalkyl, or C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4 substituents;

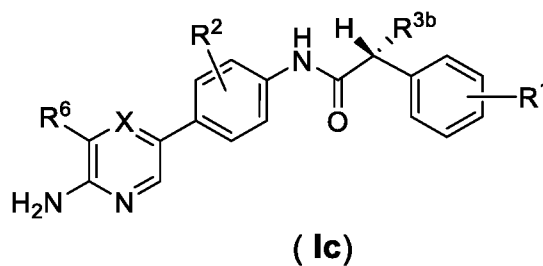
- G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , $\text{C}_{1-12}\text{alkyl}$, $\text{C}_{3-12}\text{cycloalkyl}$, $\text{C}_{3-12}\text{heterocycloalkyl}$, OR^{10} , $\text{NR}^{10}\text{R}^{11}$, C(O)R^{10} , C(O)OR^{10} , $\text{C(O)NR}^{10}\text{R}^{11}$, OC(O)R^{10} , OC(O)OR^{10} , $\text{OC(O)NR}^{10}\text{R}^{11}$, $\text{N(R}^{12})\text{C(O)R}^{10}$, $\text{N(R}^{12})\text{C(O)OR}^{10}$, $\text{N(R}^{12})\text{C(O)NR}^{10}\text{R}^{11}$, $\text{S(O)}_n\text{R}^{10}$, $\text{S(O)}_n\text{OR}^{10}$, $\text{S(O)}_n\text{NR}^{10}\text{R}^{11}$, $\text{N(R}^{12})\text{S(O)}_n\text{R}^{10}$, $\text{N(R}^{12})\text{S(O)}_n\text{OR}^{10}$, or $\text{N(R}^{12})\text{S(O)}_n\text{NR}^{10}\text{R}^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

- 10 n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

[0022] The present invention yet further provides a compound having the following structure (**Ic**):



- 15 wherein:

X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, $\text{C}_{0-6}\text{alkyl-OH}$, or $\text{C}_{0-6}\text{alkyl-O-C}_{1-12}\text{alkyl}$, optionally substituted by one or more independent G^1 substituents;

- 20 R^2 is one or more independent H, deuterium, halo, alkyl, $\text{C}_{0-6}\text{alkyl-OH}$, or $\text{C}_{0-6}\text{alkyl-O-C}_{1-12}\text{alkyl}$, optionally substituted by one or more independent G^2 substituents;

R^{3b} is OR^{3c} ;

R^{3c} is H or alkyl, optionally substituted by one or more independent G^3 substituents;

R^6 is $\text{CO}(\text{NR}^{8a}\text{R}^{8b})$;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, or C_{0-12} alkyl C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4 substituents;

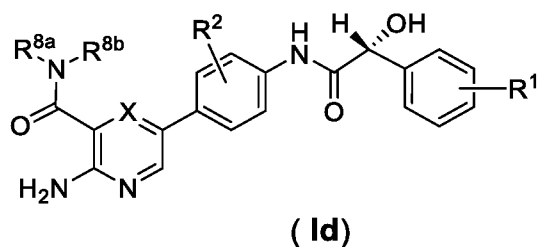
G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

[0023] The present invention yet further provides a compound having the following structure (**Id**):



wherein:

X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent H, deuterium, or halo;

R^2 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent H, deuterium or halo;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{3-12} cycloalkyl, or C_{3-12} heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$,

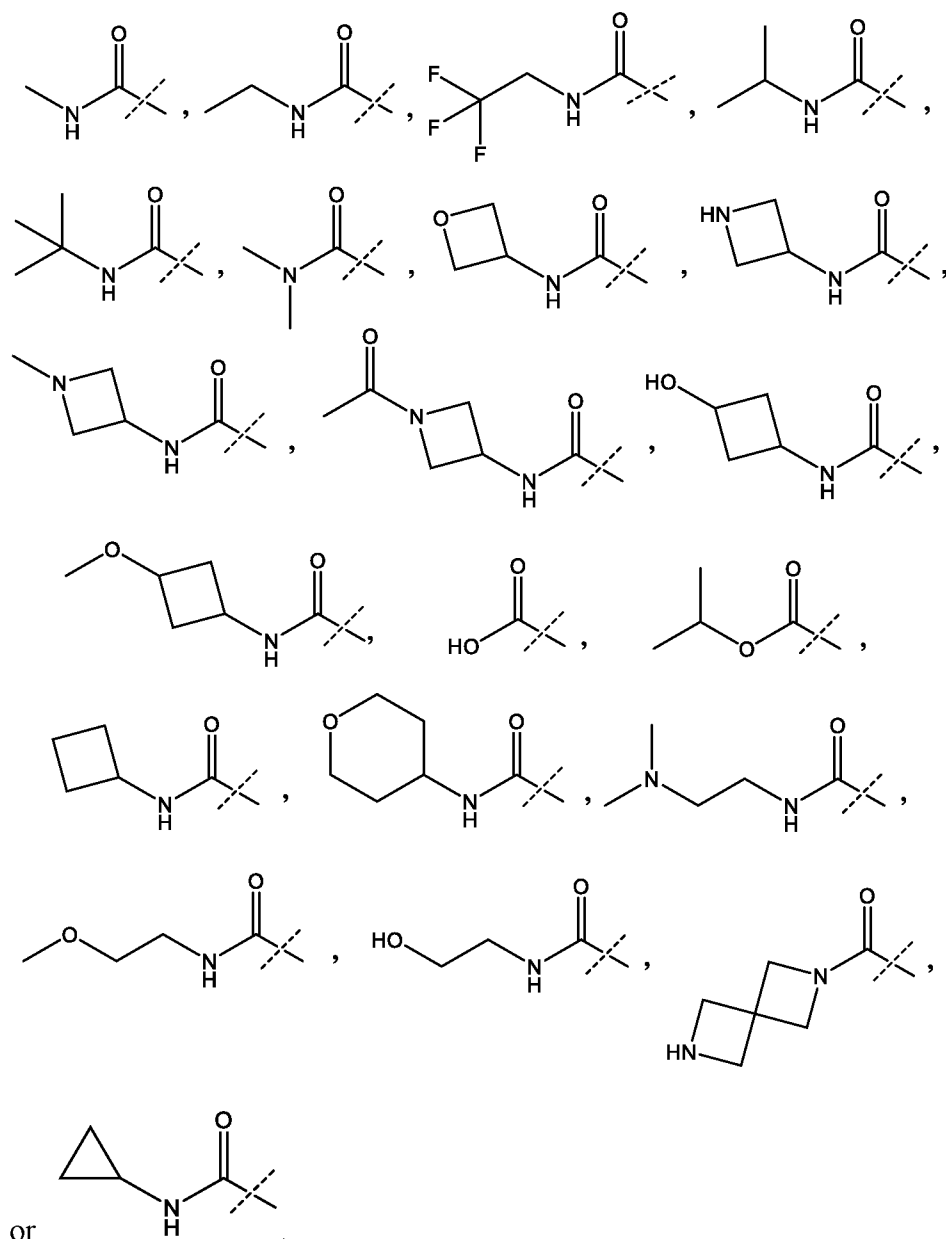
$C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$,
 $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$,
 $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 ,
 5 alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H,
 deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

[0024] In some embodiments, R^6 is H,



[0025] In some embodiments, X is CH.

[0026] In some embodiments, R₁ is H, methyl, ethyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, deuterium, CF₃, fluoro, or chloro.

[0027] In some embodiments, R₂ is H, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, fluoro, chloro, CF₃ or OCF₃.

[0028] In some embodiments, R_{8a} and R_{8b} are each independently H, C₁-6alkyl, C₀-6alkylC₃-8cycloalkyl, or C₀-6alkylC₃-8heterocycloalkyl.

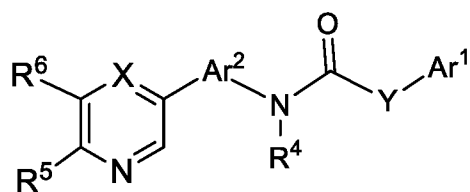
[0029] In some embodiments, R_{8a} and R_{8b} are each independently H, C₁-3alkyl, C₀-3alkylC₃-6cycloalkyl, or C₀-3alkylC₃-6heterocycloalkyl.

[0030] In some embodiments, R_{8a} and R_{8b} are each independently H, C₁-3alkyl, C₃-6cycloalkyl, or C₃-6heterocycloalkyl.

[0031] In some embodiments, G₁, G₂, G₃, or G₄ are each independently H, deuterium, halo, CN, NO₂, C₁-6alkyl, C₃-8cycloalkyl, C₃-8heterocycloalkyl, OR₁₀, NR₁₀R₁₁, C(O)R₁₀, C(O)OR₁₀, C(O)NR₁₀R₁₁, OC(O)R₁₀, OC(O)OR₁₀, OC(O)NR₁₀R₁₁, N(R₁₂)C(O)R₁₀, N(R₁₂)C(O)OR₁₀, N(R₁₂)C(O)NR₁₀R₁₁, S(O)_nR₁₀, S(O)_nOR₁₀, S(O)_nNR₁₀R₁₁, N(R₁₂)S(O)_nR₁₀, N(R₁₂)S(O)_nOR₁₀, or N(R₁₂)S(O)_nNR₁₀R₁₁, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO₂.

[0032] In some embodiments, G₁, G₂, G₃, or G₄ are each independently H, deuterium, halo, CN, NO₂, C₁-3alkyl, C₃-6cycloalkyl, C₃-6heterocycloalkyl, OR₁₀, NR₁₀R₁₁, C(O)R₁₀, C(O)OR₁₀, C(O)NR₁₀R₁₁, OC(O)R₁₀, OC(O)OR₁₀, OC(O)NR₁₀R₁₁, N(R₁₂)C(O)R₁₀, N(R₁₂)C(O)OR₁₀, N(R₁₂)C(O)NR₁₀R₁₁, S(O)_nR₁₀, S(O)_nOR₁₀, S(O)_nNR₁₀R₁₁, N(R₁₂)S(O)_nR₁₀, N(R₁₂)S(O)_nOR₁₀, or N(R₁₂)S(O)_nNR₁₀R₁₁, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO₂.

[0033] The present invention yet further provides a compound having the following structure (Ie):



(Ie)

wherein:

Ar¹ is aryl, heteroaryl, or cycloalkyl, optionally substituted by one or more independent R¹ substituents;

Ar² is aryl or heteroaryl, optionally substituted by one or more independent R² substituents;

5 Y is C(R^{3a})(R^{3b})C₀₋₆alkyl, NR^{3a}, -O-, C(O), CF₂, or a direct bond to Ar¹;

R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or NR^{3d}R^{3e};

R⁴ is H or OH;

X is CR⁷ or N;

10 R¹ is one or more independent halo, alkyl, or C₀₋₆alkyl-O-C₁₋₁₂alkyl, optionally substituted by one or more independent G¹ substituents;

R² is one or more independent halo, alkyl, or C₀₋₆alkyl-O-C₁₋₁₂alkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H or alkyl;

15 R⁵ is H, CH₃, or NH₂;

R⁶ is H, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H or alkyl;

R^{8a} and R^{8b} are each independently H, C₁₋₁₂alkyl, C₀₋₁₂alkyl-C₃₋₁₂cycloalkyl, or C₀₋₁₂alkyl-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G⁴

20 substituents; or

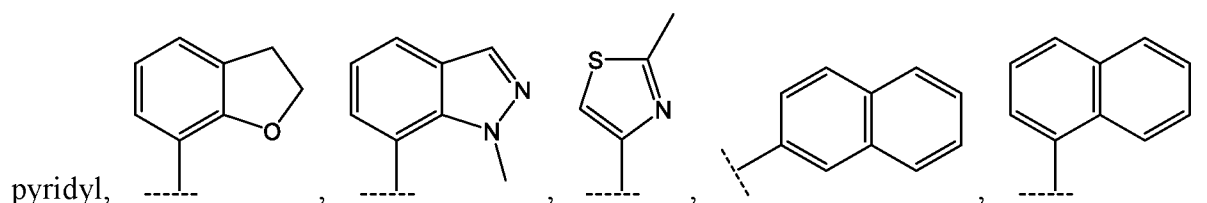
R^{8a} and R^{8b} taken together with the nitrogen to which they are attached form 5-10 membered heterocyclyl;

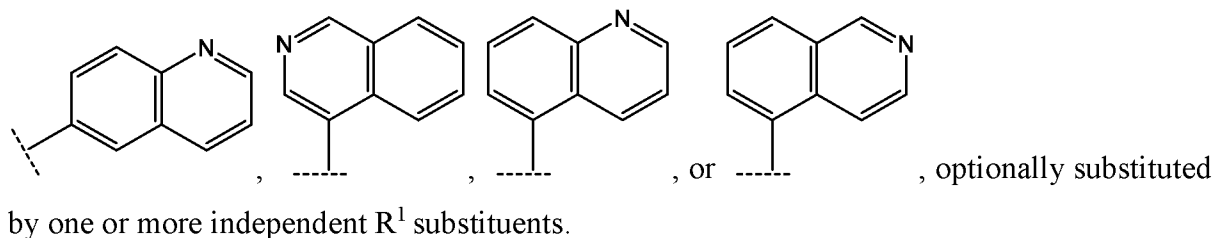
G¹, G², G³, or G⁴ are each independently halo, OR¹⁰, NR¹⁰R¹¹, C(O)R¹⁰; and

R¹⁰ or R¹¹ are each independently selected from H, or alkyl;

25 or a pharmaceutically acceptable salt thereof.

[0034] In some embodiments, Ar¹ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl,





[0035] In some embodiments, R¹, for each occurrence, is independently chloro, fluoro, methyl, ethyl, methoxy, or CF₃.

- 5 **[0036]** In some embodiments, Y is -C(H)(OH)-, -C(CH₃)(OH)-, -C(H)(OCH₃)-, -C(H)(NH₂)-, CF₂, C(O), CH₂, -CH₂CH₂-, N(CH₃), -O-, or a direct bond to Ar₁.

[0037] In some embodiments, R₄ is H. In some embodiments, R₄ is OH.

[0038] In some embodiments, Ar₂ is phenyl or pyridyl, optionally substituted by one or more independent R₂ substituents.

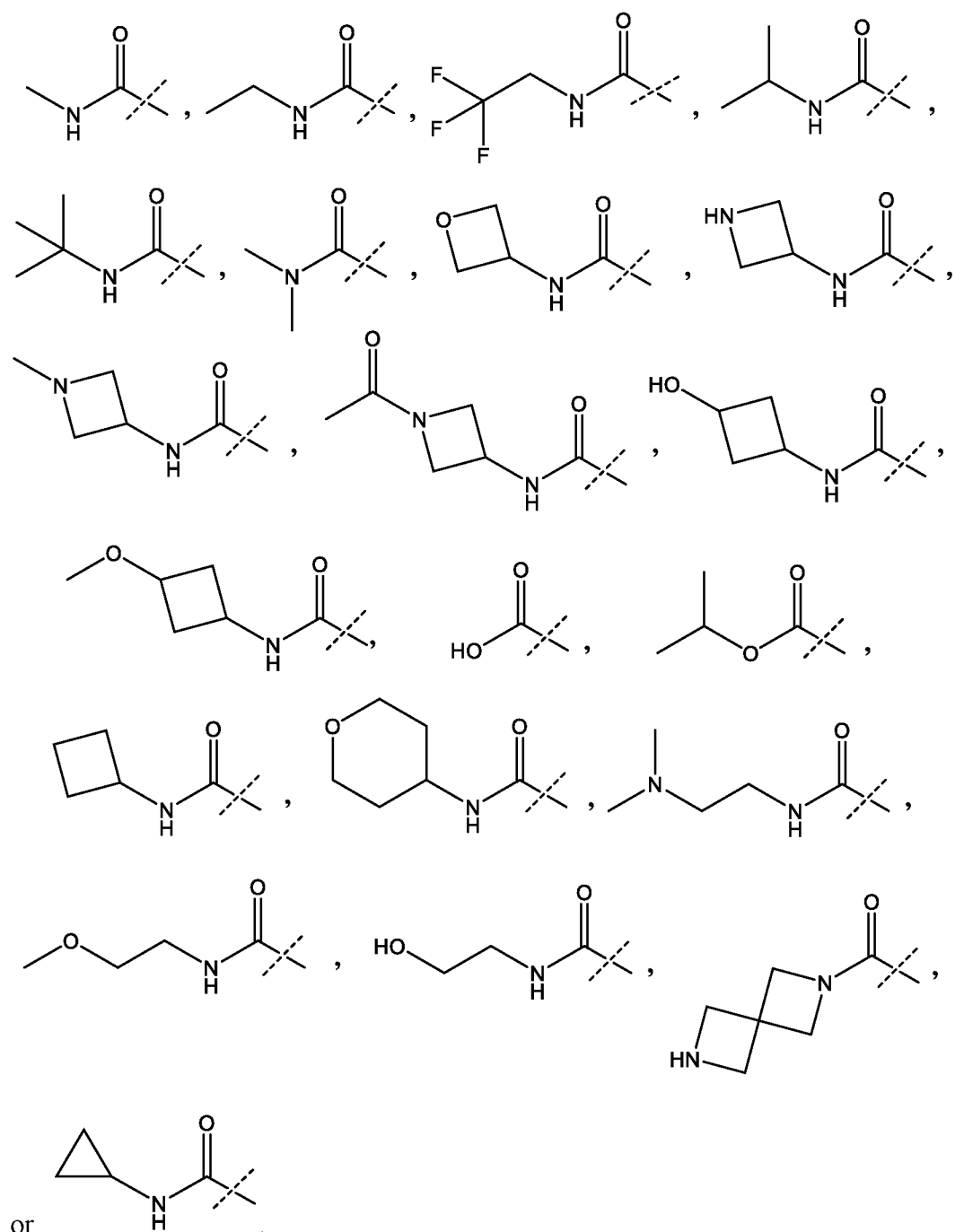
- 10 **[0039]** In some embodiments, R₂, for each occurrence, is independently methyl, ethyl, methoxy, fluoro, chloro, CF₃, or OCF₃.

[0040] In some embodiments, X is CR₇. In some embodiments, R₇ is H.

[0041] In some embodiments, X is N.

[0042] In some embodiments, R₅ is H, methyl, NH₂, or NHCH₃.

[0043] In some embodiments, R₆ is H,



[0044] In some embodiments, the compound is selected from:

- 5 2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
(R)-2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
(S)-2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
 2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropylnicotinamide;

- (*R*)-2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- (*S*)-2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- 5 2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- (*R*)-2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- (*S*)-2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- 10 2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- (*R*)-2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- (*S*)-2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- 15 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropyl nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- 20 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- 25 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethyl nicotinamide;
- 30 2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
- (*R*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;

- (*S*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
- 2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
- 5 (*R*)-2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
- (*S*)-2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-
- 10 trifluoroethyl)nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-trifluoroethyl)nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-trifluoroethyl)nicotinamide;
- 15 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isobutylnicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isobutylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-
- 20 isobutylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-dimethylnicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-dimethylnicotinamide;
- 25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-dimethylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-3-yl)nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-
- 30 3-yl)nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-3-yl)nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;

- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;
- 5 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-methoxycyclobutyl)nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-methoxycyclobutyl)nicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-methoxycyclobutyl)nicotinamide,
- 10 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylpyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylpyrazine-2-carboxamide;
- 15 (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylpyrazine-2-carboxamide;
- 3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
- 20 (*S*)-3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
- 25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
- isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate;
- 30 (*R*)-isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate;
- (*S*)-isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate;
- 2-amino-*N*-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-

- methylphenyl)nicotinamide;
(*R*)-2-amino-N-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*S*)-2-amino-N-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
5 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
10 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*R*)-2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
15 (*S*)-2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
20 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
25 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
30 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-

- methoxyethyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
5 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
10 (*R*)-N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*S*)-N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
15 (*R*)-2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
20 (*R*)-2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
25 (*R*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
30 (*R*)-2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-

- isopropylnicotinamide;
2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-
5 isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
10 (*R*)-2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-
15 isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
20 2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-
isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-
25 isopropylnicotinamide;
5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-
(methylamino)nicotinamide;
(*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-
(methylamino)nicotinamide;
30 (*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-
(methylamino)nicotinamide;
5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-
methylnicotinamide;
(*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-

- methylnicotinamide;
(*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-methylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-
- 5 isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 10 5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-
- 15 isopropylnicotinamide;
2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
(*R*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
- 20 (*S*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*R*)-N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
- 25 (*S*)-N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide;
(*R*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide;
- 30 (*S*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-

- isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-
5 ethylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide;
10 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide;
15 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
20 (*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
25 (*S*)-2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
30 (*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-

- isopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
5 (*R*)-2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
10 2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
15 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
20 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide;
30 (*R*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide;
(*S*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide;
2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;

- (*R*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
- 5 (*R*)-2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-
- 10 isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylnicotinamide;
- 15 2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-
- 20 isopropylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
- 25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-
- 30 N-isopropylnicotinamide;

- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 5 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-
- 10 ethylnicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-ethylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-ethylnicotinamide;
- 15 2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)nicotinamide;
- (*R*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)nicotinamide;
- (*S*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-
- 20 methylphenyl)nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- 25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-isopropylnicotinamide;
- (*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-
- 30 isopropylnicotinamide;
- (*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;

- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 5 2-amino-5-(4-(2,2-difluoro-2-phenylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-oxoacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(6-methylpyridin-2-yl)acetamido)phenyl)nicotinamide;
- 10 2-amino-5-(4-(2-(3,5-difluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-phenylacetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(3-phenylpropanamido)phenyl)nicotinamide;
- 2-amino-5-(4-(2-(2-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 15 2-amino-5-(4-(2-(4-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(2-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(3-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(4-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*o*-tolyl)acetamido)phenyl)nicotinamide;
- 20 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*m*-tolyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*p*-tolyl)acetamido)phenyl)nicotinamide;
- 2-amino-5-(4-(2-(2-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(4-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 25 2-amino-N-isopropyl-5-(2-methyl-4-(2-(2-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(4-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 30 2-amino-5-(4-(2-(2-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(4-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(naphthalen-1-yl)acetamido)phenyl)nicotinamide;

- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(naphthalen-2-yl)acetamido)phenyl)nicotinamide;
2-amino-N-isopropyl-5-(2-methyl-4-(2-(quinolin-6-yl)acetamido)phenyl)nicotinamide;
2-amino-N-isopropyl-5-(4-(2-(isoquinolin-4-yl)acetamido)-2-methylphenyl)nicotinamide;
2-amino-N-isopropyl-5-(4-(2-(isoquinolin-5-yl)acetamido)-2-methylphenyl)nicotinamide;
5 2-amino-N-isopropyl-5-(2-methyl-4-(2-(quinolin-5-yl)acetamido)phenyl)nicotinamide;
2-amino-5-(4-(2-cyclopropylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclobutylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclopentylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclohexylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
10 2-amino-5-(4-benzamido-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-N-isopropyl-5-(2-methyl-4-(3-methyl-3-phenylureido)phenyl)nicotinamide;
phenyl (4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl)carbamate;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
15 (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-
20 trifluoroethyl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
25 3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*R*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*S*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
30 3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*R*)-3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;

- (*S*)-3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- 5 (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-
- 10 2H-pyran-4-yl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide;
- 15 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-
- 20 (dimethylamino)ethyl)pyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
- 25 (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-
- 30 hydroxyethyl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)pyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;

- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;
- 5 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- 10 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- 15 3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- 20 (*S*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- 25 3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
- (*R*)-3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
- 30

- 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 5 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 10 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 15 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 20 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 25 or a pharmaceutically acceptable salt thereof.

[0045] Embodiments of the present invention further provide a pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof including one or more pharmaceutically acceptable carriers, diluents, or excipients.

- [0046]** Embodiments of the present invention further provide a method of treating cancer in a patient comprising administering to a patient in need thereof an effective amount of any of the above compounds, or a pharmaceutically acceptable salt thereof.

[0047] Embodiments of the present invention further provide a method of treating cancer in a

patient comprising administering to a patient in need thereof an effective amount of any of the above compounds in combination with an anti-cancer agent, or pharmaceutically acceptable salts thereof.

[0048] Embodiments of the present invention further provide a compound or pharmaceutically acceptable salt thereof for use in therapy.

[0049] Embodiments of the present invention further provide a compound or pharmaceutically acceptable salt thereof according to any of the compounds for use in the treatment of cancer.

[0050] In some embodiments, the cancer is particularly pancreatic cancer, melanoma, or breast cancer, including BrCa positive breast cancer.

[0051] Embodiments of the present invention further provide a method of treating a disease in a patient in need of such treatment, said method comprising administering a PERK kinase modulating compound according to any of the above compounds, or a pharmaceutically acceptable salt thereof, wherein the disease is cancer.

[0052] The present invention provides a method of treating cancer in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula I, Ia, Ib, Ic or Id, or a pharmaceutically acceptable salt thereof. The present invention also provides a method of inhibiting PERK activity resulting in antitumor activity in a patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula I, Ia, Ib, Ic or Id, or a pharmaceutically acceptable salt thereof.

[0053] In some embodiments of any of the above methods or uses, the subject is a human. In some embodiments of any of the above methods or uses, the compound and/or anti-cancer agent is orally administered to the subject. In some embodiments of any of the above methods or uses, the compound and/or anti-cancer agent is administered to the subject.

[0054] As used herein, the term “cancer” refers to all types of cancer, neoplasm or malignant tumors found in mammals, including leukemia, lymphoma, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound, pharmaceutical composition, or method provided herein include multiple myeloma, blood cancers, lymphoma, sarcoma, bladder cancer, bone cancer, brain tumor, cervical cancer, colon cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, leukemia, prostate cancer, breast cancer (e.g. ER positive, ER negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal

carcinoma, lobular carcinoma, primary, metastatic), ovarian cancer, pancreatic cancer, liver cancer (e.g. hepatocellular carcinoma), lung cancer (e.g. non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma, small cell lung carcinoma, carcinoid, sarcoma), glioblastoma multiforme, glioma, or melanoma. Additional
5 examples include, cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain
10 tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer,
15 papillary thyroid cancer, hepatocellular carcinoma, Paget's Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, cancer of the hepatic stellate cells, or prostate cancer.

[0055] As used herein, a “symptom” associated with cancer includes any clinical or laboratory manifestation associated with the cancer and is not limited to what the subject can
20 feel or observe.

[0056] As used herein, “treating”, e.g. of a cancer, encompasses inducing prevention, inhibition, regression, or stasis of the disease or a symptom or condition associated with the cancer.

[0057] The contents of International Application Publication No. WO/2018/194885,
25 published October 25, 2018, are hereby incorporated by reference.

[0058] If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including racemates, enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture
30 may be separated using well-known techniques and an individual enantiomer may be used alone. The compounds described in the present invention are in racemic form or as individual enantiomers. The enantiomers can be separated using known techniques, such as those

described in Pure and Applied Chemistry 69, 1469–1474, (1997) IUPAC. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention.

[0059] The compounds of the present invention may have spontaneous tautomeric forms. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

[0060] In the compound structures depicted herein, hydrogen atoms are not shown for carbon atoms having less than four bonds to non-hydrogen atoms. However, it is understood that enough hydrogen atoms exist on said carbon atoms to satisfy the octet rule.

[0061] This invention also provides isotopic variants of the compounds disclosed herein, including wherein the isotopic atom is 2H , 3H , ^{13}C , ^{14}C , ^{15}N , and/or ^{18}O . Accordingly, in the compounds provided herein hydrogen can be enriched in the deuterium isotope. It is to be understood that the invention encompasses all such isotopic forms.

[0062] In an alternative embodiment, compounds described herein may also comprise one or more isotopic substitutions. For example, hydrogen may be 2H (D or deuterium) or 3H (T or tritium); carbon may be, for example, ^{13}C or ^{14}C ; oxygen may be, for example, ^{18}O ; nitrogen may be, for example, ^{15}N , and the like. In other embodiments, a particular isotope (e.g., 3H , ^{13}C , ^{14}C , ^{18}O , or ^{15}N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

[0063] It is understood that the structures described in the embodiments of the methods hereinabove can be the same as the structures of the compounds described hereinabove.

[0064] It is understood that where a numerical range is recited herein, the present invention contemplates each integer between, and including, the upper and lower limits, unless otherwise stated.

[0065] Except where otherwise specified, if the structure of a compound of this invention includes an asymmetric carbon atom, it is understood that the compound occurs as a racemate, racemic mixture, and isolated single enantiomer. All such isomeric forms of these compounds are expressly included in this invention. Except where otherwise specified, each

stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by

5 stereochemically controlled synthesis, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, NY, 1981. For example, the resolution may be carried out by preparative chromatography on a chiral column.

[0066] The subject invention is also intended to include all isotopes of atoms occurring on
10 the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

[0067] It will be noted that any notation of a carbon in structures throughout this application,
15 when used without further notation, are intended to represent all isotopes of carbon, such as ^{12}C , ^{13}C , or ^{14}C . Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the structure of any of the compounds disclosed herein.

[0068] It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, are intended to represent all isotopes of
20 hydrogen, such as ^1H , ^2H , or ^3H . Furthermore, any compounds containing ^2H or ^3H may specifically have the structure of any of the compounds disclosed herein.

[0069] Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art using appropriate isotopically-labeled reagents in place of the non-labeled reagents employed.

25 [0070] In the compounds used in the method of the present invention, the substituents may be substituted or unsubstituted, unless specifically defined otherwise.

[0071] In the compounds used in the method of the present invention, alkyl, heteroalkyl, monocycle, bicycle, aryl, heteroaryl and heterocycle groups can be further substituted by replacing one or more hydrogen atoms with alternative non-hydrogen groups. These include,
30 but are not limited to, halo, hydroxy, mercapto, amino, carboxy, cyano, carbamoyl and aminocarbonyl and aminothiocarbonyl.

[0072] It is understood that substituents and substitution patterns on the compounds used in

the method of the present invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result.

[0073] In choosing the compounds used in the method of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R1, R2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

[0074] As used herein, "C0-4alkyl" for example is used to mean an alkyl having 0-4 carbons—that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

[0075] As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Thus, C1-Cn as in "C1-Cn alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, isopropyl, isobutyl, sec-butyl and so on. An embodiment can be C1-C12 alkyl, C2-C12 alkyl, C3-C12 alkyl, C4-C12 alkyl and so on.

[0076] "Alkoxy" or "Alkoxy" represents an alkyl group as described above attached through an oxygen bridge. Thus, an alkoxy group is represented by C0-nalkyl-O-C0-malkyl in which oxygen is a bridge between 0, 1, 2, ..., n-1, m-1, n or m carbons in a linear or branched arrangement. When n is zero, "-O-C0-malkyl" is attached directly to the preceding moiety. When m is zero, the alkoxy group is "C0-nalkyl-OH." Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, tert-butoxy and so on.

[0077] The term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present. Thus, C2-Cn alkenyl is defined to include groups having 1, 2, ..., n-1 or n carbons. For example, "C2-C6 alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and at least 1 carbon-carbon double bond, and up to, for example, 3 carbon-carbon double bonds in the case of a C6 alkenyl, respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl

group may contain double bonds and may be substituted if a substituted alkenyl group is indicated. An embodiment can be C2-C12 alkenyl, C3-C12 alkenyl, C4-C12 alkenyl and so on.

[0078] The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present. Thus, C2-C_n alkynyl is defined to include groups having 1, 2, ..., n-1 or n carbons. For example, "C2-C6 alkynyl" means an alkynyl radical having 2 or 3 carbon atoms, and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms, and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms, and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight or branched portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated. An embodiment can be a C2-C_n alkynyl. An embodiment can be C2-C12 alkynyl, C3-C12 alkynyl, C4-C12 alkynyl and so on

[0079] "Alkylene", "alkenylene" and "alkynylene" shall mean, respectively, a divalent alkane, alkene and alkyne radical, respectively. It is understood that an alkylene, alkenylene, and alkynylene may be straight or branched. An alkylene, alkenylene, and alkynylene may be unsubstituted or substituted.

[0080] As used herein, "heteroalkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and at least 1 heteroatom within the chain or branch.

[0081] As used herein, "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups (e.g., spirocyclic groups, fused bicyclic groups, bridged bicyclic compounds). "Heterocyclyl" therefore includes, but is not limited to the following: imidazolyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

[0082] As herein, "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

[0083] As used herein, "monocycle" includes any stable polyatomic carbon ring of up to 12 atoms and may be unsubstituted or substituted. Examples of such non-aromatic monocycle elements include but are not limited to: cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Examples of such aromatic monocycle elements include but are not limited to: phenyl.

5 **[0084]** As used herein, "bicycle" includes any stable polyatomic carbon ring of up to 12 atoms that is fused to a polyatomic carbon ring of up to 12 atoms with each ring being independently unsubstituted or substituted. Examples of such non-aromatic bicycle elements include but are not limited to: decahydronaphthalene. Examples of such aromatic bicycle elements include but are not limited to: naphthalene.

10 **[0085]** As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted. Examples of such aryl elements include phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-
15 aromatic, it is understood that attachment is via the aromatic ring.

[0086] As used herein, the term "polycyclic" refers to unsaturated or partially unsaturated multiple fused ring structures, which may be unsubstituted or substituted.

[0087] The term "arylalkyl" refers to alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an aryl group as described
20 above. It is understood that an "arylalkyl" group is connected to a core molecule through a bond from the alkyl group and that the aryl group acts as a substituent on the alkyl group. Examples of arylalkyl moieties include, but are not limited to, benzyl (phenylmethyl), p-trifluoromethylbenzyl (4-trifluoromethylphenylmethyl), 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

25 **[0088]** The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 12 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridazine rings that are
30 (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-

membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranal, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxaliny, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinoliny, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxaliny, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinoliny, isoquinoliny, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

[0089] The term “alkylheteroaryl” refers to alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an heteroaryl group as described above. It is understood that an “alkylheteroaryl” group is connected to a core molecule through a bond from the alkyl group and that the heteroaryl group acts as a substituent on the alkyl group. Examples of alkylheteroaryl moieties include, but are not limited to, -CH₂-(C₅H₄N), -CH₂-CH₂-(C₅H₄N) and the like.

[0090] The term "heterocycle" or “heterocyclyl” refers to a mono- or poly-cyclic ring system which can be saturated or contains one or more degrees of unsaturation and contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is either saturated or

has one or more degrees of unsaturation. The heterocycle may be unsubstituted or substituted, with multiple degrees of substitution being allowed. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s). Examples of heterocycles include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, pyrrolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, 1,3-oxathiolane, and the like.

[0091] The alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise. In the compounds of the present invention, alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl groups can be further substituted by replacing one or more hydrogen atoms with alternative non-hydrogen groups. These include, but are not limited to, halo, hydroxy, mercapto, amino, carboxy, cyano and carbamoyl.

[0092] As used herein, the term "halogen" or "halo" refers to F, Cl, Br, and I.

[0093] As used herein, the term "carbonyl" refers to a carbon atom double bonded to oxygen.

A carbonyl group is denoted as $R_xC(O)R_y$ where R_x and R_y are bonded to the carbonyl carbon atom.

[0094] The terms "substitution", "substituted" and "substituent" refer to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups described above, and halogens (i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted

by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

[0095] It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result.

[0096] In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R1, R2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

[0097] The various R groups attached to the aromatic rings of the compounds disclosed herein may be added to the rings by standard procedures, for example those set forth in Advanced Organic Chemistry: Part B: Reaction and Synthesis, Francis Carey and Richard Sundberg, (Springer) 5th ed. Edition. (2007), the content of which is hereby incorporated by reference.

[0098] The compounds used in the method of the present invention may be prepared by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art. However, these may not be the only methods by which to synthesize or obtain the desired compounds.

[0099] The compounds used in the method of the present invention may be prepared by techniques described in Vogel's Textbook of Practical Organic Chemistry, A.I. Vogel, A.R. Tatchell, B.S. Furnis, A.J. Hannaford, P.W.G. Smith, (Prentice Hall) 5th Edition (1996), March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, (Wiley-Interscience) 5th Edition (2007), and references therein, which are incorporated by reference herein. However, these may not be the only methods by which to synthesize or obtain the desired compounds.

[0100] Another aspect of the invention comprises a compound used in the method of the present invention as a pharmaceutical composition.

[0101] In some embodiments, a pharmaceutical composition comprises the compound of the present invention and a pharmaceutically acceptable carrier.

[0102] As used herein, the term “pharmaceutically active agent” means any substance or compound suitable for administration to a subject and furnishes biological activity or other direct effect in the treatment, cure, mitigation, diagnosis, or prevention of disease, or affects the structure or any function of the subject. Pharmaceutically active agents include, but are not limited to, substances and compounds described in the Physicians’ Desk Reference (PDR Network, LLC; 64th edition; November 15, 2009) and “Approved Drug Products with Therapeutic Equivalence Evaluations” (U.S. Department Of Health And Human Services, 30th edition, 2010), which are hereby incorporated by reference. Pharmaceutically active agents which have pendant carboxylic acid groups may be modified in accordance with the present invention using standard esterification reactions and methods readily available and known to those having ordinary skill in the art of chemical synthesis. Where a pharmaceutically active agent does not possess a carboxylic acid group, the ordinarily skilled artisan will be able to design and incorporate a carboxylic acid group into the pharmaceutically active agent where esterification may subsequently be carried out so long as the modification does not interfere with the pharmaceutically active agent’s biological activity or effect.

[0103] The compounds used in the method of the present invention may be in a salt form. As used herein, a “salt” is a salt of the instant compounds which has been modified by making acid or base salts of the compounds. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkaline earth metal salts, sodium, potassium or lithium.

The term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention.

These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and

isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like.

(See, e.g., Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19).

[0104] The compounds of the present invention may also form salts with basic amino acids such a lysine, arginine, etc. and with basic sugars such as N-methylglucamine, 2-amino-2-deoxyglucose, etc. and any other physiologically non-toxic basic substance.

5 **[0105]** As used herein, "administering" an agent may be performed using any of the various methods or delivery systems well known to those skilled in the art. The administering can be performed, for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery, subcutaneously,
10 intraadiposally, intraarticularly, intrathecally, into a cerebral ventricle, intraventricularly, intratumorally, into cerebral parenchyma or intraparenchymally.

[0106] The compounds used in the method of the present invention may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need
15 of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

20 **[0107]** As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically acceptable carrier as are slow-release vehicles.

25 **[0108]** The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with; and the desired
30 therapeutic effect.

[0109] A dosage unit of the compounds used in the method of the present invention may comprise a single compound or mixtures thereof with additional antitumor agents. The

compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection, topical application, or other methods, into or topically onto a site of disease or lesion, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

[0110] The compounds used in the method of the present invention can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or in carriers such as the novel programmable sustained-release multi-compartmental nanospheres (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, nasal, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone or mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

[0111] Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances

in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol. 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

[0112] For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier.

[0113] The compounds used in the method of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles.

[0114] The compounds used in the method of the present invention may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug.

[0115] Gelatin capsules may contain the active ingredient compounds and powdered carriers/diluents. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[0116] For oral administration in liquid dosage form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules.

Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

[0117] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. Solutions for parenteral administration preferably contain a water-soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. In addition, parenteral solutions can contain preservatives. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

[0118] The compounds used in the method of the present invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

[0119] Parenteral and intravenous forms may also include minerals and other materials such as solutol and/or ethanol to make them compatible with the type of injection or delivery system chosen.

[0120] The compounds and compositions of the present invention can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by topical administration, injection or other methods, to the afflicted area, such as a wound, including ulcers of the skin, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

[0121] Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U.S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton,

Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

[0122] The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, powders, and chewing gum; or in liquid dosage forms, such as elixirs, syrups, and suspensions, including, but not limited to, mouthwash and toothpaste. It can also be administered parentally, in sterile liquid dosage forms.

[0123] Solid dosage forms, such as capsules and tablets, may be enteric-coated to prevent release of the active ingredient compounds before they reach the small intestine.

[0124] The compounds and compositions of the invention can be coated onto stents for temporary or permanent implantation into the cardiovascular system of a subject.

[0125] Variations on those general synthetic methods will be readily apparent to those of ordinary skill in the art and are deemed to be within the scope of the present invention.

[0126] Each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. Thus, all combinations of the various elements described herein are within the scope of the invention.

[0127] This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter

Experimental Details

[0128] The following materials and methods are used to test the compounds of the present invention.

PERK *In Vitro* Activity Assay (isolated):

[0129] In vitro Inhibition of PERK Enzyme Activity (isolated) Recombinant human EIF2AK2 (PKR) catalytic domain (amino acids 252-551), EIF2AK3 (PERK) catalytic domain (amino acids 536 - 1116), GFP-eIF2a substrate, and Terbium-labelled phospho-eIF2a antibody is obtained (Invitrogen, Carlsbad, CA).

[0130] Express and purify HIS-SUMO-GCN2 catalytic domain (amino acids 584 - 1019) from *E. coli*. Perform TR-FRET kinase assays in the absence or presence of inhibitors in a reaction buffer consisting of 50 mM HEPES, pH 7.5, 10 mM MgCb, 1.0 mM EGTA, and 0.01% Brij-35, and 100 - 200 nM GFP-eIF2a substrate. PKR assays contain 14 ng/mL enzyme and 2.5 μ M ATP (K_m , -2.5 μ M), PERK assays contain 62.5 ng/mL enzyme and 1.5 μ M ATP (K_m , app - 1.5 μ M), and GCN2 assays contain 3 nM enzyme and 90 μ M ATP (K_m , -200 μ M). Add test compound, initiate the reaction by addition of enzyme, and incubate at room temperature for 45 minutes. Stop the reaction by addition of EDTA to a final concentration of 10 mM, add Terbium-labelled phospho-eIF2a antibody at a final concentration of 2 nM, and incubate for 90 minutes. Monitor the resulting fluorescence in an EnVision® Multilabel reader (PerkinElmer, Waltham, MA). Determine TR-FRET ratios and the resulting IC₅₀ values using a 4-parameter nonlinear logistic equation as shown: $Y = (A + ((B - A) / (1 + ((C / x)^D))))$ where, Y = % specific inhibition, A = Bottom of the curve, B = Top of the curve, C = absolute IC₅₀ (concentration causing 50% inhibition), and D = hill slope.

[0131] The compounds of Examples 1 to 219 were tested essentially as described above and exhibited IC₅₀ values shown in Table 1. These data demonstrate that the compounds of Examples 1 to 219 inhibit isolated PERK enzyme activity in vitro.

PERK Cellular Assay

[0132] Stable cell lines were created in HEK293 cells using lentiviral particles harboring an expression vector for GFP- eIF2 α . Cells were selected using puromycin and enriched using fluorescence activated cell sorting against GFP. HEK293-EGFP-eIF2 α cells were plated at 5000 cells/well in 384-well assay plates and incubated overnight at 37°C, 5% CO₂. Inhibitor compounds were added to the wells by Echo acoustic dispensing and incubated for 30 minutes at 37°C, 5% CO₂ prior to induction of ER stress by addition of tunicamycin to 1mM for 2 hours. Cells were lysed and TR-FRET was measured in an EnVision plate reader (PerkinElmer). FRET ratio data was normalized to signal from lysates treated with DMSO

vehicle control and plotted as percent inhibition against 10-point, 3-fold dilution series of inhibitors. IC₅₀ values were calculated using 4-parameter logistical fitting in XLFit.

[0133] The compounds of Examples 1 to 219 were tested essentially as described above and exhibited cellular IC₅₀ values shown in Table 1. These data demonstrate that the compounds of Examples 1 to 219 inhibit EIF2a in vitro.

[0134] The results of exemplary compounds of formula (I) are shown in Table 1. Key: A is 0.001 to 0.025 μ M; B is 0.026 to 0.050 μ M; C is 0.051 to 0.100 μ M; D is 0.101 to 0.250 μ M; E is 0.251 to 0.500 μ M; F is 0.501 to 1.00 μ M; G is 1.001 μ M to 2.00 μ M; H is 2.001 μ M to 3.00 μ M; I is 3.001 to 4.00 μ M; J is 4.001 to 5.00 μ M; K is >5.00 μ M; and N/A is “not available”.

Table 1: Biochemical and cellular IC₅₀ data of Compounds of Formula I inhibiting PERK kinase:

Example	Biochemical IC ₅₀ (μ M)	Cellular IC ₅₀ (μ M) (EIF2a)
1	A	E
2	A	D
3	D	H
4	D	I
5	G	I
6	G	I
7	G	K
8	A	B
9	B	D
10	A	C
11	F	G
12	A	B
13	A	F
14	A	B
15	B	E
16	B	D
17	E	F

18	A	B
19	D	D
20	A	B
21	D	E
22	F	H
23	K	K
24	A	C
25	B	F
26	A	D
27	C	G
28	A	B
29	B	E
30	A	F
31	C	I
32	A	C
33	D	E
34	A	A
35	C	D
36	A	C
37	D	E
38	A	A
39	D	D
40	A	B
41	D	K
42	A	B
43	C	E
44	A	I
45	C	K
46	A	F
47	A	G
48	N/A	N/A
49	N/A	N/A

50	N/A	C
51	N/A	F
52	N/A	N/A
53	N/A	N/A
54	N/A	C
55	N/A	G
56	A	E
57	D	H
58	E	N/A
59	G	N/A
60	F	N/A
61	G	N/A
62	N/A	N/A
63	N/A	N/A
64	N/A	D
65	N/A	H
66	D	G
67	A	C
68	D	F
69	A	B
70	N/A	A
71	N/A	F
72	A	A
73	D	E
74	E	G
75	D	G
76	E	I
77	F	I
78	G	K
79	G	K
80	A	E
81	D	J

82	A	B
83	A	E
84	A	A
85	A	C
86	A	A
87	B	D
88	N/A	N/A
89	N/A	N/A
90	N/A	C
91	N/A	E
92	N/A	A
93	N/A	D
94	A	A
95	B	D
96	N/A	N/A
97	N/A	N/A
98	A	A
99	B	D
100	A	A
101	A	C
102	A	A
103	B	D
104	N/A	C
105	N/A	F
106	A	A
107	C	E
108	A	A
109	C	D
110	A	A
111	D	D
112	C	E
113	C	F

114	E	K
115	A	A
116	E	G
117	A	A
118	A	B
119	A	A
120	A	C
121	A	A
122	E	F
123	A	A
124	B	C
125	D	F
126	A	D
127	E	K
128	C	K
129	N/A	N/A
130	N/A	N/A
131	N/A	N/A
132	N/A	N/A
133	C	D
134	A	B
135	A	B
136	N/A	N/A
137	N/A	N/A
138	A	B
139	A	E
140	N/A	B
141	N/A	D
142	N/A	G
143	N/A	B
144	N/A	F
145	N/A	C

146	B	D
147	N/A	B
148	N/A	F
149	N/A	N/A
150	N/A	N/A
151	A	B
152	D	D
153	A	B
154	A	A
155	D	D
156	A	A
157	D	D
158	A	A
159	B	D
160	A	A
161	C	E
162	N/A	D
163	N/A	C
164	G	E
165	C	B
166	N/A	B
167	N/A	D
168	C	D
169	A	A
170	C	H
171	E	K
172	C	G
173	D	K
174	D	J
175	G	K
176	C	F
177	B	E

178	B	D
179	D	F
180	G	K
181	K	K
182	E	H
183	D	H
184	E	D
185	A	E
186	C	D
187	C	F
188	E	H
189	D	F
190	C	F
191	C	G
192	D	H
193	C	F
194	F	H
195	S	E
196	S	E
197	D	G
198	B	F
199	B	D
200	F	F
201	C	F
202	C	D
203	H	G
204	D	N/A
205	A	D
206	E	H
207	A	E
208	B	D
209	D	G

210	C	G
211	E	H
212	G	K
213	G	K
214	E	K
215	K	K
216	G	K
217	K	F
218	G	K
219	G	G

HPLC Conditions:**Method A**

- 5 Column: Polaris C18-A 2.6 μ m C18 (100 $\times$ 3.0 mm)
 Mobile Phase A: Water containing 0.05% v/v Trifluoroacetic Acid
 Mobile Phase B: Acetonitrile containing 0.05% v/v Trifluoroacetic Acid
 Detection: 230 nm

10 Method A Gradient

Time (min)	Flow (mL/min)	%A	%B
0.0	0.8	95.0	5.0
3.0	0.8	95.0	5.0
6.0	0.8	10.0	90.0
12.0	0.8	10.0	90.0

Method B

- Column: Eclipse plus C18 3.5 μ m C18 (100 $\times$ 4.6 mm)
 Mobile Phase A: Water containing 0.05% v/v Trifluoroacetic Acid
 15 Mobile Phase B: Acetonitrile containing 0.05% v/v Trifluoroacetic Acid
 Detection: 254 nm

Method B Gradient

Time (min)	Flow (mL/min)	%A	%B
0.0	0.8	95.0	5.0
3.0	0.8	95.0	5.0
6.0	0.8	10.0	90.0
12.0	0.8	10.0	90.0

Method C

Column: Eclipse plus C18 3.5 μ m C18 (100 $\times$ 4.6 mm)

5 Mobile Phase A: Water containing 0.05% v/v Trifluoroacetic Acid

Mobile Phase B: Acetonitrile containing 0.05% v/v Trifluoroacetic Acid

Detection: 270 nm

Method C Gradient

Time (min)	Flow (mL/min)	%A	%B
0.0	0.8	95.0	5.0
3.0	0.8	95.0	5.0
6.0	0.8	10.0	90.0
12.0	0.8	10.0	90.0

10

Analytical SFC Conditions:

Method A

Column: Chiralcel OX-H

15 Mobile Phase: 30% Methanol in CO₂

Temperature: 40 °C

Run Time: 10.0 min

Detection: 210 nm

Method B

Column: Chiralpak IC
Mobile Phase: 30% Methanol in CO₂
Temperature: 40 °C
5 Run Time: 8.0 min
Detection: 215 nm

Method C

Column: Chiralcel OD-H
10 Mobile Phase: 25% Methanol in CO₂
Temperature: 40 °C
Run Time: 10.0 min
Detection: 215 nm

Abbreviations:

15 NMR: nuclear magnetic resonance;
mHz: megahertz;
DMSO-*d*₆: dimethyl sulfoxide-*d*₆;
CDCl₃: deuterated chloroform;
20 δ: chemical shift;
MS: mass spectrometry;
HPLC: high performance liquid chromatography;
SFC: *Supercritical fluid chromatography*
m/z: mass-to-charge ratio;
25 [M+H]: molecular ion peak in mass spectrum;
ESI: electrospray ionization;
ESI⁺: electrospray ionization positive mode;
ESI⁻: electrospray ionization negative mode;
rt or RT: room temperature:

min: minute(s);

h: hour(s)

mg: milligram;

g: gram;

5 kg: kilogram;

mL: milliliter;

L: liter;

mmol: millimole;

μM: micromole;

10 MTBE: methyl *tert*-butyl ether;

THF: tetrahydrofuran;

HATU: (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate;

DIPEA or DIEA: *N,N*-diisopropylethylamine;

15 HOBt: hydroxybenzotriazole;

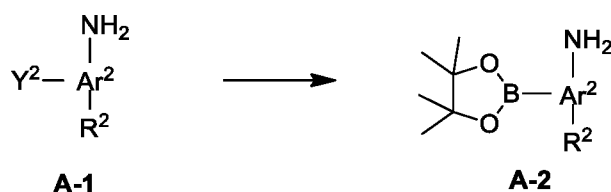
PdCl₂(dppf) or Pd(dppf)Cl₂: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II);

EDC: 1-ethyl-3-(3-*dimethylaminopropyl*)carbodiimide;

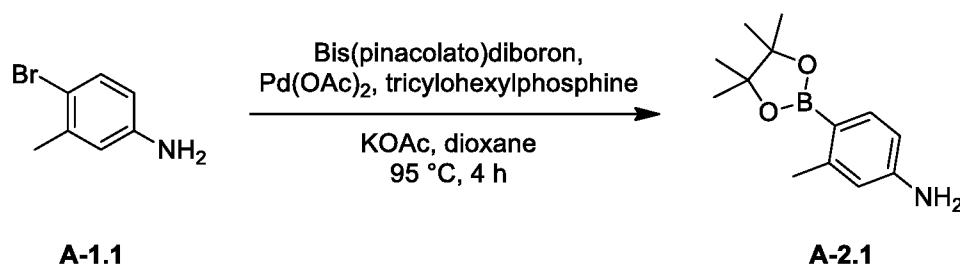
Rh/C: Rhodium on Carbon catalyst.

20

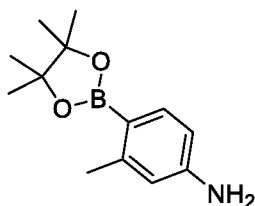
Scheme A:



[0135] Compounds of Formula **A-2** where Ar^2 = phenyl and R^2 = 3-methyl can be synthesized as described below for compound **A-2.1**:



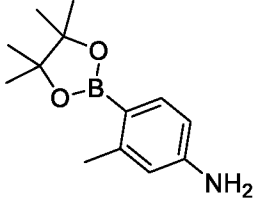
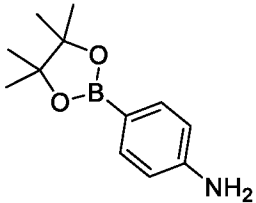
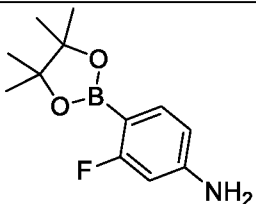
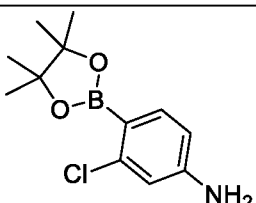
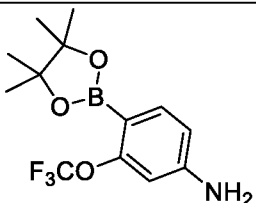
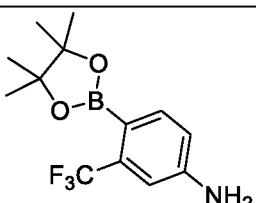
[0136] Synthesis of **3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (A-2.1)**:

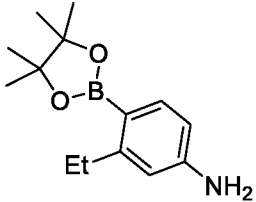
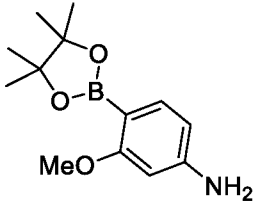


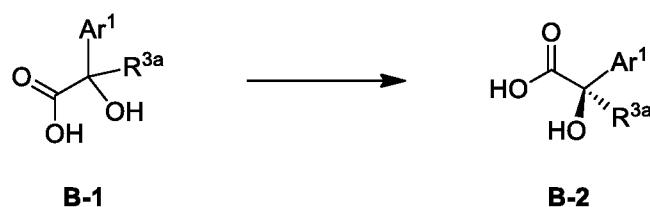
To a stirred solution of tricyclohexylphosphine (7.18 g, 25.7 mmol) in 1,4-dioxane (1.2 L) under argon atmosphere were added bis(pinacolato)diboron (89.62 g, 352.9 mmol) and potassium acetate (62.98 g, 641.7 mmol), followed by 4-bromo-3-methylaniline (**A-1.1**, 60.00 g, 320.8 mmol). The reaction mixture was purged with argon for 10 min. Palladium(II) acetate (5.77 g, 25.7 mmol) was added, and the mixture was purged with argon for 10 min. The reaction mixture was heated at 95 °C with stirring for 16 h. After this time, the reaction mixture was allowed to cool to room temperature, passed through a bed of diatomaceous earth, and washed with methyl *tert*-butyl ether (4 × 250 mL). The filtrate was washed with water (2 × 500 mL) and brine (2 × 250 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 44.80 g, yield: 60%) as a pale brown solid: ESI (m/z) 234 [$\text{C}_{13}\text{H}_{20}\text{BNO}_2 + \text{H}$]⁺.

[0137] The compounds of formula **A-2** (**Table A**) can be synthesized according to the procedures described for compound **A-2.1**:

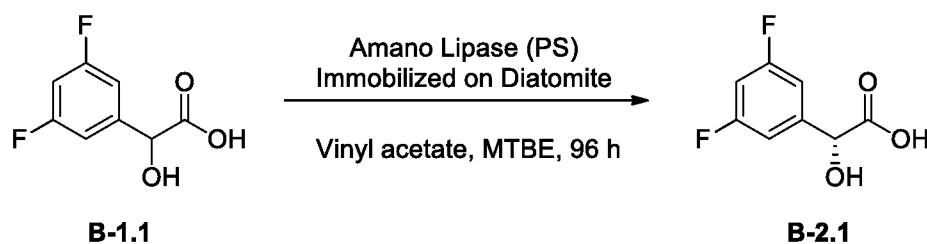
Table A: Compounds **A-2**:

Compound		Structure	MS
A-2.1	3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 234 [C ₁₃ H ₂₀ BNO ₂ + H] ⁺
A-2.2	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 220 [C ₁₂ H ₁₈ BNO ₂ + H] ⁺
A-2.3	3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 238 [C ₁₂ H ₁₇ BFNO ₂ + H] ⁺
A-2.4	3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 253, 255 [C ₁₂ H ₁₇ BClNO ₂ + H] ⁺
A-2.5	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethoxy)aniline		ESI (<i>m/z</i>) 304 [C ₁₃ H ₁₇ BF ₃ NO ₃ + H] ⁺
A-2.6	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)aniline		ESI (<i>m/z</i>) 288 [C ₁₃ H ₁₇ BF ₃ NO ₂ + H] ⁺

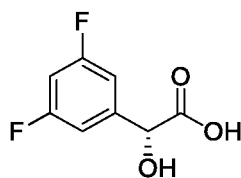
A-2.7	3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 248 [C ₁₄ H ₂₂ BNO ₂ + H] ⁺
A-2.8	3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline		ESI (<i>m/z</i>) 250 [C ₁₃ H ₂₀ BNO ₃ + H] ⁺

Scheme B:

[0138] Compounds of Formula **B-2** where Ar¹ = 3,5-difluorophenyl and R^{3a} = H can be synthesized as described below for compound **B-2.1**:



[0139] Synthesis of (*R*)-2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-2.1**):



To a stirred solution of Amano lipase (PS) supported on Diatomite (5.0 g; purchased from Sigma-Aldrich) in methyl *tert*-butyl ether (MTBE, 50 mL) were added 2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-1.1**, 2.50 g, 13.3 mmol) and vinyl acetate (5.37 g, 62.5 mmol). The reaction mixture was allowed to stir for 96 h. After this time, the supported enzyme was filtered off and washed with methyl *tert*-butyl ether (12 mL). The filtrate was concentrated under reduced pressure. The residue was stirred in methylene chloride (2.5 mL) for 10 min. The resulting white solid was isolated by filtration, washed with methylene

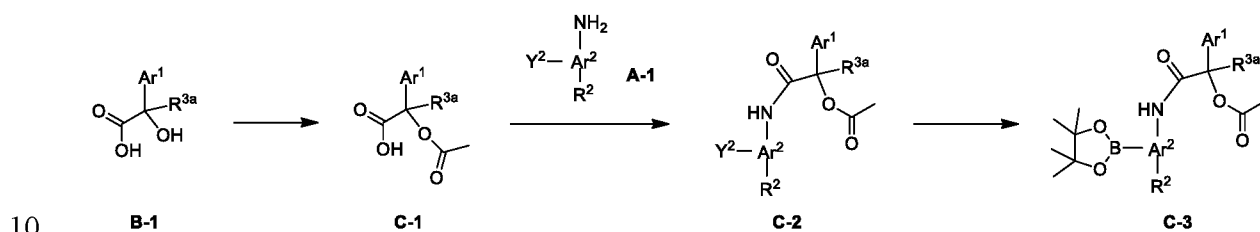
chloride (2 mL), and dried under vacuum to obtain pure (*R*)-2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-2.1**, 850 mg, yield: 34%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.18–7.10 (m, 3H), 5.10 (s, 1H); ESI (*m/z*) 187 [C₈H₆F₂O₃-H]⁻; SFC (chiral) purity >99%.

- 5 [0140] The compounds of formula **B-2** (Table B) can be synthesized according to the procedures described for compound **B-2.1**:

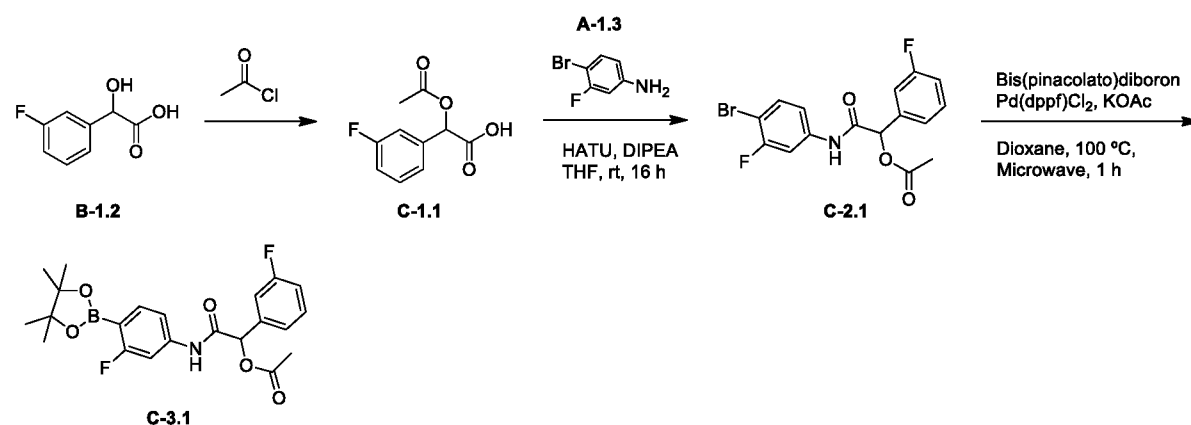
Table B: Compounds **B-2**:

Compound	Name	Structure	MS
B-2.1	(<i>R</i>)-2-(3,5-difluorophenyl)-2-hydroxyacetic acid		ESI (<i>m/z</i>): 187 [C ₈ H ₆ F ₂ O ₃ -H] ⁻
B-2.2	(<i>R</i>)-2-(3-fluorophenyl)-2-hydroxyacetic acid		ESI (<i>m/z</i>): 169 [C ₈ H ₇ FO ₃ -H] ⁻

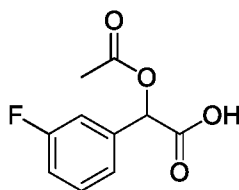
Scheme C:



[0141] Compounds of Formula **C-3** where Ar² = phenyl, R² = 3-F, Y² = Br, R^{3a} = H, Ar¹ = phenyl-R¹ and R¹ = 3-F can be synthesized as described below for compound **C-3.1**:

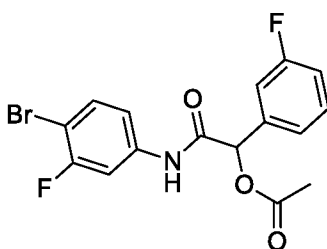


[0142] Step-1: Synthesis of 2-acetoxy-2-(3-fluorophenyl)acetic acid (C-1.1):



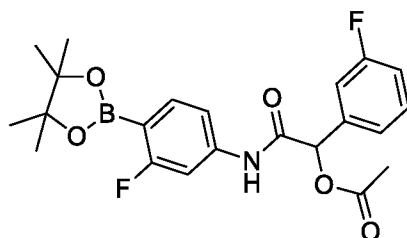
To a stirred solution of acetyl chloride (1.0 mL) at 0 °C was added 2-(3-fluorophenyl)-2-hydroxyacetic acid (**B-1.2**, 0.601 g, 3.53 mmol) portion wise. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After this time, the reaction mixture was concentrated to crude under vacuum and co-distilled with hexanes to afford 2-acetoxy-2-(3-fluorophenyl)acetic acid (**C-1.1**, 0.70 g, yield: 94%) as a white solid: ESI (m/z) 211 [$C_{10}H_9FO_4-H$]⁻.

[0143] Step-2: Synthesis of 2-((4-bromo-3-fluorophenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate (C-2.1):



To a solution of 2-acetoxy-2-(3-fluorophenyl)acetic acid (**C-1.1**, 0.558 g, 2.63 mmol) and 4-bromo-3-fluoroaniline (**A-1.3**, 0.600 g, 3.16 mmol) in tetrahydrofuran (20 mL) were added *N,N*-diisopropylethylamine (0.90 mL, 5.3 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (1.50 g, 3.94 mmol) at room temperature and stirred for 16 h. After this time, the reaction mixture was diluted with dichloromethane (6.0 mL) and washed with water (4 × 4 mL) and brine (4 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4% methanol/dichloromethane) to afford 2-((4-bromo-3-fluorophenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate (**C-2.1**, 500 mg, yield: 60%) as a pale brown solid: ESI (m/z) 385 [$C_{16}H_{12}BrF_2NO_3$]⁺.

[0144] Step-3: Synthesis of 2-((3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate (C-3.1):

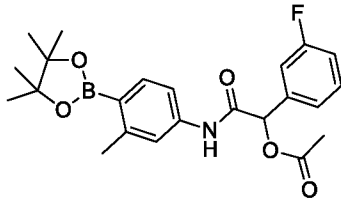
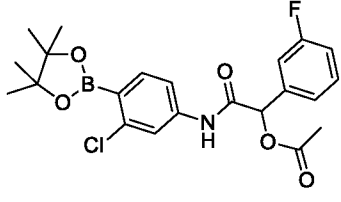
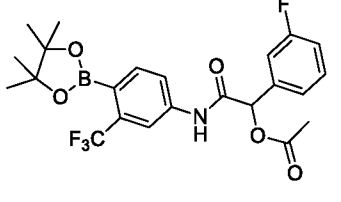
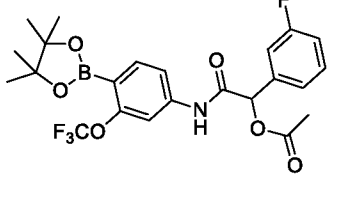
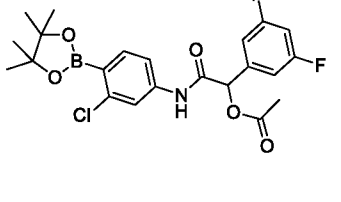


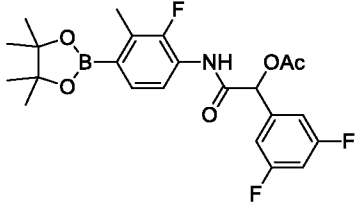
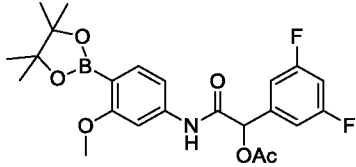
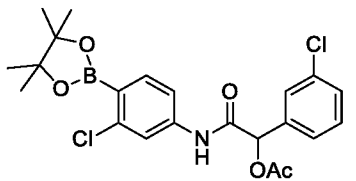
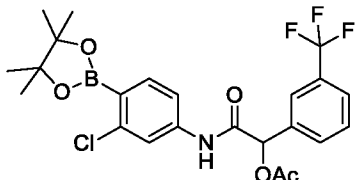
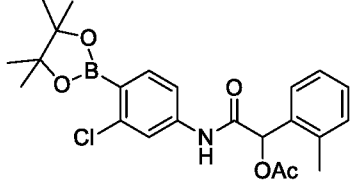
To a stirred solution of 2-((4-bromo-3-fluorophenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate (**C-2.1**, 0.10 g, 0.26 mmol) in 1,4-dioxane (3.0 mL) under argon atmosphere were added bis(pinacolato)diboron (0.13 g, 0.52 mmol) and potassium acetate (51 mg, 0.52 mmol). The reaction mixture was purged with argon for 10 min. 1,1-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (9.5 mg, 0.01 mmol) was added and the mixture was purged with argon for 10 min. The reaction mixture was exposed to microwave irradiation (SEM Company) at 100 °C for 1 h. After this time, the reaction mixture was allowed to cool to room temperature, passed through a bed of diatomaceous earth, and washed with ethyl acetate (2 × 15 mL). The filtrate was washed with water (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford 2-((3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate (**C-3.1**, 50 mg, yield: 60%) as a pale brown solid: ESI (m/z) 432 [$C_{22}H_{24}BF_2NO_5 + H$]⁺.

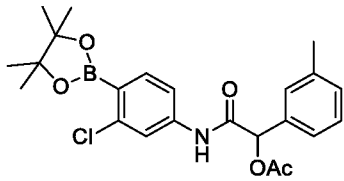
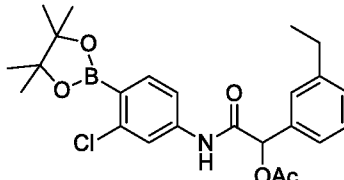
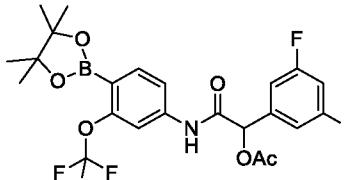
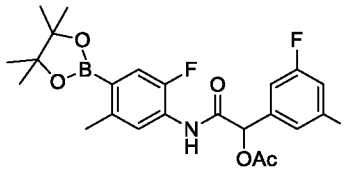
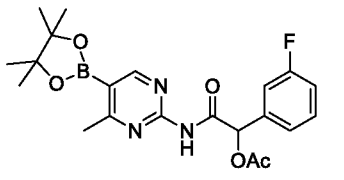
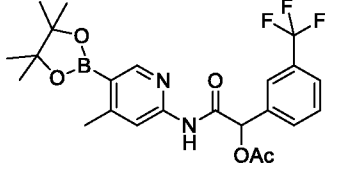
[0145] The compounds of formula **C-3** (Table C-1) can be synthesized according to the procedures described for compound **C-3.1**:

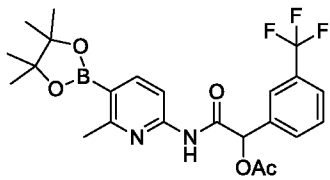
Table C-1: Compounds **C-3**:

Compound	Name	Structure	MS
C-3.1	2-((3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate		ESI (m/z) 432 [$C_{22}H_{24}BF_2NO_5 + H$] ⁺

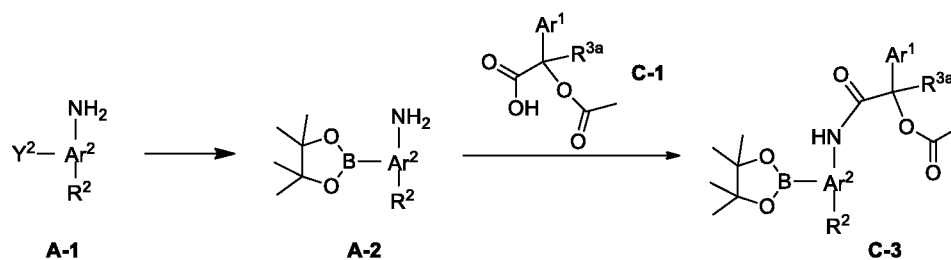
C-3.2	1-(3-fluorophenyl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 428 [C ₂₃ H ₂₇ BFNO ₅ + H] ⁺
C-3.3	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-fluorophenyl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 448, 450 [C ₂₂ H ₂₄ BClFN O ₅ + H] ⁺
C-3.4	1-(3-fluorophenyl)-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)amino)ethyl acetate		ESI (<i>m/z</i>) 482 [C ₂₃ H ₂₄ BF ₄ NO ₅ + H] ⁺
C-3.5	1-(3-fluorophenyl)-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethoxy)phenyl)amino)ethyl acetate		ESI (<i>m/z</i>) 498 [C ₂₃ H ₂₄ BF ₄ NO ₆ + H] ⁺
C-3.6	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 466 [C ₂₂ H ₂₃ BClF ₂ NO ₅ + H] ⁺

C-3.7	1-(3,5-difluorophenyl)-2-((2-fluoro-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 464 [C ₂₃ H ₂₅ BF ₃ NO ₅ + H] ⁺
C-3.8	1-(3,5-difluorophenyl)-2-((3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 462 [C ₂₃ H ₂₆ BF ₂ NO ₆ + H] ⁺
C-3.9	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-chlorophenyl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 463 [C ₂₂ H ₂₄ BCl ₂ N ₂ O ₅ + H] ⁺
C-3.10	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(3-(trifluoromethyl)phenyl)ethyl acetate		ESI (<i>m/z</i>) 497 [C ₂₃ H ₂₄ BClF ₃ NO ₅ + H] ⁺
C-3.11	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(<i>o</i> -tolyl)ethyl acetate		ESI (<i>m/z</i>) 443 [C ₂₃ H ₂₇ BCINO ₅ + H] ⁺

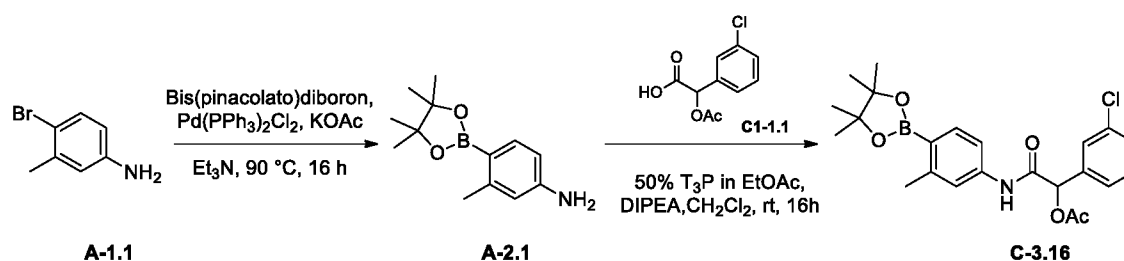
C-3.12	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(<i>m</i> -tolyl)ethyl acetate		ESI (<i>m/z</i>) 443 [C ₂₃ H ₂₇ BCINO 5 + H] ⁺
C-3.13	2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3-ethylphenyl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 457 [C ₂₄ H ₂₉ BCINO 5 + H] ⁺
C-3.14	1-(3,5-difluorophenyl)-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethoxy)phenyl)amino)ethyl acetate		ESI (<i>m/z</i>) 516 [C ₂₃ H ₂₃ BF ₅ NO 6 + H] ⁺
C-3.15	1-(3,5-difluorophenyl)-2-((2-fluoro-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 464 [C ₂₃ H ₂₅ BF ₃ NO 5 + H] ⁺
C-3.16	1-(3-fluorophenyl)-2-(((4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 430 [C ₂₁ H ₂₅ BFN ₃ O 5 + H] ⁺
C-3.17	2-((4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-		ESI (<i>m/z</i>) 479 [C ₂₃ H ₂₆ BF ₃ N ₂ O ₅ + H] ⁺

	yl)pyridin-2-yl)amino)- 2-oxo-1-(3-(trifluoromethyl)phenyl) ethyl acetate		
C-3.18	2-((6-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)amino)- 2-oxo-1-(3-(trifluoromethyl)phenyl) ethyl acetate		ESI (<i>m/z</i>) 479 [C ₂₃ H ₂₆ BF ₃ N ₂ O ₅ + H] ⁺ .

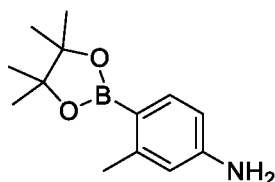
Scheme C-2:



- 5 [0146] Compounds of Formula **C-3** where Ar² = phenyl, R² = 3-CH₃, Y² = Br, R^{3a} = H, Ar¹ = phenyl-R¹ and R¹ = 3-Cl can be synthesized as described below for compound **C-3.16**:



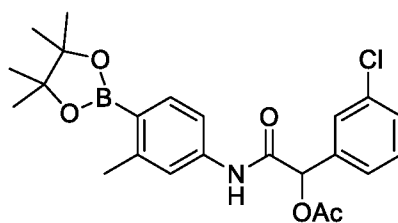
[0147] Step-1: Synthesis of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**):



To a stirred solution of 4-bromo-3-methylaniline (**A-1.1**, 50.00 g, 268 mmol) in

triethyl amine (500 mL) under argon atmosphere were added bis(pinacolato)diboron (81.03 g, 321 mmol) and potassium acetate (70.80 g, 804 mmol). The reaction mixture was purged with argon for 15 min. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (9.40 g, 13.4 mmol) was added, and the mixture was purged with argon for 10 min. The reaction mixture was heated at 90 °C with stirring for 16 h. After this time, the reaction mixture was allowed to cool to room temperature, passed through a bed of diatomaceous earth, and washed with dichloromethane (3×500 mL). The filtrate was washed with water (2×500 mL) and brine (2×250 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/hexanes) to afford 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 40.03 g, yield: 63%) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.32 (d, $J = 8.0$ Hz, 1H), 6.30 (t, $J = 7.2$ Hz, 2H), 2.30 (s, 3H), 1.24 (s, 12H); ESI (m/z) 234 [$\text{C}_{13}\text{H}_{20}\text{BNO}_2 + \text{H}$] $^+$.

[0148] Step-2: Synthesis of 1-(3-chlorophenyl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate (3):



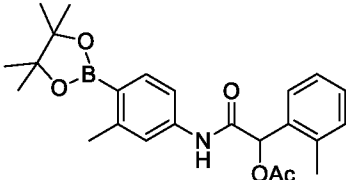
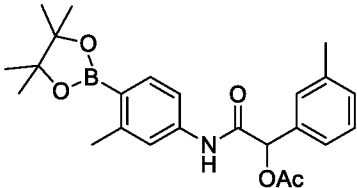
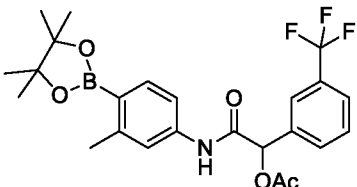
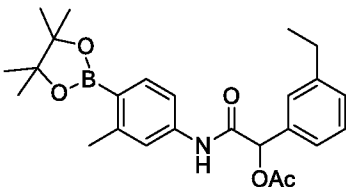
C-3.16

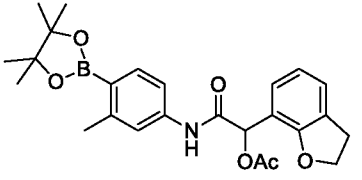
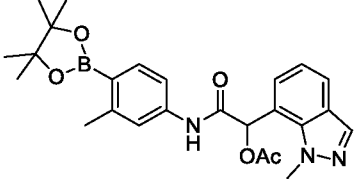
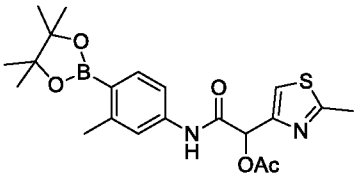
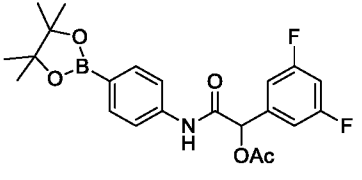
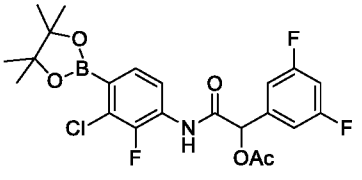
To a stirred solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 10.03 g, 42.9 mmol) and 2-acetoxy-2-(3-chlorophenyl)acetic acid (**C1-1.1**, 10.70 g, 47.2 mmol) in dichloromethane (200 mL) were added *N,N*-diisopropylethylamine (22.40 mL, 128 mmol) followed by propylphosphonic anhydride (*T3P*) (50% in EtOAc) (41.00 mL, 64.3 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Then reaction mixture was cooled to 0 °C and diluted with dichloromethane (100 mL) and sat. NaHCO_3 solution (50 mL). The organic layer was separated, washed with water (200 mL) followed by brine (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 1-(3-chlorophenyl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate (**C-3.16**, 15.00 g, yield: 75%) as off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.70 (t, $J = 7.2$ Hz, 1H), 7.52–7.42 (m, 1H), 7.43–7.36 (m, 2H), 7.28–7.23 (m, 1H), 6.22 (s, 1H), 2.17 (s,

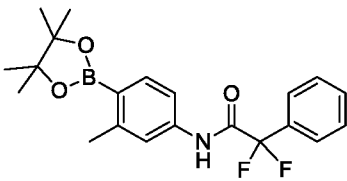
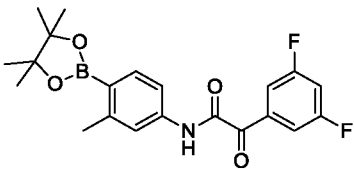
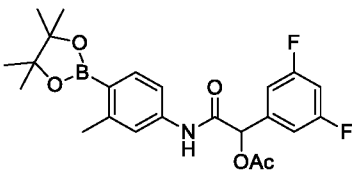
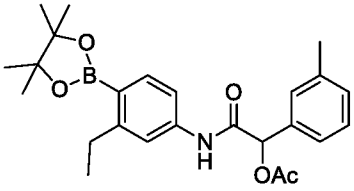
3H), 1.38 (s, 12H); ESI (m/z) 444 [$C_{23}H_{27}BClNO_5 + H$]⁺.

[0149] The compounds of formula **C-3** (Table C-2) can be synthesized according to the procedures described for compound **C-3.16**:

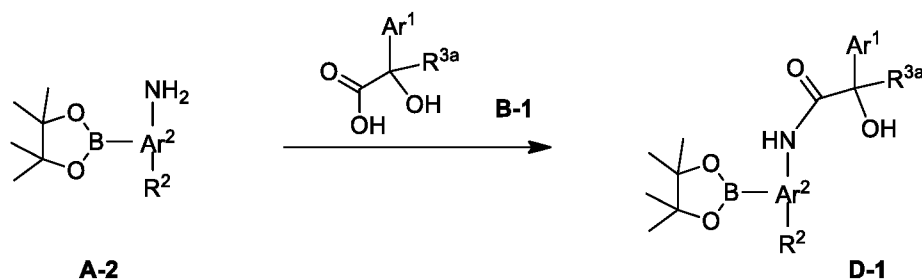
5 **Table C-2:** Compounds **C-3**:

Compound	Name	Structure	MS
C-3.17	2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(<i>o</i> -tolyl)ethyl acetate		ESI (m/z) 424 [$C_{24}H_{30}BNO_5 + H$] ⁺
C-3.18	2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(<i>m</i> -tolyl)ethyl acetate		ESI (m/z) 424 [$C_{24}H_{30}BNO_5 + H$] ⁺
C-3.19	2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(3-(trifluoromethyl)phenyl)ethyl acetate		ESI (m/z) 478 [$C_{24}H_{27}BF_3NO_5 + H$] ⁺
C-3.20	1-(3-ethylphenyl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (m/z) 438 [$C_{25}H_{32}BNO_5 + H$] ⁺

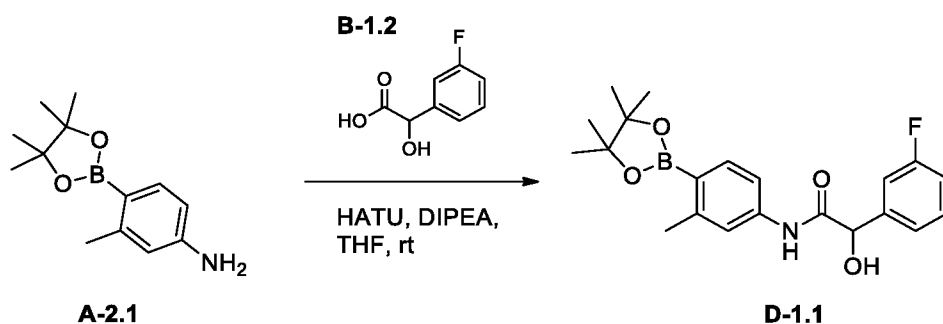
C-3.21	1-(2,3-dihydrobenzofuran-7-yl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 452 [C ₂₅ H ₃₀ BN ₃ O ₆ + H] ⁺
C-3.22	1-(1-methyl-1 <i>H</i> -indazol-7-yl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 464 [C ₂₅ H ₃₀ BN ₃ O ₅ + H] ⁺
C-3.23	2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(2-methylthiazol-4-yl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 431 [C ₂₁ H ₂₇ BN ₂ O ₅ S + H] ⁺
C-3.24	1-(3,5-difluorophenyl)-2-oxo-2-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)ethyl acetate		ESI (<i>m/z</i>) 432 [C ₂₂ H ₂₄ BF ₂ NO ₅ + H] ⁺
C-3.25	2-((3-chloro-2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate		ESI (<i>m/z</i>) 483 [C ₂₂ H ₂₂ BClF ₃ NO ₅ + H] ⁺

	2-oxoethyl acetate		
C-3.26	2,2-difluoro- <i>N</i> -(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-phenylacetamide		ESI (<i>m/z</i>) 388 [C ₂₁ H ₂₄ BF ₂ NO ₃ + H] ⁺
C-3.27	2-(3,5-difluorophenyl)- <i>N</i> -(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-oxoacetamide		ESI (<i>m/z</i>) 402 [C ₂₁ H ₂₂ BF ₂ NO ₄ + H] ⁺
C-3.28	1-(3,5-difluorophenyl)-2-((3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxoethyl acetate		ESI (<i>m/z</i>) 446 [C ₂₃ H ₂₆ BF ₂ NO ₅ + H] ⁺
C-3.29	2-((3-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-2-oxo-1-(<i>m</i> -tolyl)ethyl acetate		ESI (<i>m/z</i>) 438 [C ₂₅ H ₃₂ BNO ₅ + H] ⁺

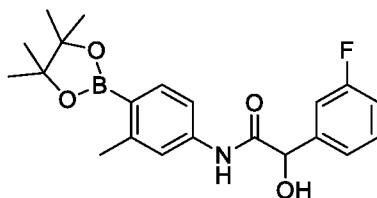
Scheme D:



[0150] Compounds of Formula **D-1** where $\text{Ar}^2 = \text{phenyl}$, $\text{R}^2 = 3\text{-methyl}$, $\text{R}^{3a} = \text{H}$, $\text{Ar}^1 = \text{phenyl-R}^1$ and $\text{R}^1 = 3\text{-F}$ can be synthesized as described below for compound **D-1.1**:



[0151] Synthesis of 2-(3-fluorophenyl)-2-hydroxy-N-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**D-1.1**):



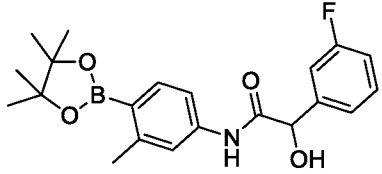
To a solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 0.298 g, 1.28 mmol) and 2-(3-fluorophenyl)-2-hydroxyacetic acid (**B-1.2**, 0.196 g, 1.15 mmol) in tetrahydrofuran (10 mL) were added *N,N*-diisopropylethylamine (0.26 mL, 1.5 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) (0.586, 1.54 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After this time, the reaction mixture was diluted with methylene chloride (6.0 mL) and washed with water (4 × 4 mL) and brine (4 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 4% methanol/dichloromethane) to afford 2-(3-fluorophenyl)-2-hydroxy-N-(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (**D-**

1.1, 0.25 g, yield: 52%) as a pale brown solid: ESI (m/z) 386 [$C_{21}H_{25}BFNO_4 + H$] $^+$.

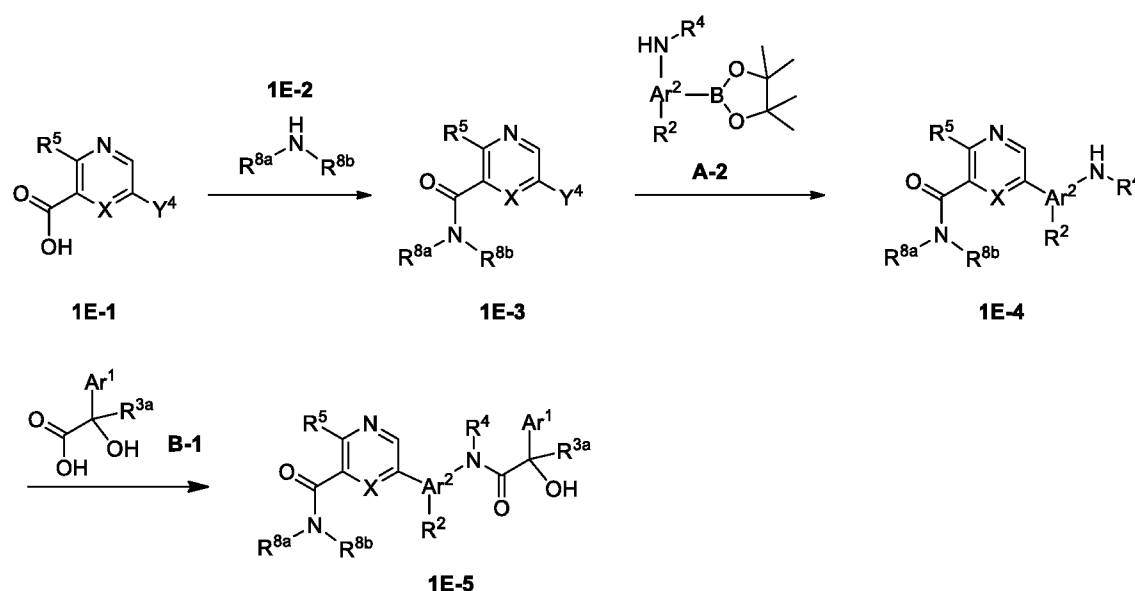
[0152] The compounds of formula **D-1** (**Table D**) can be synthesized according to the procedures described for compound **D-1.1**:

5

Table D: Compounds **D-1**:

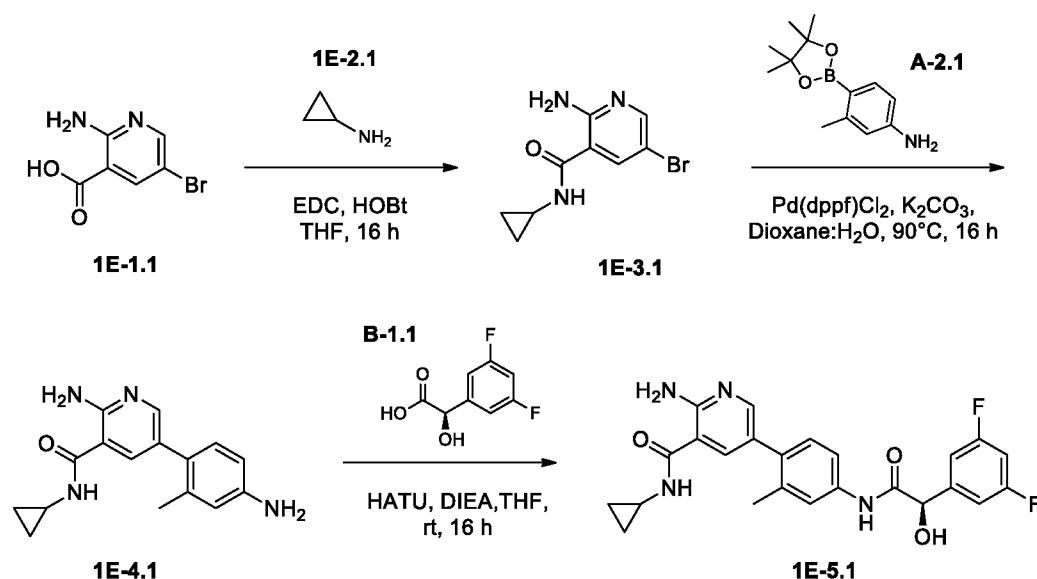
Compound	Name	Structure	MS
D-1.1	2-(3-fluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide		ESI (m/z) 386 [$C_{21}H_{25}BFNO_4 + H$] $^+$

Scheme 1E:

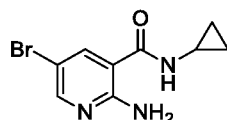


10

[0153] Compounds of Formula **1E-5** can be synthesized according to the procedures described in **Scheme 1E** wherein $R^5 = NH_2$, $X = CH$, $Y^4 = Br$, $R^{8a} = \text{cyclopropyl}$, $R^{8b} = H$, $R^2 = 3\text{-methyl}$, $Ar^2 = \text{phenyl}$, $R^4 = H$, $R^{3a} = H$, $Ar^1 = 3,5\text{-difluorophenyl}$ can be synthesized as described below for compound **1E-5.1**:



[0154] **Step-1: Synthesis of 2-amino-5-bromo-N-cyclopropylpyridine-3-carboxamide (1E-3.1):**



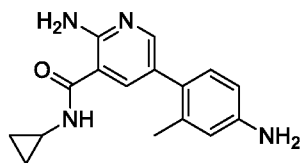
5

To a suspension of 2-amino-5-bromonicotinic acid (**1E-1.1**, 10.0 g, 46.0 mmol) in tetrahydrofuran (100 mL) at 0 °C was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (8.57 g, 55.3 mmol), hydroxybenzotriazole (7.46 g, 55.3 mmol), and *N,N*-diisopropylethylamine (16.0 mL, 92.2 mmol). After 15 min, cyclopropanamine (**1E-2.1**, 3.80 mL, 55.3 mmol) was added, and the resulting mixture was stirred at room temperature for 16 h. After this time, the reaction mixture was diluted with EtOAc (120 mL) and washed with water (2 × 100 mL) and brine (2 × 100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure.

The crude material was purified by column chromatography (silica gel, 30% ethyl acetate/hexanes) to afford 2-amino-5-bromo-*N*-cyclopropylpyridine-3-carboxamide (**1E-3.1**, 8.0 g, yield: 68%): ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (br s, 1H), 8.13 (d, *J* = 2.4 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.26 (br s, 2H), 2.81–2.77 (m, 1H), 0.69 (m, 2H), 0.56 (m, 2H); ESI (*m/z*) 256 [C₉H₁₀BrN₃O + H]⁺.

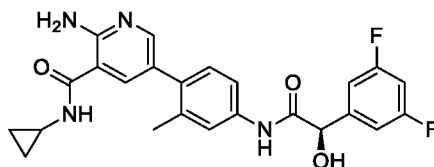
20

[0155] **Step-2:** Synthesis of **2-amino-5-(4-amino-2-methyl-phenyl)-*N*-cyclopropylpyridine-3-carboxamide (1E-4.1)**:



5 A stirred solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 6.53 g, 28.0 mmol) and 2-amino-5-bromo-*N*-cyclopropylnicotinamide (**1E-3.1**, 6.50 g, 25.5 mmol) in 1,4-dioxane (60 mL) and water (20 mL) was degassed with nitrogen gas for 10 min. Potassium carbonate (10.50 g, 76.4 mmol) was added, and the mixture was purged with nitrogen gas for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
10 (1.50 g, 2.04 mmol) was added, and the mixture was purged with nitrogen gas for 5 min. The mixture was stirred at 90 °C under a nitrogen atmosphere for 16 h. After this time, reaction mixture was allowed to cool to room temperature, filtered through a bed of diatomaceous earth and washed with ethyl acetate (2 × 100 mL). The filtrate was washed with water (2 × 100 mL) and brine (100 mL). The organic layer was separated, dried over anhydrous sodium
15 sulfate, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 70% ethyl acetate/hexanes) to afford 2-amino-5-(4-amino-2-methylphenyl)-*N*-cyclopropylnicotinamide (**1E-4.1**, 5.30 g, yield: 74%) as a light brown solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (d, *J* = 3.6 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.04 (br s, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.47–6.43 (m, 2H), 5.03
20 (br s, 2H), 2.83–2.78 (m, 1H), 2.10 (s, 3H), 0.69–0.64 (m, 2H), 0.55–0.53 (m, 2H); ESI (*m/z*) 283 [C₁₆H₁₈N₄O + H]⁺.

[0156] **Step-3:** Synthesis of **(*R*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide (Example 14: 1E-5.1)**:

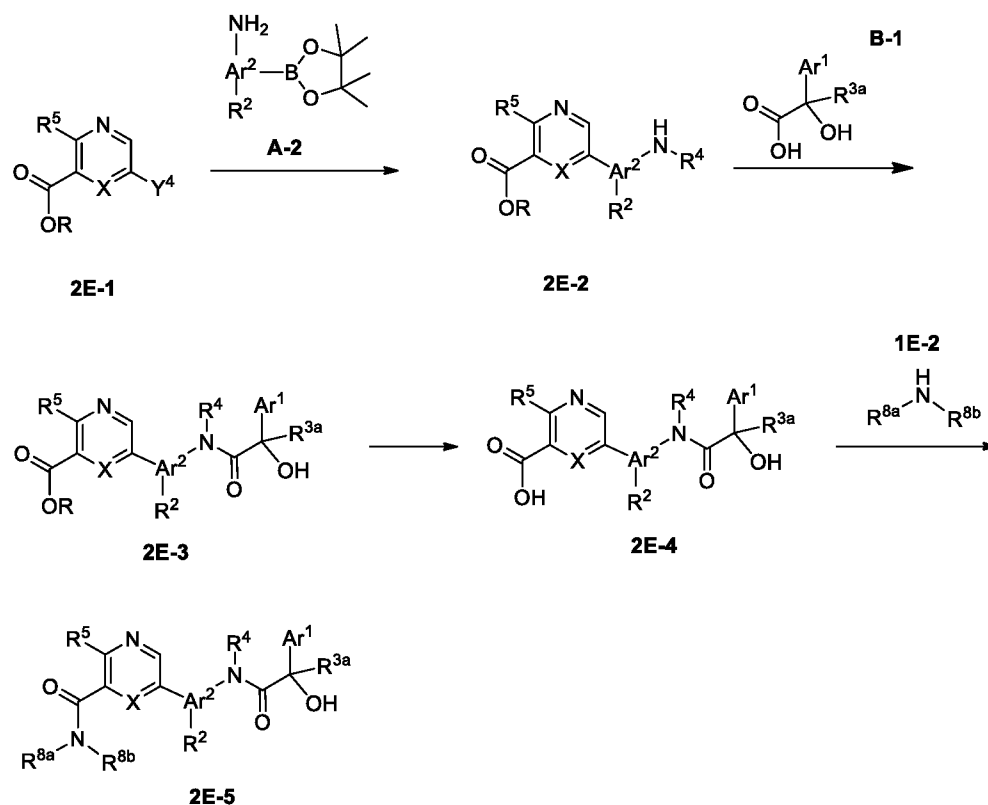


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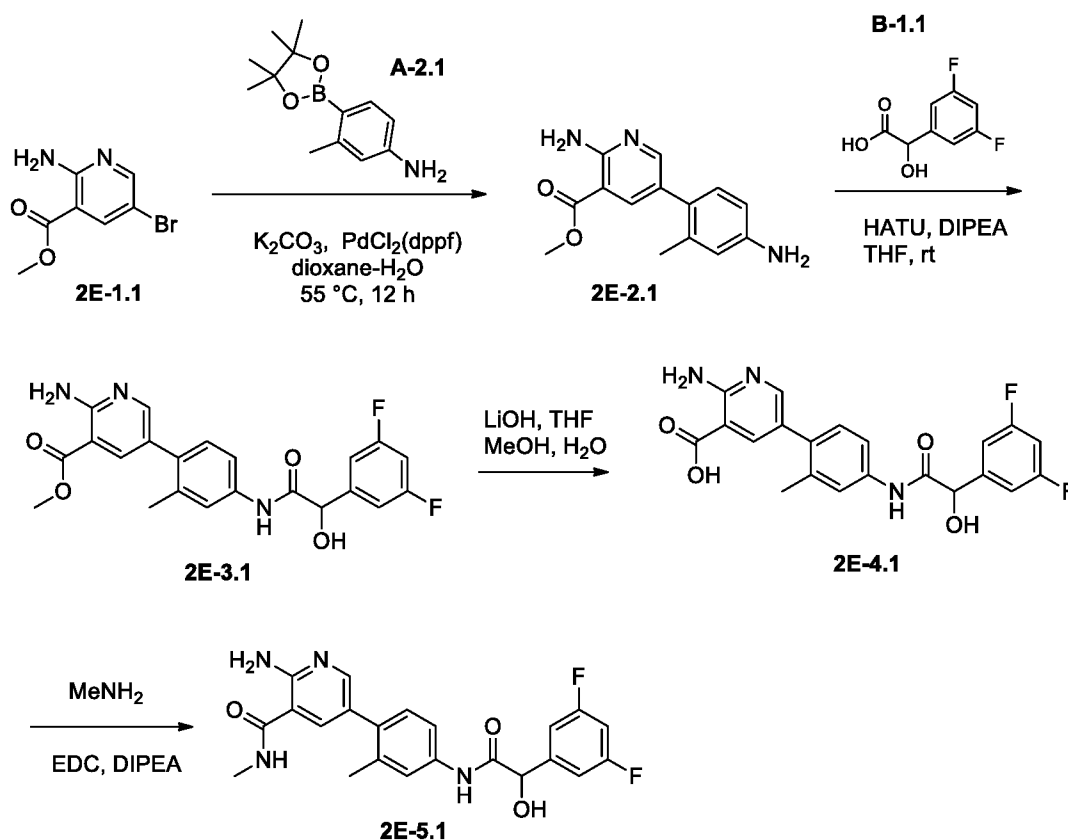
To a solution of 2-amino-5-(4-amino-2-methylphenyl)-*N*-cyclopropylnicotinamide (**1E-4.1**, 5.30 g, 18.7 mmol) and (*R*)-2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-1.1**,

3.70 g, 19.7 mmol) in THF (55 mL) were added *N,N*-diisopropylethylamine (6.50 mL, 37.4 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 8.54 g, 22.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After this time, the reaction mixture was concentrated under reduced pressure. The crude material was diluted with ethyl acetate (100 mL) and washed with water (2 × 80 mL) and brine (2 × 75 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 90% ethyl acetate/hexanes) followed by reversed phase chromatography (C18, 60% acetonitrile/water) to afford (*R*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide (**1E-5.1**, 1.20 g, yield: 14% with 98.8% chiral purity and 2.80 g impure material with 90% chiral purity) as an off white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.96 (br s, 1H), 8.41 (d, *J* = 4.0 Hz, 1H), 8.03 (d, *J* = 2.8 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 6.87 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.24–7.20 (m, 2H), 7.19–7.15 (m, 4H), 6.74 (d, *J* = 5.2 Hz, 1H), 5.17 (d, *J* = 4.8 Hz, 1H), 2.82–2.77 (m, 1H), 2.12 (s, 3H), 0.69–0.64 (m, 2H), 0.55–0.53 (m, 2H); ESI (*m/z*) 453 [C₂₄H₂₂F₂N₄O₃+H]⁺; HPLC (Method C) 97.0% (AUC), *t*_R = 8.72 min; Chiral SFC (Chiralcel OD-H, Method C) 98.8% (AUC), *t*_R = 3.40 min.

Scheme 2E:

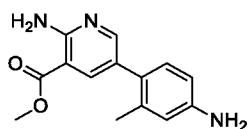


[0157] Compounds of Formula **2E-5** can be synthesized according to the procedures described in **Scheme 2E** wherein $R^5 = \text{NH}_2$, $X = \text{CH}$, $Y^4 = \text{Br}$, $R^{8a} = \text{methyl}$, $R^{8b} = \text{H}$, $R^2 = 3\text{-methyl}$, $\text{Ar}^2 = \text{phenyl}$, $R^4 = \text{H}$, $R^{3a} = \text{H}$, $\text{Ar}^1 = 3,5\text{-difluorophenyl}$ can be synthesized as described below for compound **2E-5.1**:



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[0158] **Step-1: Synthesis of methyl 2-Amino-5-(4-amino-2-methylphenyl)nicotinate (2E-2.1):**

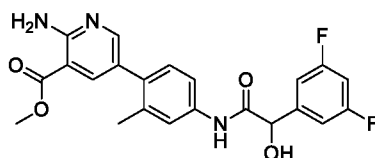


10 A stirred solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 15.20 g, 65.50 mmol) and methyl 2-amino-5-bromonicotinate (**2E-1.1**, 10.09 g, 43.66 mmol) in 1,4-dioxane (75 mL) and water (25 mL) was degassed with nitrogen for 10 min. Potassium carbonate (18.07 g, 131.0 mmol) was added, and the mixture was purged with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

15 (Pd(dppf)Cl₂, 1.60 g, 2.18 mmol) was added, and the mixture was purged with nitrogen for 5 min. The reaction mixture was stirred at 55 °C under nitrogen for overnight. After this time, the reaction mixture was allowed to cool to room temperature, filtered through a bed of

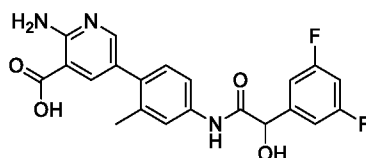
diatomaceous earth, and washed with ethyl acetate (2×75 mL). The filtrates were combined and washed with water (2×50 mL) and brine (100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 45% ethyl acetate/hexanes) to afford methyl 2-amino-5-(4-amino-2-methylphenyl)nicotinate (**2E-2.1**, 7.7 g, yield: 68%) as yellow solid: ESI (m/z): 258 [$C_{14}H_{15}N_3O_2 + H$] $^+$.

[0159] Step-2: Synthesis of methyl 2-Amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate (2E-3.1):



To a solution of methyl 2-amino-5-(4-amino-2-methylphenyl)nicotinate (**2E-2.1**, 11.0 g, 42.8 mmol) and 2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-1.1**, 8.05 g, 42.8 mmol) in tetrahydrofuran (220 mL) were added *N,N*-diisopropylethylamine (DIPEA, 15.0 mL, 85.6 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 19.5 g, 51.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After this time, the reaction mixture was concentrated under reduced pressure. The crude material was diluted with ethyl acetate (100 mL) and washed with water (2×75 mL) and brine (2×50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 40% ethyl acetate/hexanes) to afford methyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate (**2E-3.1**, 8.0 g, yield: 44%) as a yellow solid: ESI (m/z): 428 [$C_{22}H_{19}F_2N_3O_4 + H$] $^+$.

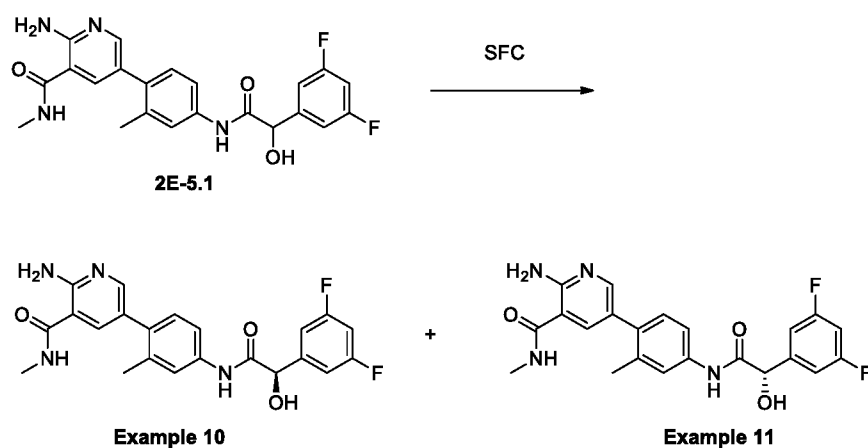
[0160] Step-3: Synthesis of 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid (2E-4.1):



To a solution of methyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate (**2E-3.1**, 8.01 g, 18.7 mmol) in a mixture of

tetrahydrofuran:methanol:water (5:3:2, 80 mL) was added lithium hydroxide monohydrate (1.18 g, 28.1 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. After this time, the reaction mixture was concentrated under reduced pressure. The crude material was acidified with 2N hydrochloric acid solution and stirred for 15 min. The solids were filtered and washed with methyl *tert*-butyl ether (40 mL) to give 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid (**2E-4.1**, 5.8 g, yield: 75%) as a pale yellow solid: ESI (*m/z*): 414 [C₂₁H₁₇F₂N₃O₄+H]⁺.

[0161] **Step-4:** Synthesis of **2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylnicotinamide** (Racemate, **Example 10** and **Example 11: 2E-5.1**):



To a solution of 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid (**2E-4.1**, 0.40 g, 0.96 mmol) and methyl amine hydrochloride (0.098 g, 1.45 mmol) in tetrahydrofuran (8 mL) were added *N,N*-diisopropylethylamine (DIPEA, 0.40 mL, 2.4 mmol) followed by 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 0.441 g, 1.16 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for overnight. After this time, the reaction mixture was concentrated under reduced pressure. The crude material was diluted with ethyl acetate (20 mL) and washed with water (2 × 15 mL) and brine (2 × 15 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 50% ethyl acetate/hexanes) followed by reversed phase chromatography (C18, 52% acetonitrile/water) to afford methyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylnicotinamide (**2E-5.1**, 0.16 g, yield: 39%) as an off-white solid: ESI (*m/z*): 427 [C₂₂H₂₀F₂N₄O₃+H]⁺.

[0162] The mixture of enantiomers was purified by chiral supercritical fluid chromatography

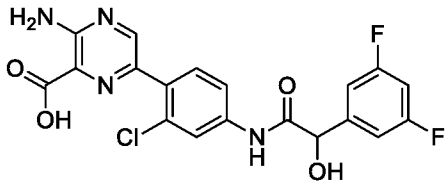
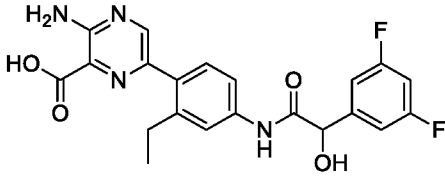
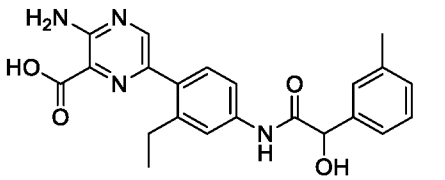
(SFC) (Chiralcel® OX-H column, 30% methanol in CO₂, 40 °C temperature) to afford:

Isomer 1 (Example 10) as an off-white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.95 (s, 1H), 8.42 (d, *J* = 4.0 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.84 (s, 1H), 7.60 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.24–7.03 (m, 6H), 6.72 (d, *J* = 4.8 Hz, 1H), 5.18 (d, *J* = 4.8 Hz, 1H), 2.73 (d, *J* = 4.4 Hz, 3H), 2.22 (s, 3H); ESI (*m/z*): 427 [C₂₂H₂₀F₂N₄O₃ + H]⁺; HPLC (Method B) >99% (AUC), *t*_R = 7.11 min; Chiral SFC (Chiralpak IC, Method B) >99% (AUC), *t*_R = 2.17 min.

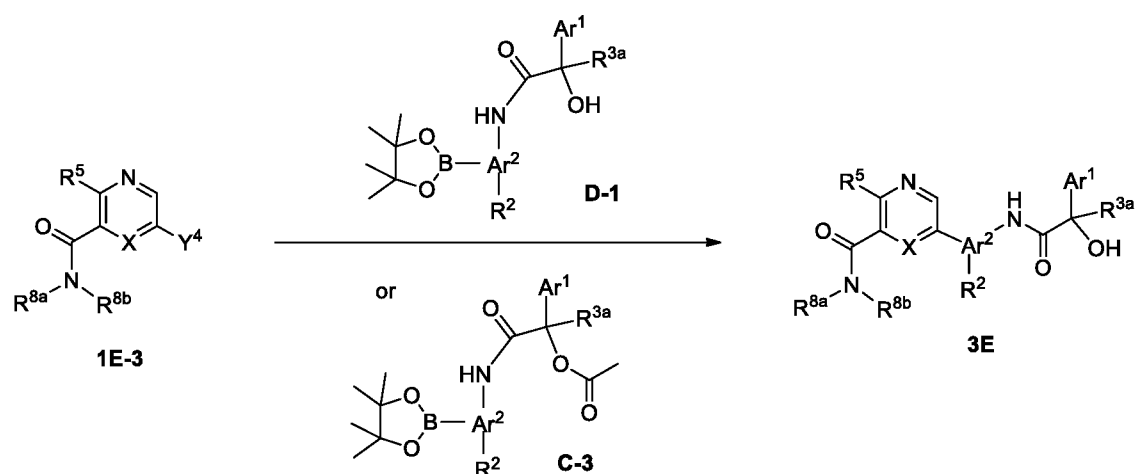
Isomer 2 (Example 11) as an off-white solid: ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.97 (s, 1H), 8.53 (d, *J* = 4.0 Hz, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.98 (s, 1H), 7.62 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.46–7.15 (m, 6H), 6.73 (d, *J* = 4.8 Hz, 1H), 5.18 (d, *J* = 4.8 Hz, 1H), 2.74 (d, *J* = 4.4 Hz, 3H), 2.23 (s, 3H); ESI (*m/z*): 427 [C₂₂H₂₀F₂N₄O₃ + H]⁺; HPLC (Method B) 98.1% (AUC), *t*_R = 7.10 min; Chiral SFC (Chiralpak IC, Method B) >99% (AUC), *t*_R = 3.36 min.

Table E-1: Compounds **2E-4**:

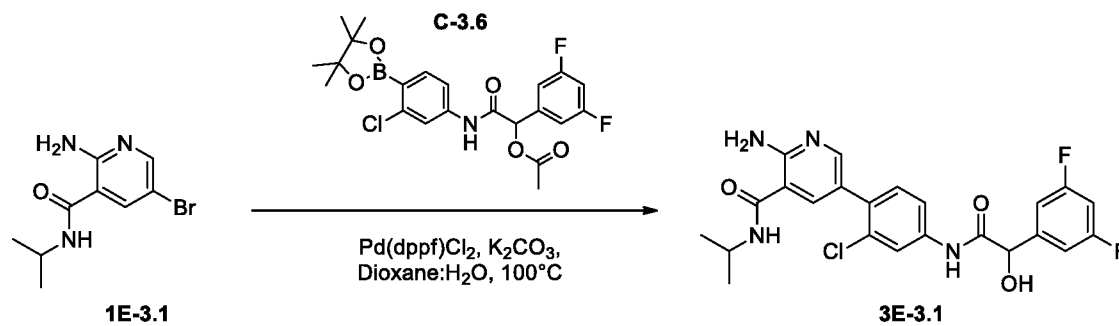
Compound	Name	Structure	MS
2E-4.1	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid		ESI (<i>m/z</i>) 414 [C ₂₁ H ₁₇ F ₂ N ₃ O ₄ + H] ⁺
2E-4.2	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxylic acid		ESI (<i>m/z</i>) 415 [C ₂₀ H ₁₆ F ₂ N ₄ O ₄ + H] ⁺

2E-4.3	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)pyrazine-2-carboxylic acid		ESI (<i>m/z</i>) 435 [C ₁₉ H ₁₃ ClF ₂ N ₄ O ₄ + H] ⁺
2E-4.4	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxylic acid		ESI (<i>m/z</i>) 429 [C ₂₁ H ₁₈ ClF ₂ N ₄ O ₄ + H] ⁺
2E-4.5	3-amino-6-(2-ethyl-4-(2-hydroxy-2-(<i>m</i> -tolyl)acetamido)phenyl)pyrazine-2-carboxylic acid		ESI (<i>m/z</i>) 407 [C ₂₂ H ₂₂ N ₄ O ₄ + H] ⁺

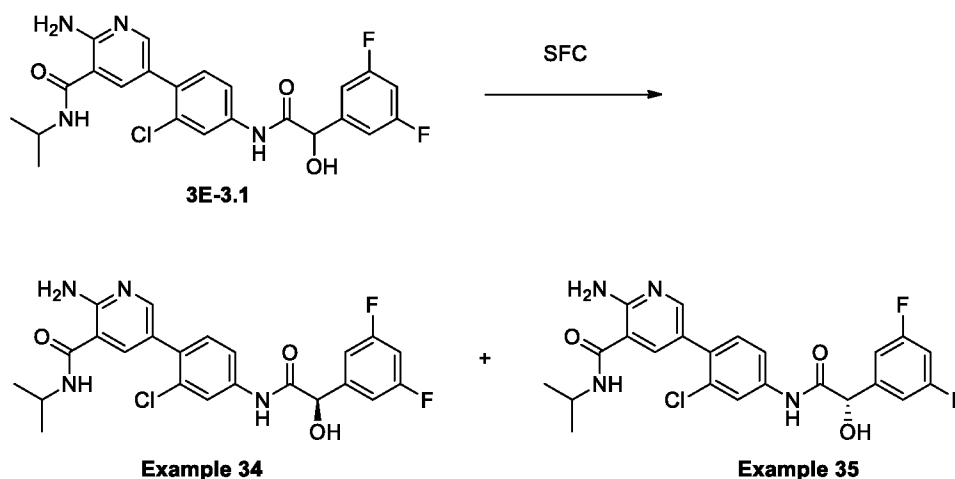
Scheme 3E:



[0163] Compounds of Formula **3E** can be synthesized according to the procedures described in **Scheme 3E** wherein $R^5 = \text{NH}_2$, $X = \text{CH}$, $Y^4 = \text{Br}$, $R^{8a} = \text{Isopropyl}$, $R^{8b} = \text{H}$, $R^2 = 3\text{-Cl}$, $\text{Ar}^2 = \text{phenyl}$, $R^{3a} = \text{H}$, $\text{Ar}^1 = 3,5\text{-difluorophenyl}$ can be synthesized as described below for compound **3E-3.1**:



[0164] Synthesis of (*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-*N*-isopropylpyridin-3-ylidenehydrazide (**Example 34**) and (*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-*N*-isopropylpyridin-3-ylidenehydrazide (**Example 35**):



A stirred solution of 2-amino-5-bromo-*N*-isopropylpyridin-3-ylidenehydrazide (**3E-3.1**, 0.50 g, 1.9 mmol) and 2-((3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**C-3.6**, 1.0 g, 2.3 mmol) in a mixture of 1,4-dioxane and water (3:1, 20 mL) was purged with argon for 5 min. Potassium carbonate (0.53 g, 3.8 mmol) was added, followed by [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.056 g, 0.077 mmol.), and the mixture was purged with argon for 10 min. The resulting reaction mixture was heated to 90 °C for 16 h. After this time, the reaction mixture was allowed to cool to room temperature, passed through a bed of diatomaceous earth and washed

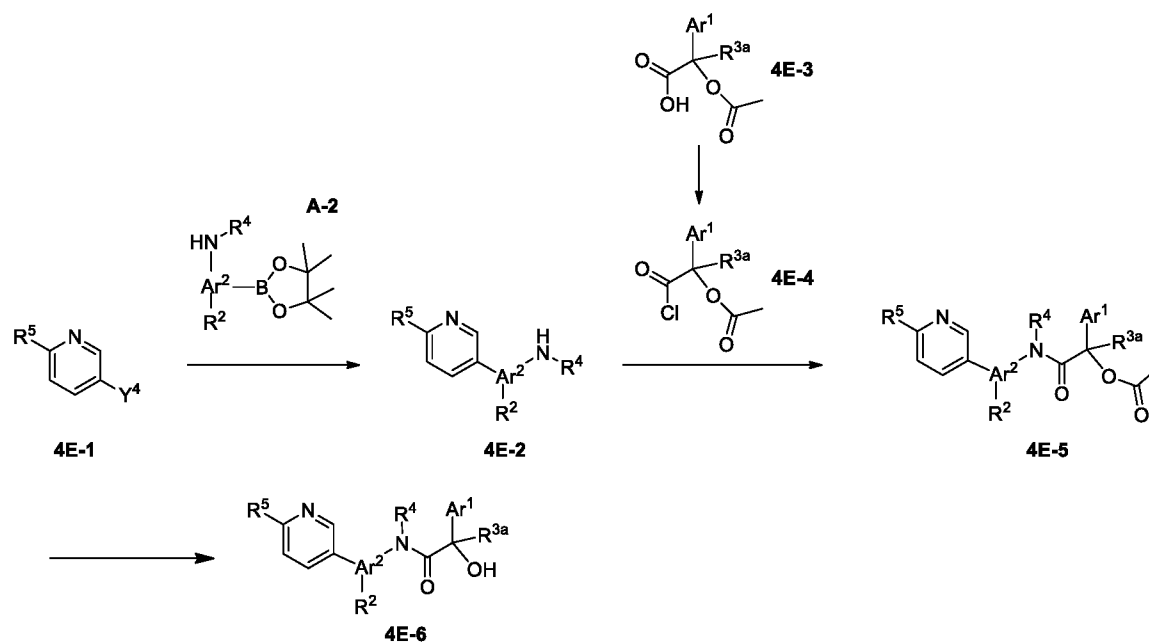
with ethyl acetate (2×15 mL). The filtrate was washed with water (15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by reverse phase column chromatography (C18, 35% acetonitrile/water) to afford 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-*N*-isopropylnicotinamide (**I-E.3**, 150 mg, yield: 18%) as a mixture of enantiomers as an off-white solid: ESI (m/z) 475 [$C_{23}H_{21}ClF_2N_4O_3 + H$] $^+$.

The mixture of enantiomers was purified by chiral supercritical fluid chromatography (SFC) (Chiralpak IC column, 30% methanol in CO₂, 40 °C temperature).

Isomer 1 (Example 34) as an off-white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 (d, $J = 7.6$ Hz, 2H), 8.11 (d, $J = 2.4$ Hz, 2H), 8.02 (d, $J = 2$ Hz, 2H), 7.94 (d, $J = 2$ Hz, 1H), 7.74 (d, $J = 2.4$ Hz, 2H), 7.72 (d, $J = 2$ Hz, 2H), 7.42 (s, 1H), 7.40 (s, 1H), 7.24–7.15 (m, 10H), 6.81 (d, $J = 2$ Hz, 2H), 5.20 (d, $J = 5.2$ Hz, 2H), 4.10–4.03 (m, 1H), 1.14 (d, $J = 6.4$ Hz, 6H); ESI (m/z) 475 [$C_{23}H_{21}ClF_2N_4O_3 + H$] $^+$; HPLC (Method C) 98.1% (AUC), $t_R = 9.28$ min; Chiral SFC (Chiralpak IC, Method B) 96.2% (AUC), $t_R = 1.85$ min.

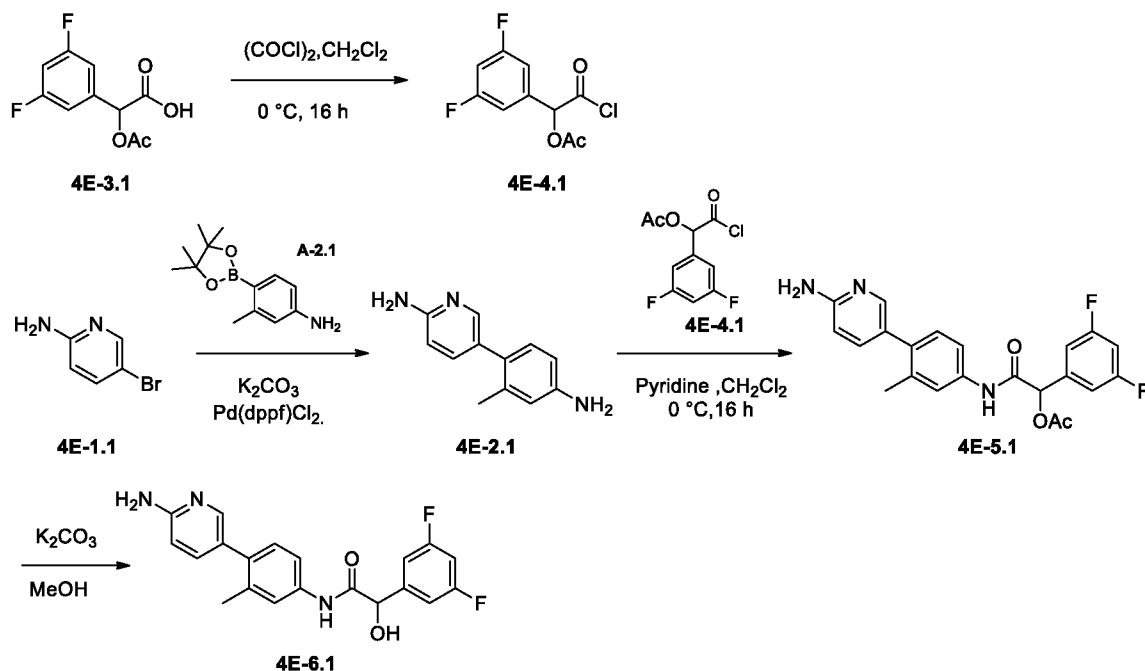
Isomer 2 (Example 35) as off-white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 (d, $J = 7.6$ Hz, 2H), 8.11 (d, $J = 2.4$ Hz, 2H), 8.02 (d, $J = 2$ Hz, 2H), 7.94 (d, $J = 2$ Hz, 1H), 7.74 (d, $J = 2.4$ Hz, 2H), 7.72 (d, $J = 2$ Hz, 2H), 7.42 (s, 1H), 7.40 (s, 1H), 7.24–7.15 (m, 10H), 6.81 (d, $J = 2$ Hz, 2H), 5.20 (d, $J = 5.2$ Hz, 2H), 4.10–4.03 (m, 1H), 1.14 (d, $J = 6.4$ Hz, 6H); ESI (m/z) 475 [$C_{23}H_{21}ClF_2N_4O_3 + H$] $^+$; HPLC (Method C) 95.6% (AUC), $t_R = 9.30$ min; Chiral SFC (Chiralpak IC, Method B) 92.6% (AUC), $t_R = 2.51$ min.

Scheme 4E:

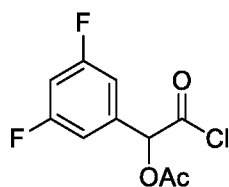


[0165] Compounds of Formula 4E-6 can be synthesized according to the procedures

- 5 described in **Scheme 4E** wherein $R^5 = \text{NHCH}_3$, $Y^4 = \text{Br}$, $R^4 = \text{H}$, $R^2 = 3\text{-CH}_3$, $\text{Ar}^2 = \text{phenyl}$, $R^{3a} = \text{H}$, $\text{Ar}^1 = 3,5\text{-difluorophenyl}$ can be synthesized as described below for compound 4E-6.1:



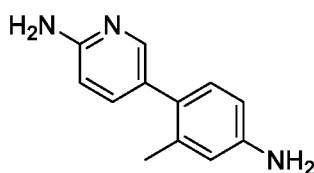
[0166] **Step-1: Synthesis of 2-chloro-1-(3,5-difluorophenyl)-2-oxoethyl acetate (4E-4.1):**



4E-4.1

To a stirred solution of 2-acetoxy-2-(3,5-difluorophenyl)acetic acid (**4E-3.1**, 0.60 g, 2.60 mmol) in dichloromethane (6.0 mL), oxalyl chloride (0.671 mL, 7.82 mmol) was added drop-wise. After addition completed, the reaction mixture was stirred for 5 h at room temperature. After this time, the solvent was concentrated under reduced pressure to afford 2-chloro-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-4.1**, 0.65 g crude) as an off white solid, which was taken to next step without any purification.

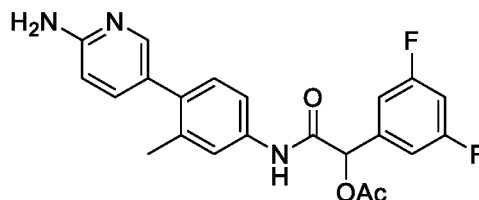
[0167] **Step-2: Synthesis of 5-(4-amino-2-methylphenyl)pyridin-2-amine (4E-2.1):**



4E-2.1

To a stirred solution of 5-bromopyridin-2-amine (**4E-1.1**, 1.00 g, 5.81 mmol), 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**A-2.1**, 2.03 g, 8.72 mmol) in 1,4-dioxane (7 mL): H₂O (3 mL) was added K₂CO₃ (2.0 g, 14.53 mmol). After addition completed, resulting reaction mixture was purged with N₂ gas for 5 min. then PdCl₂(dppf) (0.21 g, 0.29 mmol) was added and again purged with N₂ gas for 1 min. The reaction mixture was sealed and heated at 110 °C for 24 h. After this time the reaction mixture was allowed to cool to room temperature, filtered through celite bed, washed with EtOAc (100 x 2 mL). The filtrate was washed with H₂O (100 x 2 mL) and brine (100 mL). The organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude was purified by column chromatography (silica gel, 70% ethyl acetate in hexanes) to afford 5-(4-amino-2-methylphenyl)pyridin-2-amine (**4E-2.1**, 0.52 g, yield 45%) as an off white solid; ESI (*m/z*) 200 [C₁₂H₁₃N₃ + H]⁺.

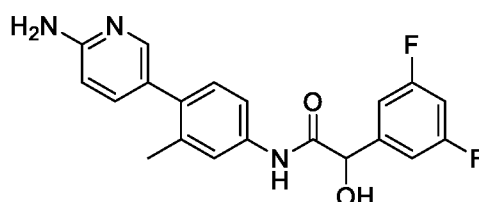
[0168] **Step-3:** Synthesis of 2-((4-(6-aminopyridin-3-yl)-3-methylphenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-5.1**):



4E-5.1

To a stirred solution of 5-(4-amino-2-methylphenyl)pyridin-2-amine (**4E-2.1**, 0.50 g, 2.51 mmol) in dichloromethane (5 mL), pyridine (1.01 mL, 12.56 mmol) was added at 0 °C followed by drop-wise addition of 2-chloro-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-4.1**, 0.68 g, 2.76 mmol) at same temperature. After addition, completed resulting reaction mixture was stirred at room temperature for 16 h. After this time, the reaction mass was diluted with sat NaHCO₃ (50 mL), and an aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by column chromatography (silica gel, 50% to 70% ethyl acetate in hexanes) to afford 2-((4-(6-aminopyridin-3-yl)-3-methylphenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-5.1**, 0.39 g, yield: 38%); ESI (*m/z*) 412 [C₂₂H₁₉F₂N₃O₃ + H]⁺.

[0169] **Step-4:** Synthesis of *N*-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide (**I-E.4**):



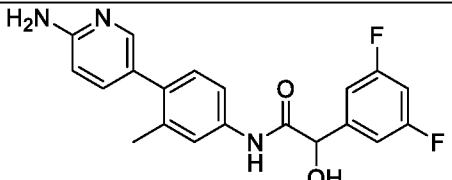
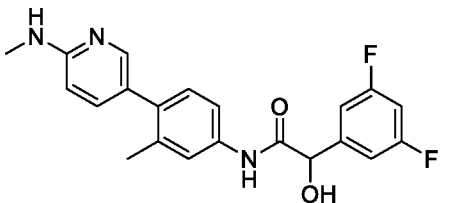
4E-6.1

To a stirred solution of 2-((4-(6-aminopyridin-3-yl)-3-methylphenyl)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-5.1**, 0.39 g, 0.94 mmol) in MeOH (5.0 mL), K₂CO₃ (0.39 g, 2.84 mmol) was added portion wise at room temperature. After addition completed, resulting reaction mixture was stirred for 4 h at room temperature. After this time, the solvent was concentrated under reduced pressure to afford viscous mass, which was diluted with water (20 mL). An aqueous layer extracted using EtOAc (2 × 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated to obtain crude material, which was purified

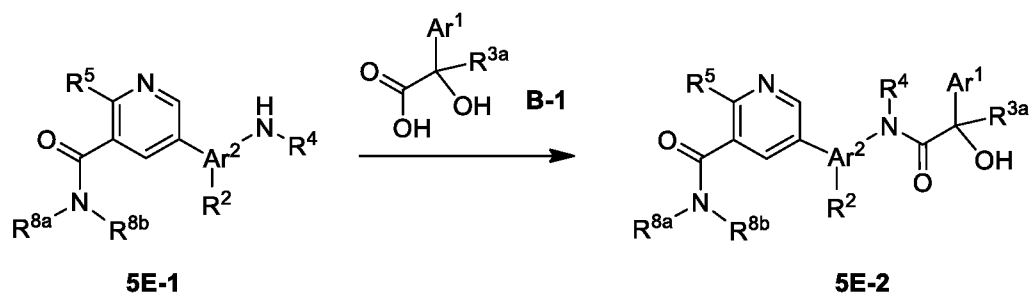
by column chromatography (silica gel, 50% to 70% ethyl acetate in hexanes) to afford *N*-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxy acetamide (**4E-6.1**, 0.25 g, yield: 71%) as an off white solid; ¹H-NMR (400 MHz, DMSO-*d*₆): δ 9.95 (brs, 1H), 7.84–7.83 (m, 1H), 7.58–7.52 (m, 2H), 7.36–7.33 (m, 1H), 7.25–7.15 (m, 3H), 7.08 (d, *J* = 8.00 Hz, 1H), 6.72 (d, *J* = 4.80 Hz, 1H), 6.48 (dd, *J* = 0.80, 8.40 Hz, 1H), 5.97 (brs, 2H), 5.17 (d, *J* = 4.80 Hz, 1H), 2.20 (s, 3H); ESI (*m/z*) 370 [C₂₀H₁₇F₂N₃O₂ + H]⁺.

[0170] The compounds of formula **4E** (Table 4E) can be synthesized according to the procedures described for compound **4E-6.1**:

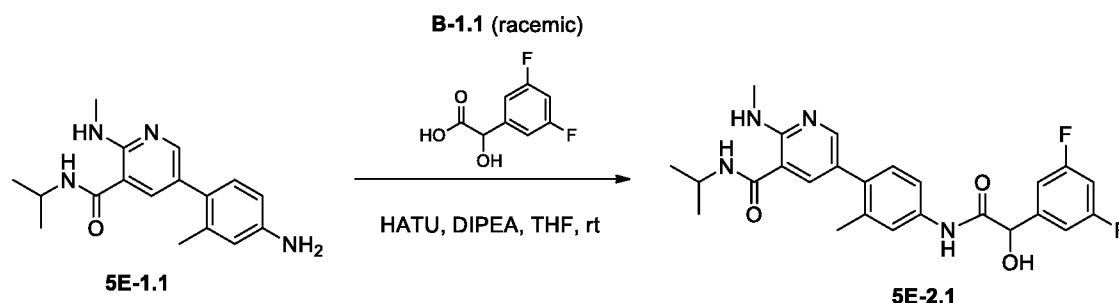
10 Table 4E: Compounds **4E**:

Compound	Name	Structure	MS
4E-6.1	<i>N</i> -(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide		ESI (<i>m/z</i>) 370 [C ₂₀ H ₁₇ F ₂ N ₃ O ₂ + H] ⁺
4E-6.2	2-(3,5-difluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide		ESI (<i>m/z</i>) 384 [C ₂₁ H ₁₉ F ₂ N ₃ O ₂ + H] ⁺

Scheme 5E:



[0171] Compounds of Formula **5E-2** can be synthesized according to the procedures described in **Scheme 5E** wherein $R^5 = \text{NHCH}_3$, $R^4 = \text{H}$, $R^2 = 3\text{-CH}_3$, $\text{Ar}^2 = \text{phenyl}$, $R^{8a} = \text{Isopropyl}$, $R^{8b} = \text{H}$, $R^{3a} = \text{H}$, $\text{Ar}^1 = 3,5\text{-difluorophenyl}$ can be synthesized as described below for compound **5E-2.1**:



Synthesis of 5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropyl-2-(methylamino)nicotinamide (**5E-2.1**):

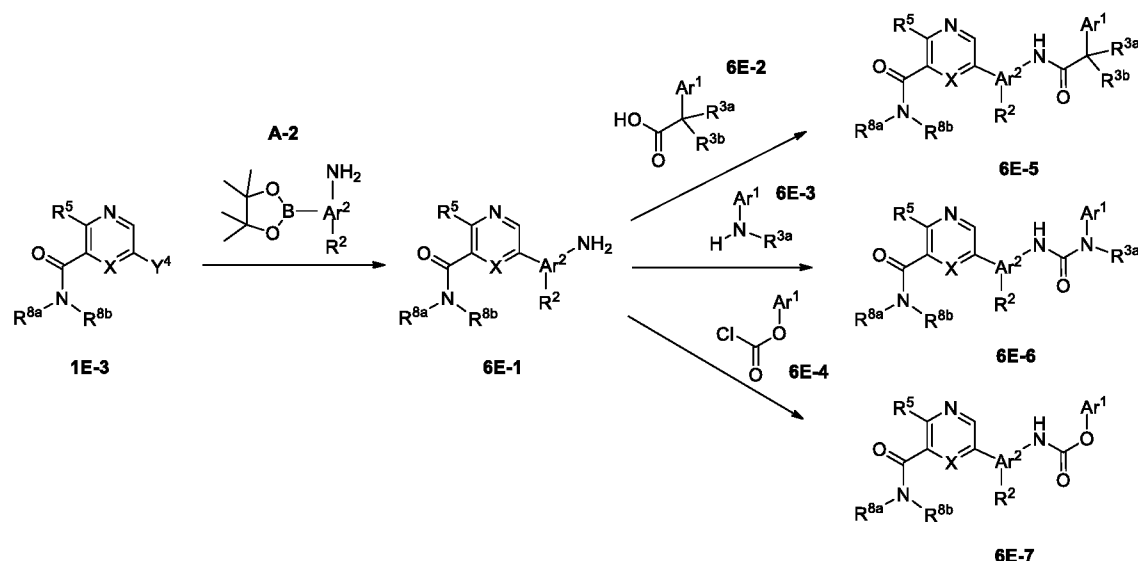
To a stirred solution of 5-(4-amino-2-methylphenyl)-*N*-isopropyl-2-methylnicotinamide (**5E-1.1**, 0.31 g, 1.04 mmol), 2-(3,5-difluorophenyl)-2-hydroxyacetic acid (**B-1.1** (racemic), 35.2, 0.26 g, 1.14 mmol) in dichloromethane (10 mL), *N,N*-diisopropylethylamine (0.4 mL, 2.08 mmol), HATU (0.470 g, 1.20 mmol) were added and resulting reaction mixture was stirred at room temperature for 16 h. After this time the reaction mass was diluted with sat NaHCO_3 solution (50 mL), an aqueous layer extracted with dichloromethane (2×50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain crude material, which was purified by column chromatography (silica gel, 20 % to 30% ethyl acetate in hexanes) to afford 5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropyl-2-(methylamino)nicotinamide (**5E-2.1**, 0.40 g, yield: 82%); ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.95 (brs, 1H), 8.24–8.17 (m, 2H), 8.13 (d, $J = 2.00$ Hz, 1H), 7.89 (d, $J = 2.40$ Hz, 1H), 7.62–7.57 (m, 2H), 7.24–7.15 (m, 4H), 6.73 (d, $J = 5.60$ Hz, 1H), 5.19 (d, $J = 4.80$ Hz, 1H), 4.11–4.02 (m, 1H), 2.93 (d, $J = 4.00$ Hz, 3H), 2.20 (s, 3H), 1.14 (d, $J = 6.80$ Hz, 6H); ESI (m/z) 469 [$\text{C}_{25}\text{H}_{26}\text{F}_2\text{N}_4\text{O}_3 + \text{H}$] $^+$.

[0172] The compounds of formula **5E** (**Table 5E**) can be synthesized according to the procedures described for compound **5E-2.1**:

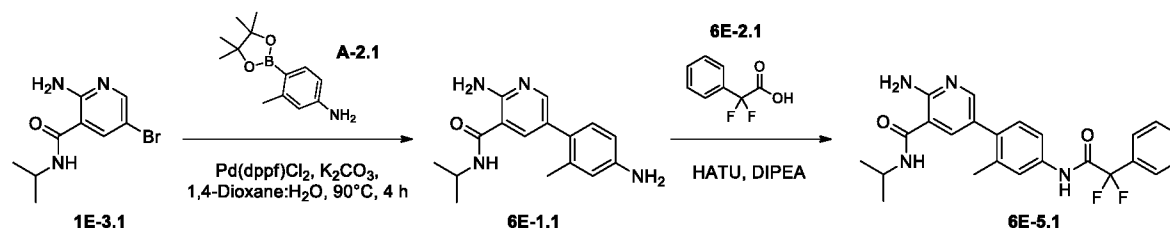
Table 5E: Compounds **5E**:

Compound	Name	Structure	MS
5E-2.1	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-(methylamino)nicotinamide		ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O ₃ +H] ⁺
5E-2.2	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-methylnicotinamide		ESI (<i>m/z</i>) 454 [C ₂₅ H ₂₅ F ₂ N ₃ O ₃ +H] ⁺
5E-2.3	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-methylnicotinamide		ESI (<i>m/z</i>) 440 [C ₂₄ H ₂₃ F ₂ N ₃ O ₃ +H] ⁺
5E-2.4	2-(3,5-difluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide		ESI (<i>m/z</i>) 369 [C ₂₁ H ₁₈ F ₂ N ₂ O ₂ +H] ⁺

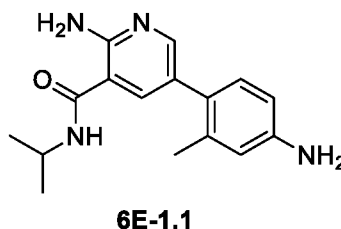
Scheme 6E:



[0173] Compounds of Formula 6E-5 can be synthesized according to the procedures described in **Scheme 6E** wherein R⁵ = NH₂, X = CH, Y⁴ = Br, R^{8a} = Isopropyl, R^{8b} = H, R² = 3-CH₃, Ar² = phenyl, R^{3a} = F, R^{3b} = F, Ar¹ = phenyl can be synthesized as described below for compound 6E-5.1:



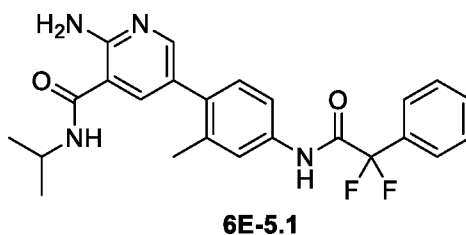
[0174] **Step-1: Synthesis of 2-Amino-5-(4-amino-2-methyl-phenyl)-N-isopropyl-pyridine-3-carbox amide (6E-1.1):**



To a stirred solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (A-2.1, 25.20 g, 108.5 mmol), 2-amino-5-bromo-N-isopropyl-pyridine-3-carboxamide (A-2.1, 20.00 g, 77.5 mmol) in a mixture of 1,4-dioxane (225 mL): H₂O (75 mL), was degassed with nitrogen gas for 10 min. Then K₂CO₃ (32.0 g, 232.5 mmol) followed by PdCl₂(dppf) (4.50 g, 6.2 mmol) was added and resulting reaction mixture was purged with

N₂ gas for 5 min. After, this reaction mixture was heated to 90 °C for 4 h. The reaction mixture was allowed to cool to room temperature; the reaction mixture was filtered through celite bed, washed with EtOAc (100 × 2 mL). The filtrate was washed with H₂O (100 × 2 mL) and brine (150 mL). The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford crude material, which was purified by column chromatography (silica gel, 80% EtOAc in hexanes) to afford 2-amino-5-(4-amino-2-methylphenyl)-*N*-isopropyl-pyridine-3-carbox amide (**6E-1.1**, 17.00 g, yield: 80%) as light brown solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19-8.18 (d, *J* = 7.6 Hz, 1H), 7.95 (s, 1H), 7.83 (s, 1H), 6.99 (s, 2H), 6.89-6.87 (d, *J* = 7.6 Hz, 1H), 6.47-6.44 (m, 2H), 5.03 (s, 2H), 4.10-4.01 (m, 1H), 2.10 (s, 3H), 1.14-1.12 (d, *J* = 6.4 Hz, 6H); ESI *m/z* 285 [C₁₆H₂₀N₄O + H]⁺.

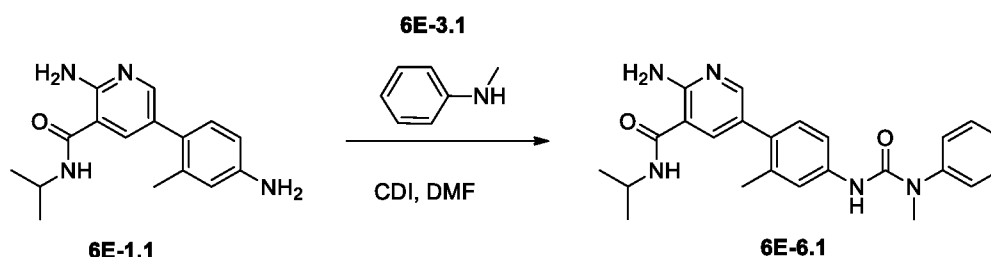
[0175] Step-2: Synthesis of 5-(4-(2,2-difluoro-2-phenylacetamido)-2-methylphenyl)-*N*-isopropyl-2-methylnicotinamide (6E-5.1):



To a solution of 5-(4-amino-2-methylphenyl)-*N*-isopropyl-2-methylnicotinamide (**6E-5.1**, 0.30 g, 1.06 mmol), 2,2-difluoro-2-phenylacetic acid (**6E-2.1**, 0.20 g, 1.16 mmol) in DMF (6.0 mL) were added DIPEA (1.00 mL, 5.30 mmol) followed by HATU (0.805 g, 2.12 mmol) at room temperature and stirred for 16h at same temperature. After this time, reaction mixture was diluted with EtOAc (20 mL), washed with water (20 mL × 2) followed by brine (15 mL × 2). The organic layer was washed brine (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 5% methanol in dichloromethane) to afford 5-(4-(2,2-difluoro-2-phenylacetamido)-2-methyl phenyl)-*N*-isopropyl-2-methylnicotinamide (**6E-5.1**, 0.15 g, yield: 32%) as an off white solid: ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.78 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.91 (d, *J* = 4.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.62-7.59 (m, 5H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 2H), 4.12-4.05 (m, 1H), 2.24 (s, 3H), 1.13 (d, *J* = 8.0 Hz, 6H); ESI (*m/z*) 437 [C₂₅H₂₅F₂N₃O₂ + H]⁺.

[0176] The compounds of formula **6E-5** (Examples **183**, **185-217**) can be synthesized according to the procedures described for compound **6E-5.1**.

[0177] Compounds of Formula **6E-6** can be synthesized according to the procedures described in **Scheme 6E** wherein $R^5 = NH_2$, $X = CH$, $Y^4 = Br$, $R^{8a} = Isopropyl$, $R^{8b} = H$, $R^2 = 3-CH_3$, $Ar^2 = phenyl$, $R^{3a} = CH_3$, $Ar^1 = phenyl$ can be synthesized as described below for compound **6E-6.1**:

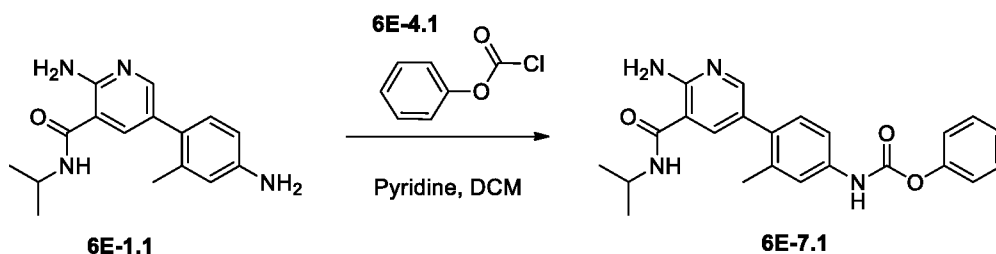


[0178] Synthesis of 2-amino-*N*-isopropyl-5-(2-methyl-4-(3-methyl-3-phenylureido)phenyl)nicotinamide (**6E-6.1**):

To a solution of 2-amino-5-(4-amino-2-methylphenyl)-*N*-isopropylpyridine-3-carbox amide (**6E-1.1**, 167.8 mg, 0.59 mmol), *N*-methyl aniline (**6E-3.1**, 0.95 g, 0.89 mmol) in DMF (10 mL) was added 1,1'-carbonyldiimidazole (CDI, 0.192 g, 1.18 mmol) at room temperature and stirred for 16 h at same temperature. The reaction mixture was quenched with water (10 mL), solid was precipitated out, was filtered and dried afforded crude material, which was purified by column chromatography (silica gel, 5% MeOH in chloroform) afforded 2-amino-*N*-isopropyl-5-(2-methyl-4-(3-methyl-3-phenylureido)phenyl)nicotinamide (**6E-6.1**); ^1H -NMR (400 MHz, DMSO- d_6): δ 8.21 (d, $J = 6.80$ Hz, 1H), 8.16 (s, 1H), 8.02 (d, $J = 2.40$ Hz, 1H), 7.90 (d, $J = 2.00$ Hz, 1H), 7.44–7.32 (m, 6H), 7.27–7.24 (m, 1H), 7.11–7.09 (m, 3H), 4.12–4.03 (m, 1H), 3.28 (s, 3H), 2.15 (s, 3H), 1.14 (d, $J = 6.80$ Hz, 6H); ESI (m/z) 418 [$C_{24}H_{27}N_5O_2 + H$] $^+$.

[0179] The compounds of formula **6E-6** (Example **218**) can be synthesized according to the procedures described for compound **6E-6.1**.

[0180] Compounds of Formula **6E-7** can be synthesized according to the procedures described in **Scheme 6E** wherein $R^5 = \text{NH}_2$, $X = \text{CH}$, $Y^4 = \text{Br}$, $R^{8a} = \text{Isopropyl}$, $R^{8b} = \text{H}$, $R^2 = 3\text{-CH}_3$, $\text{Ar}^2 = \text{phenyl}$, $\text{Ar}^1 = \text{phenyl}$ can be synthesized as described below for compound **6E-7.1**:

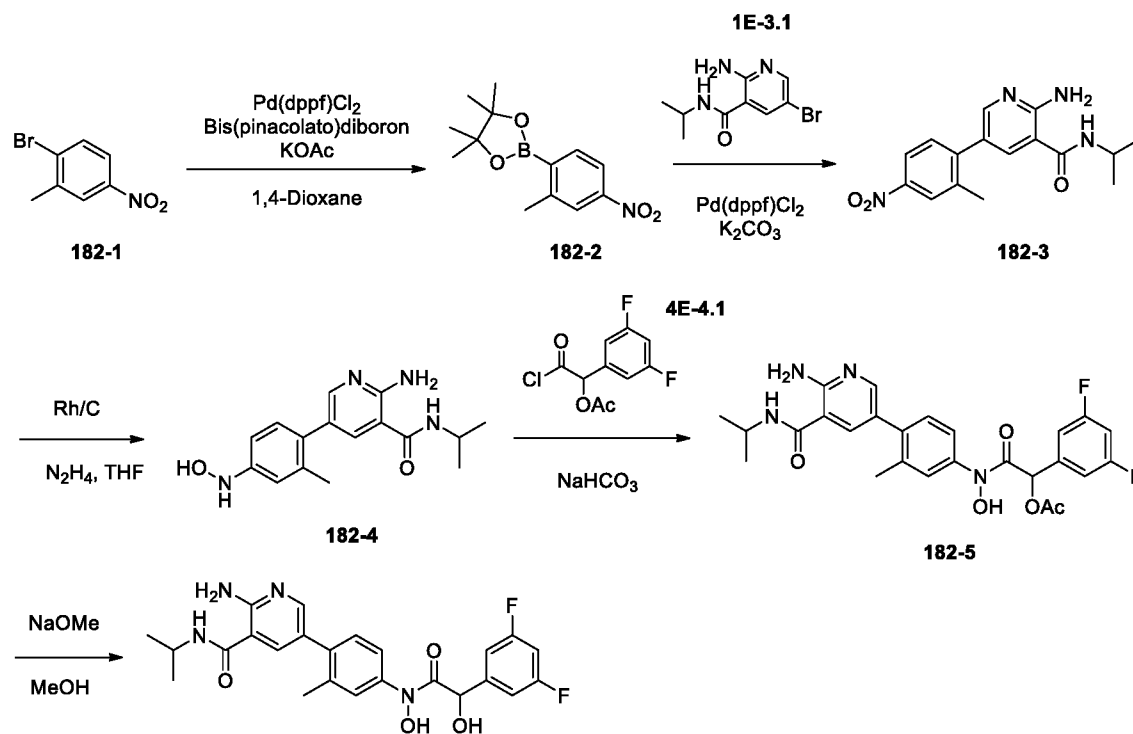


[0181] Synthesis of **phenyl (4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl)carbamate (6E-7.1)**:

To a solution of 2-amino-5-(4-amino-2-methylphenyl)-*N*-isopropylpyridine-3-carbox amide (**6E-1.1**, 224.6 mg, 0.79 mmol) and in CH_2Cl_2 (15 mL) were added pyridine (1.27 mL, 0.95 mmol), phenyl carbonochloridate (**6E-4.1**, 1.18 mL, 0.95 mmol) at 0 °C and resulting reaction mixture was allowed to warm to room temperature and stirred for 1 h. After this, reaction mixture was concentrated under vacuum afforded crude product, which was purified by column chromatography (silica gel, 5% MeOH in chloroform) afforded phenyl (4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl)carbamate (**6E-7.1**); 1H NMR (400 MHz, DMSO-d_6): δ 10.22 (brs, 1H), 8.19 (d, $J=7.60$ Hz, 1H), 8.04 (d, $J=2.00$ Hz, 1H), 7.91 (d, $J=1.60$ Hz, 1H), 7.46–7.41 (m, 4H), 7.29–7.19 (m, 4H), 7.11 (s, 2H), 4.12–4.02 (m, 1H), 2.24 (s, 3H), 1.14 (d, $J=6.40$ Hz, 6H); ESI (m/z) 404 [$\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_3 + \text{H}$] $^+$.

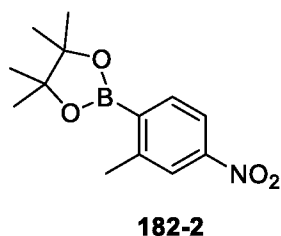
[0182] The compounds of formula **6E-7** (Example **219**) can be synthesized according to the procedures described for compound **6E-7.1**.

[0183] Scheme 7E: Preparation of 2-amino-5-(4-(2-(3,5-difluorophenyl)-*N*,2-dihydroxyacetamido)-2-methyl phenyl)-*N*,2-dihydroxyacetamide (Example 182):



Example 182

[0184] Step-1: Synthesis of 4,4,5,5-tetramethyl-2-(2-methyl-4-nitrophenyl)-1,3,2-dioxaborolane (182-2):

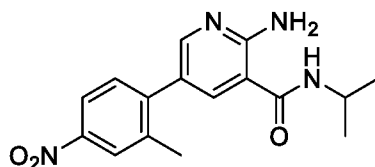


To a stirred solution of 1-bromo-2-methyl-4-nitrobenzene (**182-1**, 2.00 g, 9.3 mmol) in 1,4-dioxane (30 mL) under argon atmosphere were added bis(pinacolato)diboron (3.53 g, 13.95 mmol) and potassium acetate (1.82 g, 18.6 mmol). The reaction mixture was purged with argon for 10 min. followed by addition of PdCl₂(dppf) (682 mg, 0.93 mmol.) and again the reaction mixture was purged with argon for 10 min. After addition completed, the reaction mixture was heated to 100 °C for 16 h. After this time, the reaction mixture was allowed to cool to room temperature, diluted with water (50 mL), extracted with EtOAc (3 × 300 mL). The filtrate was washed with water (2 × 25 mL) and brine (2 × 15 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 50% ethyl

acetate/hexanes to afford 4,4,5,5-tetramethyl-2-(2-methyl-4-nitrophenyl)-1,3,2-dioxaborolane (**182-2**, 2.20 g, yield: 90%) as a white solid. ESI (m/z) 264 [$C_{13}H_{18}BNO_4 + H$]⁺.

[0185] Step-2: Synthesis of 2-amino-*N*-isopropyl-5-(2-methyl-4-

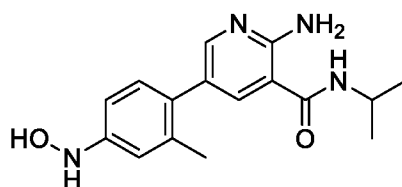
5 nitrophenyl)nicotinamide (**182-3**):



182-3

To a stirred solution of 2-amino-5-bromo-*N*-isopropylnicotinamide (**1E-3.1**, 1.95 g, 7.6 mmol), 4,4,5,5-tetramethyl-2-(2-methyl-4-nitrophenyl)-1,3,2-dioxaborolane (**182-2**, 2.00 g, 7.6 mmol) in a mixture of 1,4-dioxane and water (3:1, 60 mL), potassium carbonate (3.67 g, 26.6 mmol) was added at room temperature and resulting reaction mixture was purged with argon for 10 min. After 10 min. PdCl₂(dppf) (550 mg, 0.76 mmol.) was added and the mixture was again purged with argon for 10 min. The resulting reaction mixture was heated to 90 °C and stirred for 16 h. After this time, the reaction mixture was allowed to cool to room temperature, diluted with water (100 mL). An aqueous layer washed with CH₂Cl₂ (2 × 100 mL), the combined organic layer was washed with water (20 mL) followed by brine (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, 60% ethyl acetate/hexanes to afford 2-amino-*N*-isopropyl-5-(2-methyl-4-nitrophenyl)nicotinamide (**182-3**, 2.2 g, yield: 90%) as an off white solid: ESI (m/z) 315 [$C_{16}H_{18}N_4O_3 + H$]⁺.

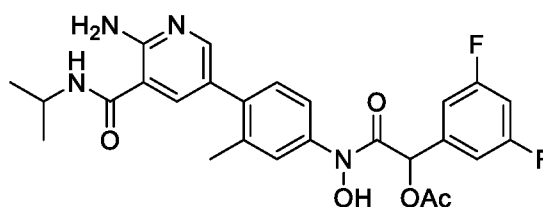
[0186] Step-3: Synthesis of 2-amino-*N*-isopropyl-5-(2-methyl-4-nitrophenyl)nicotinamide (**182-4**):



182-4

To a stirred solution of 2-amino-*N*-isopropyl-5-(2-methyl-4-nitrophenyl)nicotinamide (**182-3**, 0.30 g, 0.955 mmol) in THF (15.0 mL) was added Rh/C (40 mg) at 0-5 °C followed by drop-wise addition of hydrazine hydrate (0.14 g, 2.86 mmol) and stirred for 2 h at same temperature. After this time reaction mixture was passed through a bed of diatomaceous earth, washed with EtOAc (2 × 50 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford 2-amino-5-(4-(hydroxyamino)-2-methylphenyl)-*N*-isopropylnicotinamide (**182-4**, 0.25 g) as a yellow solid. ESI (*m/z*) 301 [C₁₆H₂₀N₄O₂ + H]⁺.

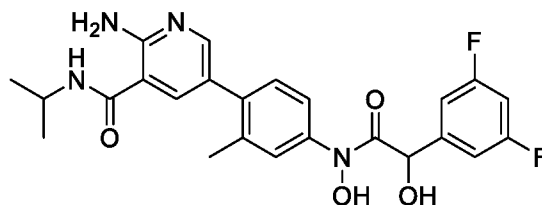
- 10 **[0187] Step-4: Synthesis of 2-((4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl) (hydroxy)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (182-5):**



182-5

- 15 **[0188]** To a stirred solution of 2-amino-*N*-isopropyl-5-(2-methyl-4-nitrophenyl)nicotinamide (**182-4**, 0.25 g, 0.83 mmol) in THF (10.0 mL) were added NaHCO₃ (0.14 mg, 1.66 mmol) at 0-5 °C followed by addition of 2-chloro-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**4E-4.1**, 0.29 g, 2.86 mmol). After this time, the reaction mixture was allowed to cool to room temperature, diluted with 100 ml water, washed with CH₂Cl₂ (2 × 100 mL). The organic layer was washed with water (20 mL), brine (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford crude material. The crude material was
- 20 purified by column chromatography (silica gel, 60% ethyl acetate/hexanes) to afford 2-((4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl)(hydroxy)amino)-1-(3,5-difluorophenyl)-2-oxoethyl acetate (**182-5**, 0.20 g, yield: 47%) as an off white solid: ESI (*m/z*) 513 [C₂₆H₂₆F₂N₄O₅ + H]⁺.

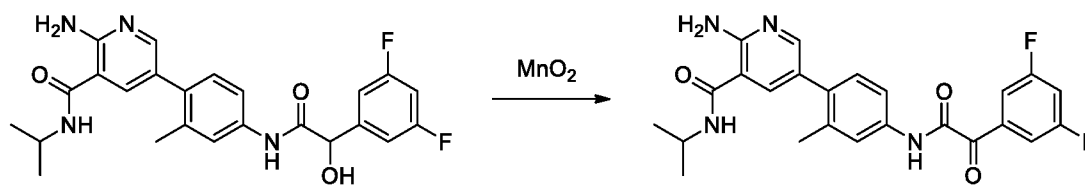
[0189] **Step-5:** Synthesis of 2-amino-5-(4-(2-(3,5-difluorophenyl)-*N*,2-dihydroxyacetamido)-2-methyl phenyl)-*N*-isopropyl nicotinamide (**Example 182**):



Example 182

To a stirred solution of 2-amino-*N*-isopropyl-5-(2-methyl-4-nitrophenyl)nicotinamide (**182-5**, 0.20 g, 0.39 mmol.) in MeOH (10.0 mL) was added NaOMe (0.42 g, 0.78 mmol) at 0-5 °C and stirred for 4 h at RT. After this time, the reaction mixture diluted with water (50 mL), washed with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (20 mL), brine (10 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude material was purified by reverse phase column chromatography eluted with 10% water/Acetonitrile to afford 2-amino-5-(4-(2-(3,5-difluorophenyl)-*N*,2-dihydroxyacetamido)-2-methyl phenyl)-*N*-isopropyl nicotinamide (**Example 182**, 0.11 g, yield: 56%) as an off white solid. ¹H-NMR (400 MHz, DMSO-*d*₆) δ: 10.90 (s, 1H), 8.22 (d, *J*=7.60 Hz, 1H), 8.06 (s, 1H), 7.93 (d, *J*=1.60 Hz, 1H), 7.54-7.52 (m, 2H), 7.27 (d, *J*=8.00 Hz, 1H), 7.21-7.16 (m, 5H), 6.01 (d, *J*=7.20 Hz, 1H), 5.77 (d, *J*=5.60 Hz, 1H), 4.13-4.03 (m, 1H), 2.27 (s, 3H), 1.14 (d, *J*= 6.00 Hz, 6H); ESI *m/z* 471 [C₂₄H₂₄F₂N₄O₄ + H]⁺.

[0190] **Scheme 8E:** Preparation of 2-amino-5-(4-(2-(3, 5-difluorophenyl)-2-oxoacetamido)-2-methyl phenyl)-*N*-isopropyl nicotinamide (**Example 184**):



Example 8/9

Example 184

To a solution of 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methyl phenyl)-*N*-isopropyl nicotinamide (**Example 8/9**, 0.50 g, 1.101 mmol) in dichloromethane (10.0 mL) MnO₂ (0.96 g, 11.01 mmol) was added at rt and resulting reaction mixture was stirred at room temperature for 10 h. After this time, the reaction mixture was diluted with dichloromethane (50 mL), and passed through celite bed. The filtrate was dried over

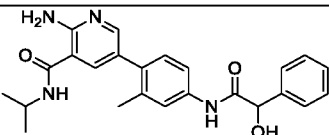
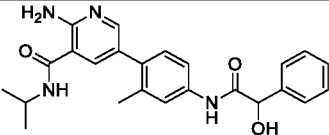
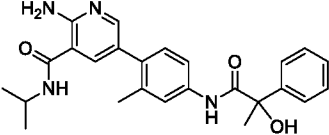
anhydrous sodium sulfate, concentrated under reduced pressure to afford crude material, which was purified by column chromatography (silica gel, 50% Ethyl Acetate in Hexanes) to afford 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-oxoacetamido)-2-methylphenyl)-*N*-

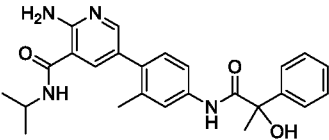
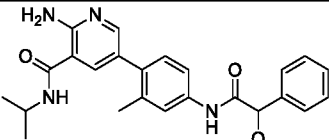
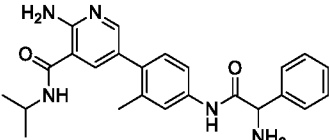
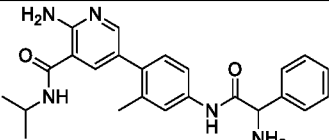
isopropyl nicotinamide (**Example 184**, 0.25 g, yield: 52%); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$):

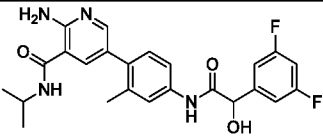
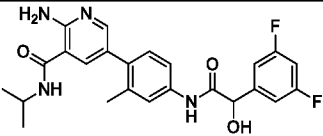
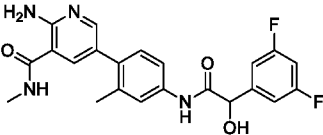
5 δ 10.98 (s, 1H), 8.22 (d, $J = 8.00$ Hz, 1H), 8.07 (s, 1H), 7.93 (s, 1H), 7.64-7.78 (m, 5H), 7.28 (d, $J = 8.00$ Hz, 1H), 7.15 (s, 2H), 4.06-4.11 (m, 1H), 2.28 (s, 3H), 1.13-1.15 (m, 6H). ESI (m/z) 453 [$\text{C}_{24}\text{H}_{22}\text{F}_2\text{N}_4\text{O}_3 + \text{H}$] $^+$.

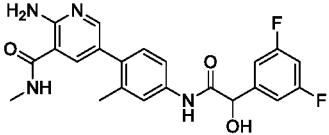
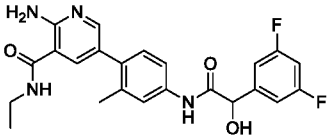
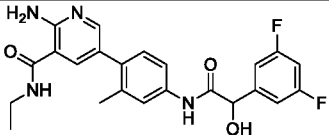
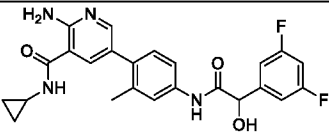
[0191] The compounds of formula **I** (**Table 1**) can be synthesized according to the procedures described in **Scheme 1E** to **Scheme 8E**:

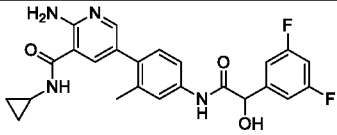
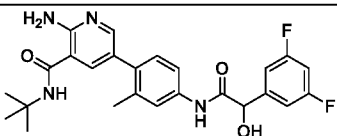
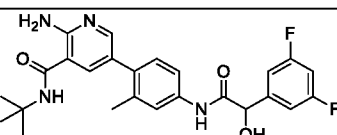
Table I: Compounds of Formula I:

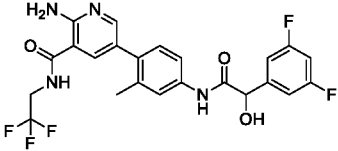
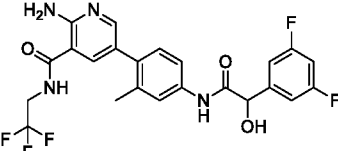
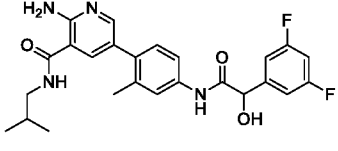
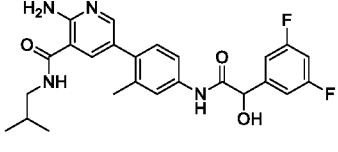
Example	Name	Compounds I	MS	Synthetic Method
1	2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)- <i>N</i> -isopropyl nicotinamide		ESI (m/z) 419 [$\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_3 + \text{H}$] $^+$	Scheme 1E
2	2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)- <i>N</i> -isopropyl nicotinamide	 Isomer 1	ESI (m/z) 419 [$\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_3 + \text{H}$] $^+$	Scheme 2E
3	2-amino-5-(4-(2-hydroxy-2-phenylpropana		ESI (m/z) 433 [$\text{C}_{25}\text{H}_{28}\text{N}_4\text{O}_3 + \text{H}$] $^+$	Scheme 2E

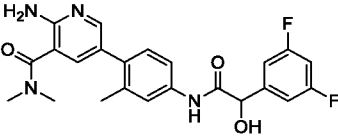
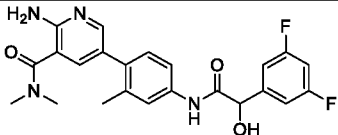
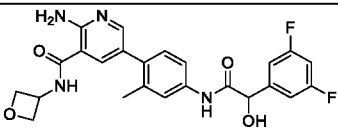
	mido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	Isomer 1		
4	2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ +H] ⁺	Scheme 2E
5	2-amino- <i>N</i> -isopropyl-5-(4-(2-methoxy-2-phenylacetamid o)-2-methylphenyl)n icotinamide	 Isomer 1	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ +H] ⁺	Scheme 2E
6	2-amino-5-(4-(2-amino-2-phenylacetamid o)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 418 [C ₂₄ H ₂₇ N ₅ O ₂ +H] ⁺	Scheme 2E
7	2-amino-5-(4-(2-amino-2-phenylacetamid o)-2-methylphenyl)-	 Isomer 2	ESI (<i>m/z</i>) 418 [C ₂₄ H ₂₇ N ₅ O ₂ +H] ⁺	Scheme 2E

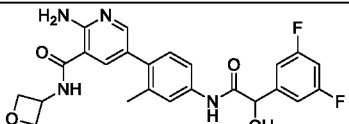
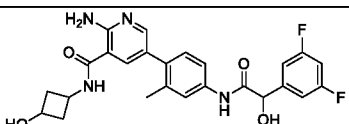
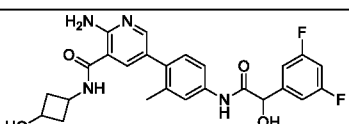
	<i>N</i> -isopropylnicotinamide			
8	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 1E
9	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 1E
10	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -methylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 427 [C ₂₂ H ₂₀ F ₂ N ₄ O ₃ + H] ⁺	Scheme 2E

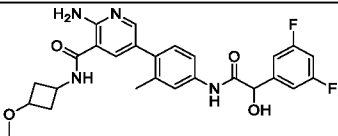
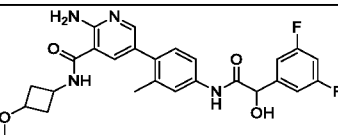
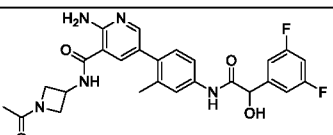
11	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -methylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 427 [C ₂₂ H ₂₀ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
12	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -ethylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
13	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -ethylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
14	2-amino- <i>N</i> -cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-nicotinamide		ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₂ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E

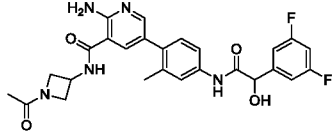
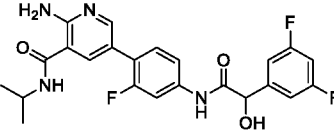
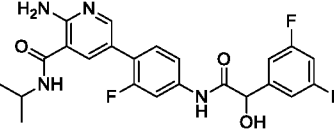
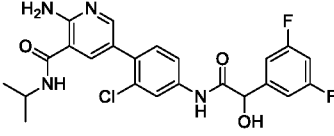
	difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)n icotinamide	Isomer 1		
15	2-amino- <i>N</i> - cyclopropyl-5- (4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)n icotinamide	 Isomer 2	ESI (<i>m/z</i>) 453 $[\text{C}_{24}\text{H}_{22}\text{F}_2\text{N}_4\text{O}]^{3+ \text{ H}}^+$	Scheme 2E
16	2-amino- <i>N</i> - (<i>tert</i> -butyl)-5- (4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)n icotinamide	 Isomer 1	ESI (<i>m/z</i>) 469 $[\text{C}_{25}\text{H}_{26}\text{F}_2\text{N}_4\text{O}]^{3+ \text{ H}}^+$	Scheme 2E
17	2-amino- <i>N</i> - (<i>tert</i> -butyl)-5- (4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)n icotinamide	 Isomer 2	ESI (<i>m/z</i>) 469 $[\text{C}_{25}\text{H}_{26}\text{F}_2\text{N}_4\text{O}]^{3+ \text{ H}}^+$	Scheme 2E

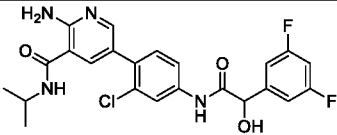
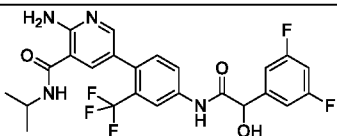
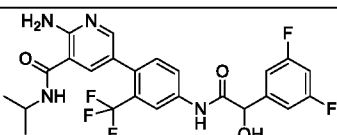
18	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 495 [C ₂₃ H ₁₉ F ₅ N ₄ O 3+ H] ⁺	Scheme 2E
19	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 495 [C ₂₃ H ₁₉ F ₅ N ₄ O 3+ H] ⁺	Scheme 2E
20	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isobutylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
21	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isobutylnicotinamide		ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E

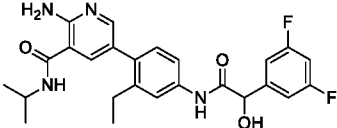
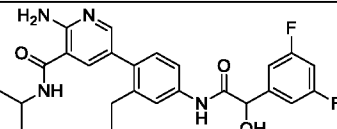
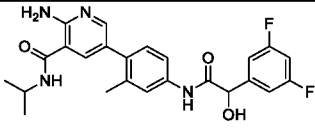
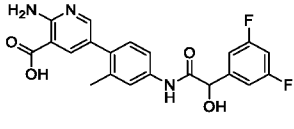
	-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isobutylnicotinamide	Isomer 2		
22	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N,N</i> -dimethylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
23	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N,N</i> -dimethylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
24	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-	 Isomer 1	ESI (<i>m/z</i>) 469 [C ₂₄ H ₂₂ F ₂ N ₄ O 4+ H] ⁺	Scheme 2E

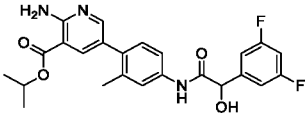
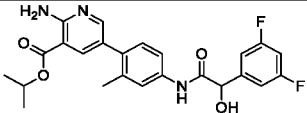
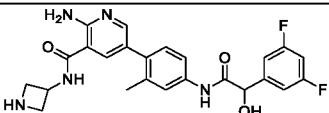
	methylphenyl)- <i>N</i> -(oxetan-3-yl)nicotinamide			
25	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(oxetan-3-yl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 469 $[C_{24}H_{22}F_2N_4O_4 + H]^+$	Scheme 2E
26	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(3-hydroxycyclobutyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 483 $[C_{25}H_{24}F_2N_4O_4 + H]^+$	Scheme 2E
27	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(3-hydroxycyclobutyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 483 $[C_{25}H_{24}F_2N_4O_4 + H]^+$	Scheme 2E

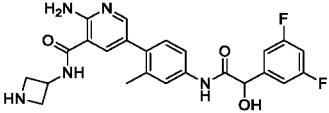
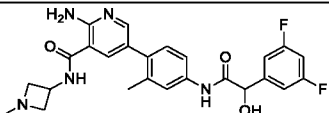
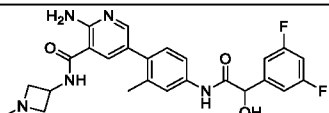
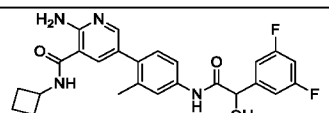
	e			
28	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(3-methoxycyclobutyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 497 [C ₂₆ H ₂₆ F ₂ N ₄ O 4+ H] ⁺	Scheme 2E
29	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(3-methoxycyclobutyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 497 [C ₂₆ H ₂₆ F ₂ N ₄ O 4+ H] ⁺	Scheme 2E
30	N-(1-acetylazetidin-3-yl)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 510 [C ₂₆ H ₂₅ F ₂ N ₅ O 4+ H] ⁺	Scheme 2E

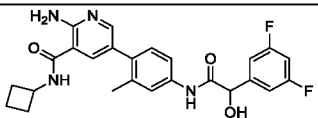
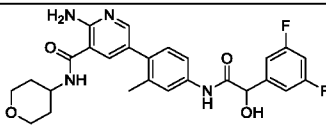
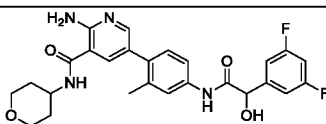
31	<i>N</i> -(1-acetylazetidin-3-yl)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 510 [C ₂₆ H ₂₅ F ₂ N ₅ O 4+ H] ⁺	Scheme 2E
32	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-fluorophenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
33	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-fluorophenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O 3+ H] ⁺	Scheme 2E
34	2-amino-5-(2-chloro-4-(2-(3,5-		ESI (<i>m/z</i>) 475, 477 [C ₂₃ H ₂₁ ClF ₂ N	Scheme 2E

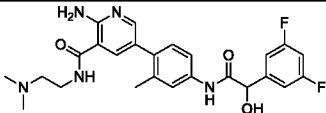
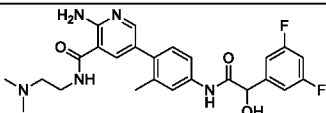
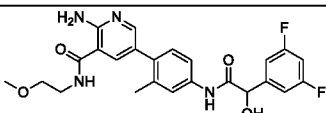
	difluorophenyl) -2- hydroxyacetami do)phenyl)- <i>N</i> - isopropylnicotin amide	Isomer 1	$4\text{O}_3 + \text{H}]^+$	
35	2-amino-5-(2- chloro-4-(2- (3,5- difluorophenyl) -2- hydroxyacetami do)phenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 475, 477 $[\text{C}_{23}\text{H}_{21}\text{ClF}_2\text{N}_4\text{O}_3 + \text{H}]^+$	Scheme 3E
36	2-amino-5-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- (trifluoromethyl)phenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 509 $[\text{C}_{24}\text{H}_{21}\text{F}_5\text{N}_4\text{O}_3 + \text{H}]^+$	Scheme 3E
37	2-amino-5-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- (trifluoromethyl)phenyl)- <i>N</i> -	 Isomer 2	ESI (<i>m/z</i>) 509 $[\text{C}_{24}\text{H}_{21}\text{F}_5\text{N}_4\text{O}_3 + \text{H}]^+$	Scheme 2E

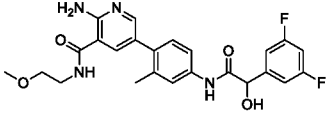
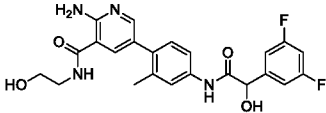
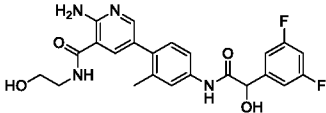
	isopropylnicotin amide			
38	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O ₃ + H] ⁺	Scheme 2E
39	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O ₃ + H] ⁺	Scheme 2E
40	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotin amide	 Racemate	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 1E
41	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotin amide		ESI (<i>m/z</i>) 414 [C ₂₁ H ₁₇ F ₂ N ₃ O ₄ + H] ⁺	Scheme 2E

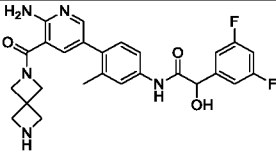
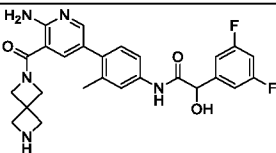
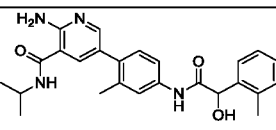
	-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid			
42	isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate	 Isomer 1	ESI (<i>m/z</i>) 456 [C ₂₄ H ₂₃ F ₂ N ₃ O ₄ + H] ⁺	Scheme 2E
43	isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate	 Isomer 2	ESI (<i>m/z</i>) 456 [C ₂₄ H ₂₃ F ₂ N ₃ O ₄ + H] ⁺	Scheme 2E
44	2-amino- <i>N</i> -(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E

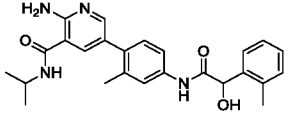
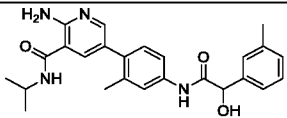
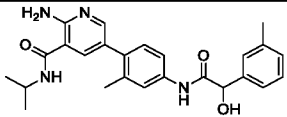
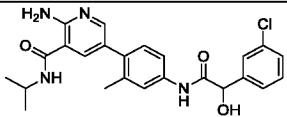
45	2-amino- <i>N</i> -(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
46	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(1-methylazetidin-3-yl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 482 [C ₂₅ H ₂₅ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
47	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(1-methylazetidin-3-yl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 482 [C ₂₅ H ₂₅ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
48	2-amino- <i>N</i> -cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 2E

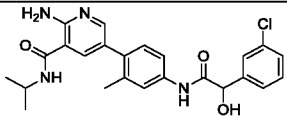
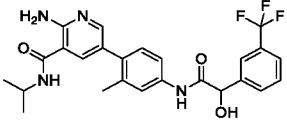
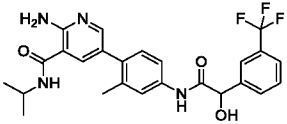
	(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	Isomer 1	$3 + \text{H}]^+$	
49	2-amino- <i>N</i> -cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₄ F ₂ N ₄ O 3 + H] ⁺	Scheme 2E
50	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-4-yl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 497 [C ₂₆ H ₂₆ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E
51	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-4-yl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 497 [C ₂₆ H ₂₆ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E

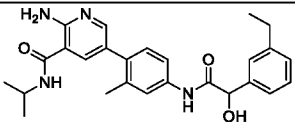
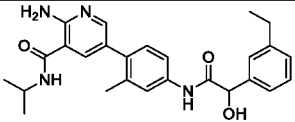
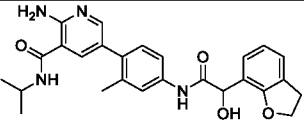
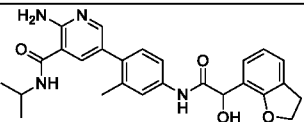
	<i>N</i> -(tetrahydro-2 <i>H</i> -pyran-4-yl)nicotinamide			
52	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(2-(dimethylamino)ethyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 484 [C ₂₅ H ₂₇ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
53	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(2-(dimethylamino)ethyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 484 [C ₂₅ H ₂₇ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
54	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(2-(dimethylamino)ethyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 471 [C ₂₄ H ₂₄ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E

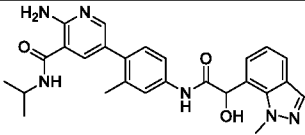
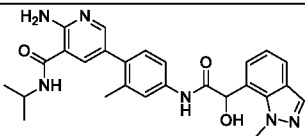
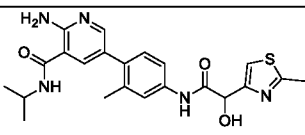
	methoxyethyl)n icotinamide			
55	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)n icotinamide	 Isomer 2	ESI (<i>m/z</i>) 471 [C ₂₄ H ₂₄ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E
56	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)ni cotinamide	 Isomer 1	ESI (<i>m/z</i>) 457 [C ₂₃ H ₂₂ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E
57	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)ni cotinamide	 Isomer 2	ESI (<i>m/z</i>) 457 [C ₂₃ H ₂₂ F ₂ N ₄ O ₄ + H] ⁺	Scheme 2E

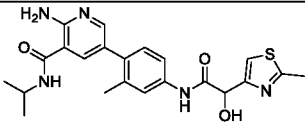
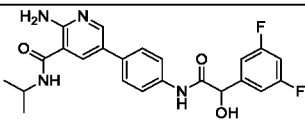
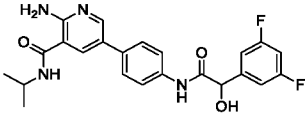
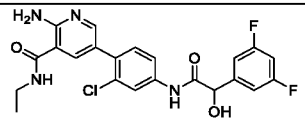
62	<i>N</i> -(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide	 Isomer 1	ESI (<i>m/z</i>) 494 [C ₂₆ H ₂₅ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
63	<i>N</i> -(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide	 Isomer 2	ESI (<i>m/z</i>) 494 [C ₂₆ H ₂₅ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
64	2-amino-5-(4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 3E

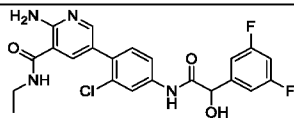
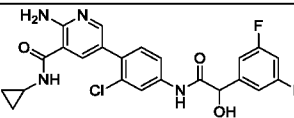
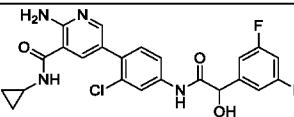
65	2-amino-5-(4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 3E
66	2-amino-5-(4-(2-hydroxy-2-(<i>m</i> -tolyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 3E
67	2-amino-5-(4-(2-hydroxy-2-(<i>m</i> -tolyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 3E
68	2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E

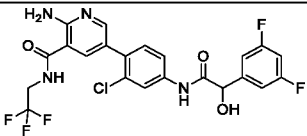
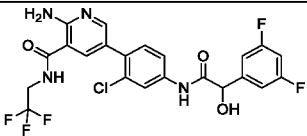
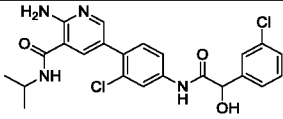
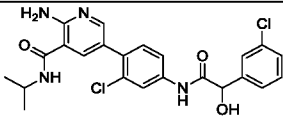
	methylphenyl)- <i>N</i> - isopropylnicotin amide			
69	2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E
70	2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 487 [C ₂₅ H ₂₅ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
71	2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotin	 Isomer 2	ESI (<i>m/z</i>) 487 [C ₂₅ H ₂₅ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E

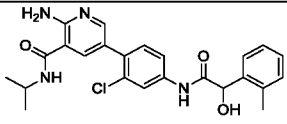
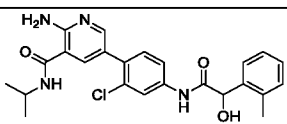
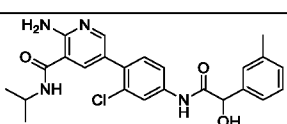
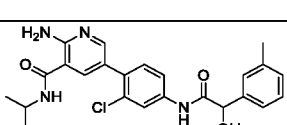
	amide			
72	2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 447 [C ₂₆ H ₃₀ N ₄ O ₃ + H] ⁺	Scheme 3E
73	2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 447 [C ₂₆ H ₃₀ N ₄ O ₃ + H] ⁺	Scheme 3E
74	2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 460 [C ₂₆ H ₂₈ N ₄ O ₄ + H] ⁺	Scheme 3E
75	2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 460 [C ₂₆ H ₂₈ N ₄ O ₄ + H] ⁺	Scheme 3E

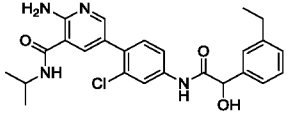
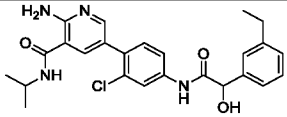
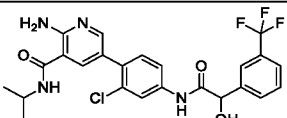
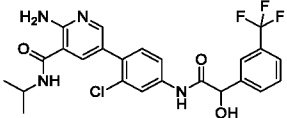
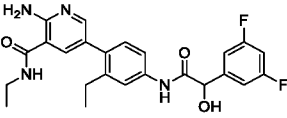
	hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide			
76	2-amino-5-(4-(2-hydroxy-2-(1-methyl-1 <i>H</i> -indazol-7-yl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 473 [C ₂₆ H ₂₈ N ₆ O ₃ + H] ⁺	Scheme 3E
77	2-amino-5-(4-(2-hydroxy-2-(1-methyl-1 <i>H</i> -indazol-7-yl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 473 [C ₂₆ H ₂₈ N ₆ O ₃ + H] ⁺	Scheme 3E
78	2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 440 [C ₂₂ H ₂₅ N ₅ O ₃ S + H] ⁺	Scheme 3E

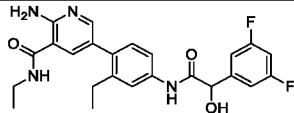
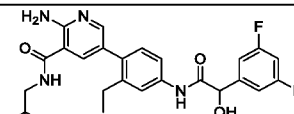
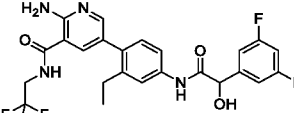
	methylphenyl)- <i>N</i> - isopropylnicotin amide			
79	2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol- 4- yl)acetamido)- 2-methylphenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 440 [C ₂₂ H ₂₅ N ₅ O ₃ S + H] ⁺	Scheme 3E
80	2-amino-5-(4-(2-(3,5- difluorophenyl)- 2-hydroxyacetami do)phenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
81	2-amino-5-(4-(2-(3,5- difluorophenyl)- 2-hydroxyacetami do)phenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 441 [C ₂₃ H ₂₂ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
82	2-amino-5-(2- chloro-4-(2- hydroxy-2-(2- methylthiazol-4- yl)acetamido)- 2-methylphenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 461 [C ₂₂ H ₁₉ ClF ₂ N + H] ⁺	Scheme 3E

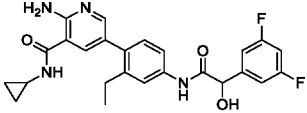
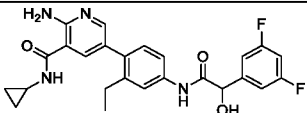
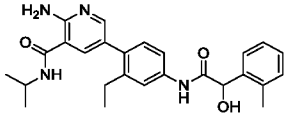
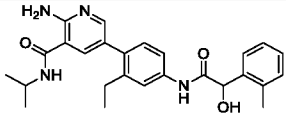
	(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide	Isomer 1	$4O_3 + H]^+$	
83	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 461 [C ₂₂ H ₁₉ ClF ₂ N 4O ₃ + H] ⁺	Scheme 3E
84	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 474 [C ₂₃ H ₁₉ ClF ₂ N 4O ₃ + H] ⁺	Scheme 3E
85	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnico	 Isomer 2	ESI (<i>m/z</i>) 474 [C ₂₃ H ₁₉ ClF ₂ N 4O ₃ + H] ⁺	Scheme 3E

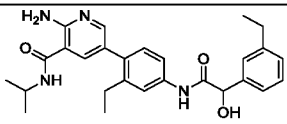
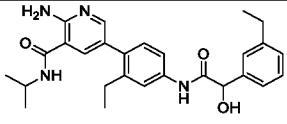
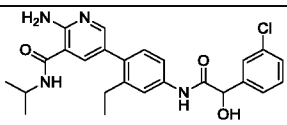
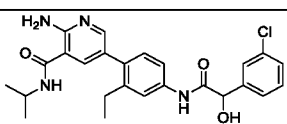
	tinamide			
86	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 515 [C ₂₂ H ₁₆ ClF ₅ N 4O ₃ + H] ⁺	Scheme 3E
87	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 515 [C ₂₂ H ₁₆ ClF ₅ N 4O ₃ + H] ⁺	Scheme 3E
88	2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 473 [C ₂₃ H ₂₂ Cl ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
89	2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 473 [C ₂₃ H ₂₂ Cl ₂ N ₄ O ₃ + H] ⁺	Scheme 3E

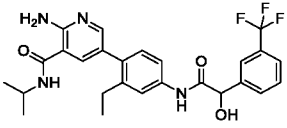
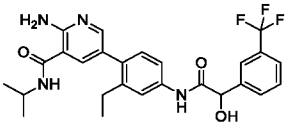
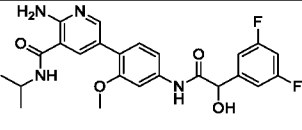
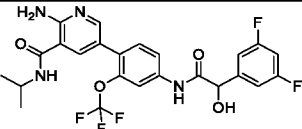
	hydroxyacetamido)phenyl)- <i>N</i> -isopropylnicotinamide			
90	2-amino-5-(2-chloro-4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E
91	2-amino-5-(2-chloro-4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E
92	2-amino-5-(2-chloro-4-(2-hydroxy-2-(<i>m</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E
93	2-amino-5-(2-chloro-4-(2-hydroxy-2-(<i>m</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₅ ClN ₄ O ₃ + H] ⁺	Scheme 3E

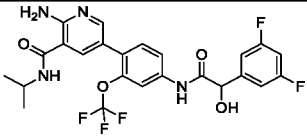
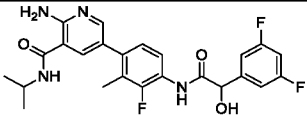
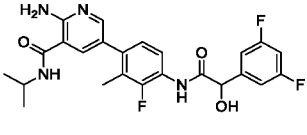
94	2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₇ ClN ₄ O ₃ + H] ⁺	Scheme 3E
95	2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₇ ClN ₄ O ₃ + H] ⁺	Scheme 3E
96	2-amino-5-(2-chloro-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 507 [C ₂₄ H ₂₂ ClF ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
97	2-amino-5-(2-chloro-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 507 [C ₂₄ H ₂₂ ClF ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
98	2-amino-5-(4-(2-(3,5-difluorophenyl))phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E

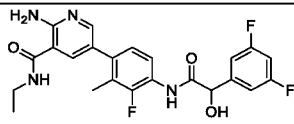
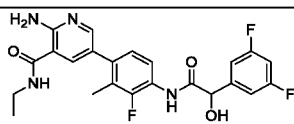
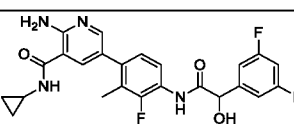
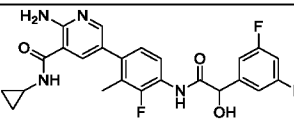
	-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -ethylnicotinamide			
99	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -ethylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 455 [C ₂₄ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
100	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(2,2,2-trifluoroethyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 509 [C ₂₄ H ₂₁ F ₅ N ₄ O ₃ + H] ⁺	Scheme 3E
101	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(2,2,2-	 Isomer 2	ESI (<i>m/z</i>) 509 [C ₂₄ H ₂₁ F ₅ N ₄ O ₃ + H] ⁺	Scheme 3E

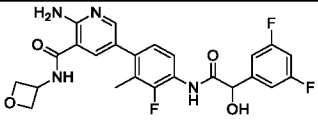
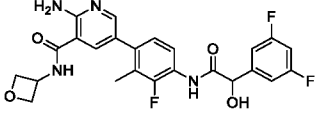
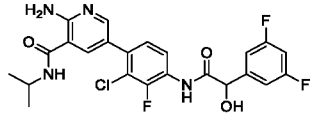
	trifluoroethyl)nicotinamide			
102	2-amino- <i>N</i> -cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
103	2-amino- <i>N</i> -cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₄ F ₂ N ₄ O ₃ + H] ⁺	Scheme 3E
104	2-amino-5-(2-ethyl-4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 447 [C ₂₆ H ₃₀ F ₅ N ₄ O ₃ + H] ⁺	Scheme 3E
105	2-amino-5-(2-ethyl-4-(2-hydroxy-2-(<i>o</i> -tolyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 447 [C ₂₆ H ₃₀ F ₅ N ₄ O ₃ + H] ⁺	Scheme 3E

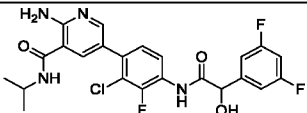
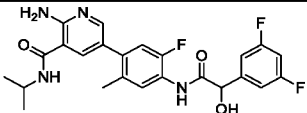
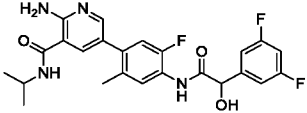
	amide			
106	2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 461 [C ₂₇ H ₃₂ N ₄ O ₃ + H] ⁺	Scheme 3E
107	2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 461 [C ₂₇ H ₃₂ N ₄ O ₃ + H] ⁺	Scheme 3E
108	2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₇ ClN ₄ O ₃ + H] ⁺	Scheme 3E
109	2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 467 [C ₂₅ H ₂₇ ClN ₄ O ₃ + H] ⁺	Scheme 3E

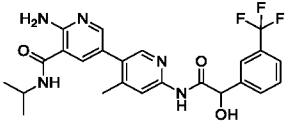
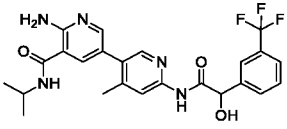
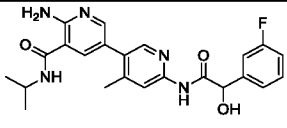
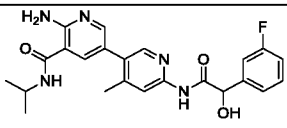
110	2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 501 [C ₂₆ H ₂₇ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
111	2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 501 [C ₂₆ H ₂₇ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
112	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 471 [C ₂₄ H ₂₄ F ₂ N ₄ O ₄ + H] ⁺	Scheme 3E
113	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 525 [C ₂₄ H ₂₁ F ₅ N ₄ O ₄ + H] ⁺	Scheme 3E

	xy)phenyl)- <i>N</i> -isopropylnicotinamide			
114	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 525 [C ₂₄ H ₂₁ F ₅ N ₄ O ₄ + H] ⁺	Scheme 3E
115	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 472 [C ₂₄ H ₂₃ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
116	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 472 [C ₂₄ H ₂₃ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E

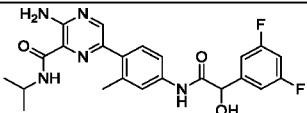
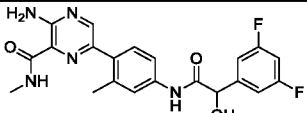
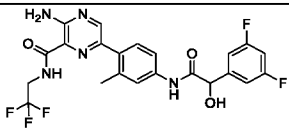
117	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)- <i>N</i> -ethylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 459 [C ₂₃ H ₂₁ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
118	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)- <i>N</i> -ethylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 459 [C ₂₃ H ₂₁ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
119	2-amino- <i>N</i> -cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)n icotinamide	 Isomer 1	ESI (<i>m/z</i>) 471 [C ₂₄ H ₂₁ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E
120	2-amino- <i>N</i> -cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)n icotinamide	 Isomer 2	ESI (<i>m/z</i>) 471 [C ₂₄ H ₂₁ F ₃ N ₄ O ₃ + H] ⁺	Scheme 3E

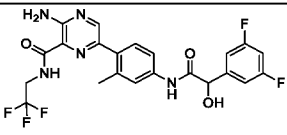
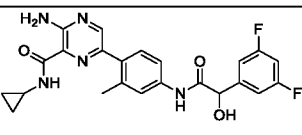
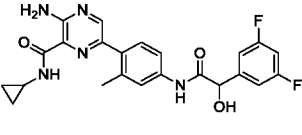
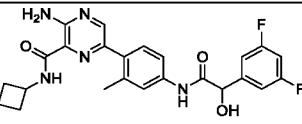
	-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)nicotinamide			
121	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 487 [C ₂₄ H ₂₁ F ₃ N ₄ O ₄ + H] ⁺	Scheme 3E
122	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 487 [C ₂₄ H ₂₁ F ₃ N ₄ O ₄ + H] ⁺	Scheme 3E
123	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-isopropylpyridine-3-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 493 [C ₂₃ H ₂₀ ClF ₃ N ₄ O ₃ + H] ⁺	Scheme 3E

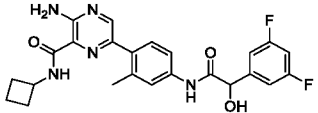
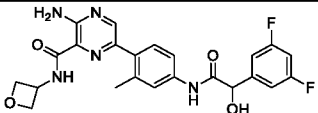
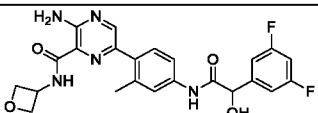
	amide			
124	2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 493 [C ₂₃ H ₂₀ ClF ₃ N 4O ₃ + H] ⁺	Scheme 3E
125	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 1	ESI (<i>m/z</i>) 473 [C ₂₄ H ₂₃ F ₃ N ₄ O 3 + H] ⁺	Scheme 3E
126	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)- <i>N</i> -isopropylnicotinamide	 Isomer 2	ESI (<i>m/z</i>) 473 [C ₂₄ H ₂₃ F ₃ N ₄ O 3 + H] ⁺	Scheme 3E

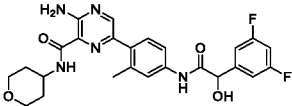
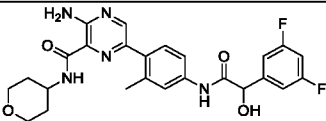
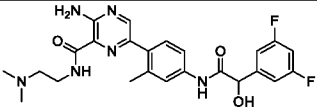
127	6-amino-6'-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)- <i>N</i> -isopropyl-4'-methyl-[3,3'-bipyridine]-5-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 488 [C ₂₄ H ₂₄ F ₃ N ₅ O ₃ + H] ⁺	Scheme 3E
128	6-amino-6'-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)- <i>N</i> -isopropyl-4'-methyl-[3,3'-bipyridine]-5-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 488 [C ₂₄ H ₂₄ F ₃ N ₅ O ₃ + H] ⁺	Scheme 3E
129	6-amino-6'-(2-(3-fluorophenyl)-2-hydroxyacetamido)- <i>N</i> -isopropyl-4'-methyl-[3,3'-bipyridine]-5-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 438 [C ₂₃ H ₂₄ FN ₅ O ₃ + H] ⁺	Scheme 3E
130	6-amino-6'-(2-(3-fluorophenyl)-2-hydroxyacetamido)- <i>N</i> -isopropyl-4'-methyl-[3,3'-bipyridine]-5-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 438 [C ₂₃ H ₂₄ FN ₅ O ₃ + H] ⁺	Scheme 3E

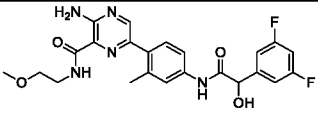
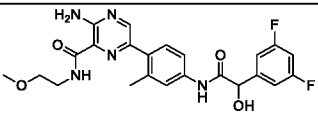
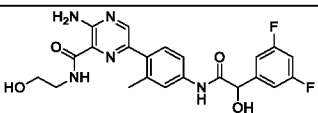
	do)- <i>N</i> -isopropyl-4'-methyl-[3,3'-bipyridine]-5-carboxamide			
131	6-amino-6'-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)- <i>N</i> -isopropyl-2'-methyl-[3,3'-bipyridine]-5-carboxamide	Isomer 1	ESI (<i>m/z</i>) 488 [C ₂₄ H ₂₄ F ₃ N ₅ O ₃ + H] ⁺	Scheme 3E
132	6-amino-6'-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)- <i>N</i> -isopropyl-2'-methyl-[3,3'-bipyridine]-5-carboxamide	Isomer 2	ESI (<i>m/z</i>) 488 [C ₂₄ H ₂₄ F ₃ N ₅ O ₃ + H] ⁺	Scheme 3E
133	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylpyrazine-2-	Isomer 1	ESI (<i>m/z</i>) 456 [C ₂₃ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E

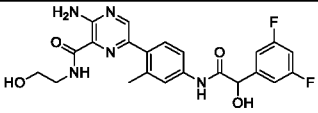
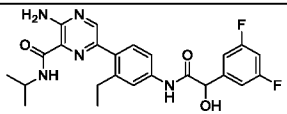
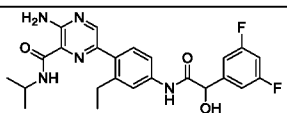
	carboxamide			
134	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylpyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 456 [C ₂₃ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
135	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -methylpyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 427 [C ₂₁ H ₁₉ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
136	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 494 [C ₂₂ H ₁₈ F ₅ N ₅ O ₃ - H] ⁻	Scheme 2E

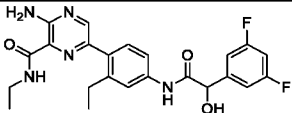
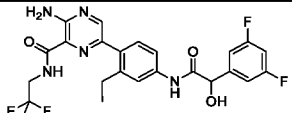
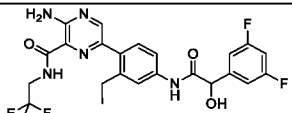
137	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 494 [C ₂₂ H ₁₈ F ₅ N ₅ O ₃ - H] ⁻	Scheme 2E
138	3-amino- <i>N</i> -cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 454 [C ₂₃ H ₂₁ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
139	3-amino- <i>N</i> -cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 454 [C ₂₃ H ₂₁ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
140	3-amino- <i>N</i> -cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide		ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E

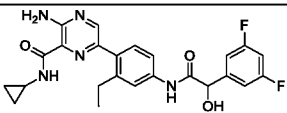
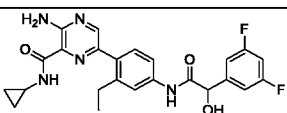
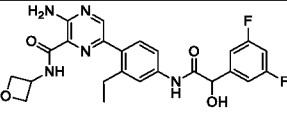
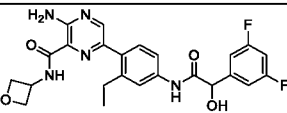
	(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide	Isomer 1	$3 + \text{H}]^+$	
141	3-amino- <i>N</i> -cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O 3 + H] ⁺	Scheme 2E
142	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 470 [C ₂₃ H ₂₁ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
143	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetami	 Isomer 2	ESI (<i>m/z</i>) 470 [C ₂₃ H ₂₁ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E

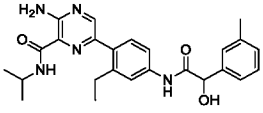
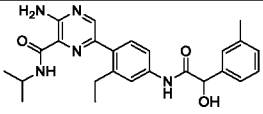
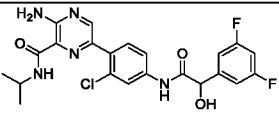
	do)-2-methylphenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide			
144	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 498 [C ₂₅ H ₂₅ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
145	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 498 [C ₂₅ H ₂₅ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
146	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide	 Racemate	ESI (<i>m/z</i>) 485 [C ₂₄ H ₂₆ F ₂ N ₆ O 3 + H] ⁺	Scheme 2E

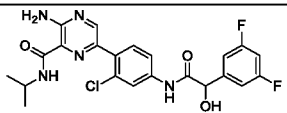
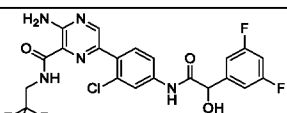
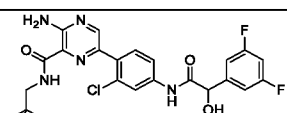
	methylphenyl)- <i>N</i> -(2- (dimethylamino))ethyl)pyrazine- 2-carboxamide			
147	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> -(2- methoxyethyl)p yrazine-2- carboxamide	 Isomer 1	ESI (<i>m/z</i>) 472 [C ₂₃ H ₂₃ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
148	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> -(2- methoxyethyl)p yrazine-2- carboxamide	 Isomer 2	ESI (<i>m/z</i>) 472 [C ₂₃ H ₂₃ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
149	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2-	 Isomer 1	ESI (<i>m/z</i>) 458 [C ₂₂ H ₂₁ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E

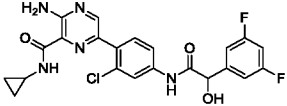
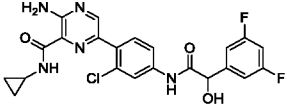
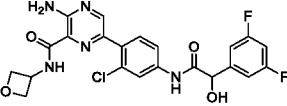
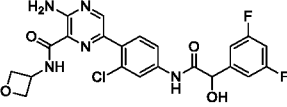
	methylphenyl)- <i>N</i> -(2- hydroxyethyl)p yrazine-2- carboxamide			
150	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> -(2- hydroxyethyl)p yrazine-2- carboxamide	 Isomer 2	ESI (<i>m/z</i>) 458 [C ₂₂ H ₂₁ F ₂ N ₅ O 4 + H] ⁺	Scheme 2E
151	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- ethylphenyl)- <i>N</i> - isopropylpyrazi ne-2- carboxamide	 Isomer 1	ESI (<i>m/z</i>) 470 [C ₂₄ H ₂₅ F ₂ N ₅ O 3 + H] ⁺	Scheme 3E
152	3-amino-6-(4- (2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- ethylphenyl)- <i>N</i> -	 Isomer 2	ESI (<i>m/z</i>) 470 [C ₂₄ H ₂₅ F ₂ N ₅ O 3 + H] ⁺	Scheme 3E

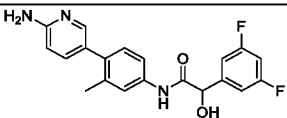
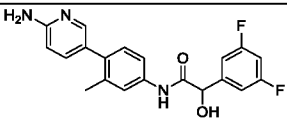
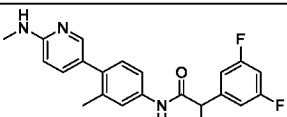
	isopropylpyrazine-2-carboxamide			
153	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -ethylpyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 456 [C ₂₃ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
154	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 510 [C ₂₃ H ₂₀ F ₅ N ₅ O ₃ + H] ⁺	Scheme 2E
155	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-	 Isomer 2	ESI (<i>m/z</i>) 510 [C ₂₃ H ₂₀ F ₅ N ₅ O ₃ + H] ⁺	Scheme 2E

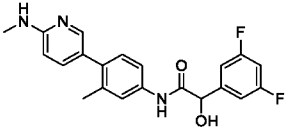
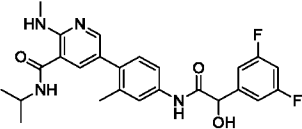
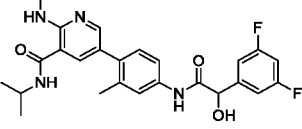
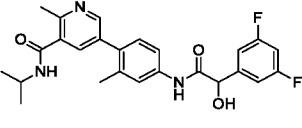
	carboxamide			
156	3-amino- <i>N</i> -cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
157	3-amino- <i>N</i> -cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 468 [C ₂₄ H ₂₃ F ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
158	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 484 [C ₂₄ H ₂₃ F ₂ N ₅ O ₄ + H] ⁺	Scheme 2E
159	3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide		ESI (<i>m/z</i>) 484 [C ₂₄ H ₂₃ F ₂ N ₅ O ₄ + H] ⁺	Scheme 2E

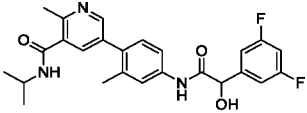
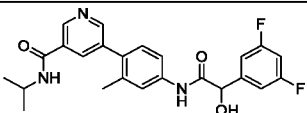
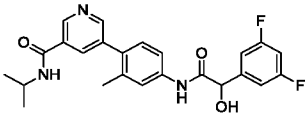
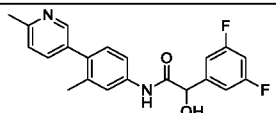
	difluorophenyl) -2- hydroxyacetami do)-2- ethylphenyl)- <i>N</i> - (oxetan-3- yl)pyrazine-2- carboxamide	Isomer 2	$4 + \text{H}]^+$	
160	3-amino-6-(2- ethyl-4-(2- hydroxy-2-(<i>m</i> - tolyl)acetamido)phenyl)- <i>N</i> - isopropylpyrazi ne-2- carboxamide	 Isomer 1	ESI (<i>m/z</i>) 447 $[\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_3 + \text{H}]^+$	Scheme 3E
161	3-amino-6-(2- ethyl-4-(2- hydroxy-2-(<i>m</i> - tolyl)acetamido)phenyl)- <i>N</i> - isopropylpyrazi ne-2- carboxamide	 Isomer 2	ESI (<i>m/z</i>) 447 $[\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_3 + \text{H}]^+$	Scheme 3E
162	3-amino-6-(2- chloro-4-(2- (3,5- difluorophenyl) -2- hydroxyacetami do)phenyl)- <i>N</i> - isopropylpyrazi ne-2-	 Isomer 1	ESI (<i>m/z</i>) 476 $[\text{C}_{22}\text{H}_{20}\text{ClF}_2\text{N}_5\text{O}_3 + \text{H}]^+$	Scheme 3E

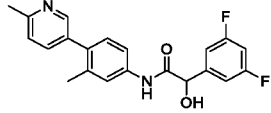
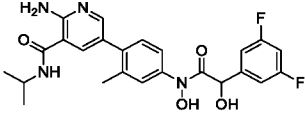
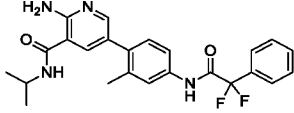
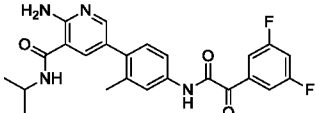
	carboxamide			
163	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -isopropylpyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 476 [C ₂₂ H ₂₀ ClF ₂ N ₅ O ₃ + H] ⁺	Scheme 3E
164	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 516 [C ₂₁ H ₁₅ ClF ₅ N ₅ O ₃ + H] ⁺	Scheme 2E
165	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -(2,2,2-trifluoroethyl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 516 [C ₂₁ H ₁₅ ClF ₅ N ₅ O ₃ + H] ⁺	Scheme 2E

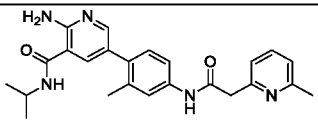
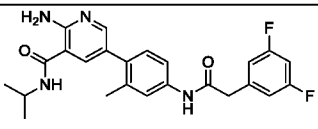
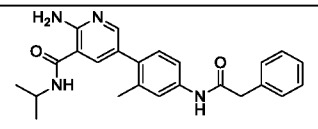
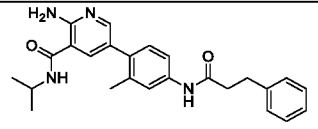
166	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -cyclopropylpyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 474 [C ₂₂ H ₁₈ ClF ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
167	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -cyclopropylpyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 474 [C ₂₂ H ₁₈ ClF ₂ N ₅ O ₃ + H] ⁺	Scheme 2E
168	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide	 Isomer 1	ESI (<i>m/z</i>) 490 [C ₂₂ H ₁₈ ClF ₂ N ₅ O ₄ + H] ⁺	Scheme 2E
169	3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)- <i>N</i> -(oxetan-3-yl)pyrazine-2-carboxamide	 Isomer 2	ESI (<i>m/z</i>) 490 [C ₂₂ H ₁₈ ClF ₂ N ₅ O ₄ + H] ⁺	Scheme 2E

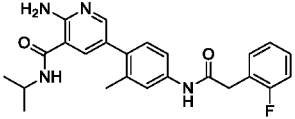
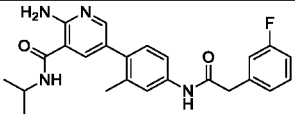
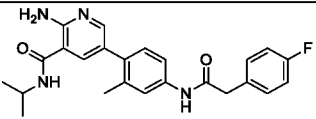
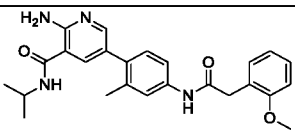
	difluorophenyl) -2- hydroxyacetami do)phenyl)- <i>N</i> - (oxetan-3- yl)pyrazine-2- carboxamide			
170	<i>N</i> -(4-(6- aminopyridin-3- yl)-3- methylphenyl)- 2-(3,5- difluorophenyl) -2- hydroxyacetami de	 Isomer 1	ESI (<i>m/z</i>) 370 [C ₂₀ H ₁₇ F ₂ N ₃ O ₂ + H] ⁺	Scheme 4E
171	<i>N</i> -(4-(6- aminopyridin-3- yl)-3- methylphenyl)- 2-(3,5- difluorophenyl) -2- hydroxyacetami de	 Isomer 2	ESI (<i>m/z</i>) 370 [C ₂₀ H ₁₇ F ₂ N ₃ O ₂ + H] ⁺	Scheme 4E
172	2-(3,5- difluorophenyl) -2-hydroxy- <i>N</i> - (3-methyl-4-(6- (methylamino)p yridin-3- yl)phenyl)aceta mide	 Isomer 1	ESI (<i>m/z</i>) 384 [C ₂₁ H ₁₉ F ₂ N ₃ O ₂ + H] ⁺	Scheme 4E

173	2-(3,5-difluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide	 Isomer 2	ESI (<i>m/z</i>) 384 [C ₂₁ H ₁₉ F ₂ N ₃ O ₂ + H] ⁺	Scheme 4E
174	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-(methylamino)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O ₃ + H] ⁺	Scheme 5E
175	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-(methylamino)nicotinamide	 Isomer 2	ESI (<i>m/z</i>) 469 [C ₂₅ H ₂₆ F ₂ N ₄ O ₃ + H] ⁺	Scheme 5E
176	5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropyl-2-(methylamino)nicotinamide	 Isomer 1	ESI (<i>m/z</i>) 454 [C ₂₅ H ₂₅ F ₂ N ₃ O ₃ + H] ⁺	Scheme 5E

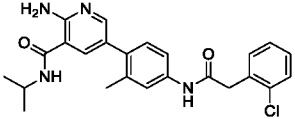
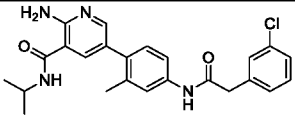
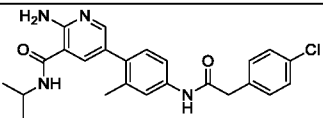
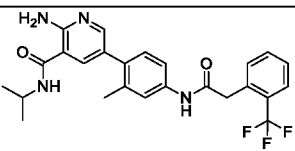
	methylnicotina mide			
177	5-(4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> -isopropyl-2- methylnicotina mide	 Isomer 2	ESI (<i>m/z</i>) 454 [C ₂₅ H ₂₅ F ₂ N ₃ O ₃ + H] ⁺	Scheme 5E
178	5-(4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 1	ESI (<i>m/z</i>) 440 [C ₂₄ H ₂₃ F ₂ N ₃ O ₃ + H] ⁺	Scheme 5E
179	5-(4-(2-(3,5- difluorophenyl) -2- hydroxyacetami do)-2- methylphenyl)- <i>N</i> - isopropylnicotin amide	 Isomer 2	ESI (<i>m/z</i>) 440 [C ₂₄ H ₂₃ F ₂ N ₃ O ₃ + H] ⁺	Scheme 5E
180	2-(3,5- difluorophenyl) -2-hydroxy- <i>N</i> - (3-methyl-4-(6-	 Isomer 1	ESI (<i>m/z</i>) 369 [C ₂₁ H ₁₈ F ₂ N ₂ O ₂ + H] ⁺	Scheme 5E

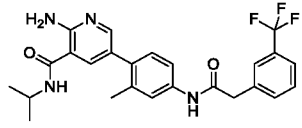
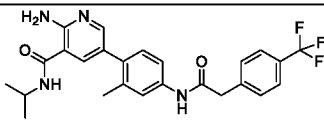
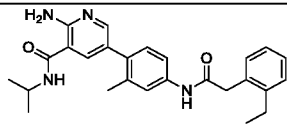
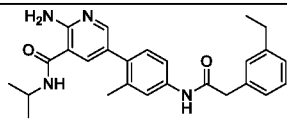
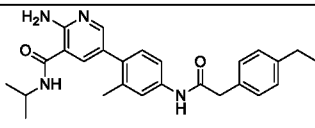
	methylypyridin-3-yl)phenyl)acetamide			
181	2-(3,5-difluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide	 Isomer 2	ESI (<i>m/z</i>) 369 [C ₂₁ H ₁₈ F ₂ N ₂ O ₂ + H] ⁺	Scheme 5E
182	2-amino-5-(4-(2-(3,5-difluorophenyl)- <i>N</i> ,2-dihydroxyacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI <i>m/z</i> 471 [C ₂₄ H ₂₄ F ₂ N ₄ O ₄ + H] ⁺	Scheme 7E
183	2-amino-5-(4-(2,2-difluoro-2-phenylacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 439 [C ₂₄ H ₂₄ F ₂ N ₄ O ₂ + H] ⁺	Scheme 6E
184	2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxy- <i>N</i> -(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 453 [C ₂₄ H ₂₂ F ₂ N ₄ O ₃ + H] ⁺	Scheme 8E

	-2-oxoacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide			
185	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(6-methylpyridin-2-yl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 418 [C ₂₄ H ₂₇ N ₅ O ₂ + H] ⁺	Scheme 6E
186	2-amino-5-(4-(2-(3,5-difluorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 439 [C ₂₄ H ₂₄ F ₂ N ₄ O ₂ + H] ⁺	Scheme 6E
187	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-phenylacetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 403 [C ₂₄ H ₂₆ N ₄ O ₂ + H] ⁺	Scheme 6E
188	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(3-phenylpropana		ESI (<i>m/z</i>) 417 [C ₂₅ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E

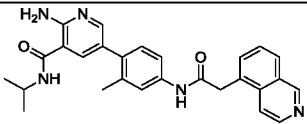
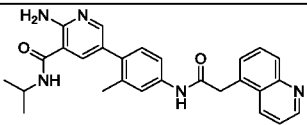
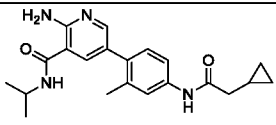
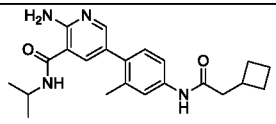
	mido)phenyl)nicotinamide			
189	2-amino-5-(4-(2-(2-fluorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 421 [C ₂₄ H ₂₅ FN ₄ O ₂ + H] ⁺	Scheme 6E
190	2-amino-5-(4-(2-(3-fluorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 421 [C ₂₄ H ₂₅ FN ₄ O ₂ + H] ⁺	Scheme 6E
191	2-amino-5-(4-(2-(4-fluorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 421 [C ₂₄ H ₂₅ FN ₄ O ₂ + H] ⁺	Scheme 6E
192	2-amino- <i>N</i> -isopropyl-5-(4-(2-(2-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide		ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 6E

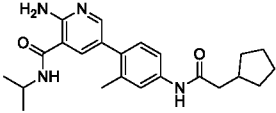
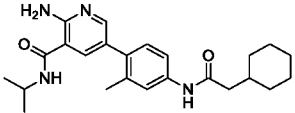
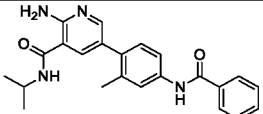
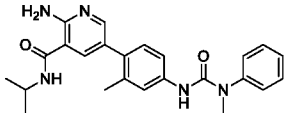
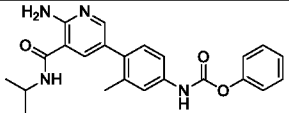
193	2-amino- <i>N</i> -isopropyl-5-(4-(2-(3-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide		ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 6E
194	2-amino- <i>N</i> -isopropyl-5-(4-(2-(4-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide		ESI (<i>m/z</i>) 433 [C ₂₅ H ₂₈ N ₄ O ₃ + H] ⁺	Scheme 6E
195	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(<i>o</i> -tolyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 417 [C ₂₅ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E
196	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(<i>m</i> -tolyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 417 [C ₂₅ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E
197	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(<i>p</i> -tolyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 417 [C ₂₅ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E

198	2-amino-5-(4-(2-(2-chlorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 437 [C ₂₄ H ₂₅ ClN ₄ O ₂ + H] ⁺	Scheme 6E
199	2-amino-5-(4-(2-(3-chlorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 437 [C ₂₄ H ₂₅ ClN ₄ O ₂ + H] ⁺	Scheme 6E
200	2-amino-5-(4-(2-(4-chlorophenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 437 [C ₂₄ H ₂₅ ClN ₄ O ₂ + H] ⁺	Scheme 6E
201	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(2-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 471 [C ₂₅ H ₂₅ F ₃ N ₄ O ₂ + H] ⁺	Scheme 6E

202	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 471 [C ₂₅ H ₂₅ F ₃ N ₄ O ₂ + H] ⁺	Scheme 6E
203	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(4-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 471 [C ₂₅ H ₂₅ F ₃ N ₄ O ₂ + H] ⁺	Scheme 6E
204	2-amino-5-(4-(2-(2-ethylphenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 431 [C ₂₆ H ₃₀ N ₄ O ₂ + H] ⁺	Scheme 6E
205	2-amino-5-(4-(2-(3-ethylphenyl)acetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 431 [C ₂₆ H ₃₀ N ₄ O ₂ + H] ⁺	Scheme 6E
206	2-amino-5-(4-(2-(4-ethylphenyl)ace		ESI (<i>m/z</i>) 431 [C ₂₂ H ₁₆ D ₃ F ₂ N ₅ O ₂ + H] ⁺	Scheme 6E

	tamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide			
207	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(naphthalen-1-yl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 453 [C ₂₈ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E
208	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(naphthalen-2-yl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 453 [C ₂₈ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E
209	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(quinolin-6-yl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 454 [C ₂₇ H ₂₇ N ₅ O ₃ + H] ⁺	Scheme 6E
210	2-amino- <i>N</i> -isopropyl-5-(4-(2-(isoquinolin-4-yl)acetamido)-2-methylphenyl)n		ESI (<i>m/z</i>) 454 [C ₂₇ H ₂₇ N ₅ O ₂ + H] ⁺	Scheme 6E

	icotinamide			
211	2-amino- <i>N</i> -isopropyl-5-(4-(2-(isoquinolin-5-yl)acetamido)-2-methylphenyl)nicotinamide		ESI (<i>m/z</i>) 454 [C ₂₇ H ₂₇ N ₅ O ₂ + H] ⁺	Scheme 6E
212	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(2-(quinolin-5-yl)acetamido)phenyl)nicotinamide		ESI (<i>m/z</i>) 454 [C ₂₇ H ₂₇ N ₅ O ₂ + H] ⁺	Scheme 6E
213	2-amino-5-(4-(2-cyclopropylacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 366 [C ₂₁ H ₂₆ N ₄ O ₂ + H] ⁺	Scheme 6E
214	2-amino-5-(4-(2-cyclobutylacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 381 [C ₂₂ H ₂₈ N ₄ O ₂ + H] ⁺	Scheme 6E

215	2-amino-5-(4-(2-cyclopentylacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 394 [C ₂₃ H ₃₀ N ₄ O ₂ + H] ⁺	Scheme 6E
216	2-amino-5-(4-(2-cyclohexylacetamido)-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 409 [C ₂₄ H ₃₂ N ₄ O ₂ + H] ⁺	Scheme 6E
217	2-amino-5-(4-benzamido-2-methylphenyl)- <i>N</i> -isopropylnicotinamide		ESI (<i>m/z</i>) 389 [C ₂₃ H ₂₄ N ₄ O ₂ + H] ⁺	Scheme 6E
218	2-amino- <i>N</i> -isopropyl-5-(2-methyl-4-(3-methyl-3-phenylureido)phenyl)nicotinamide		ESI (<i>m/z</i>) 418 [C ₂₄ H ₂₇ N ₅ O ₂ + H] ⁺	Scheme 6E
219	phenyl (4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-		ESI (<i>m/z</i>) 404 [C ₂₃ H ₂₄ N ₄ O ₃ + H] ⁺	Scheme 6E

	yl)-3-methylphenyl)c arbamate			
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References

- Adrian L. Smith et al., Discovery of 1H-Pyrazol-3(2H)-ones as Potent and Selective Inhibitors of Protein Kinase R-like Endoplasmic Reticulum Kinase (PERK), *J. Med. Chem.*, **2015**, 58 (3), pp 1426–1441
- 5 Ron, D.; Walter, P. Signal integration in the endoplasmic reticulum unfolded protein response *Nat. Rev. Mol. Cell Biol.* **2007**, 8, 519– 529
- Shore, G. C.; Papa, F. R.; Oakes, S. A. Signaling cell death from the endoplasmic reticulum stress response *Curr. Opin. Cell Biol.* **2011**, 23, 143– 149
- 10 Carrara, M.; Prischi, F.; Ali, M. M. U. UPR signal activation by luminal sensor domains *Int. J. Mol. Sci.* **2013**, 14, 6454– 6466
- Ma, Y.; Hendershot, L. M. The role of the unfolded protein response in tumor development: friend or foe? *Nat. Rev. Cancer* **2004**, 4, 966– 977
- Walter, P.; Ron, D. The unfolded protein response: from stress pathway to homeostatic regulation *Science* **2011**, 334, 1081– 1086
- 15 Vandewynckel, Y.P.; Laukens, D.; Geerts, A.; Bogaerts, E.; Paridaens, A.; Verhelst, X.; Janssens, S.; Heindryckx, F.; van Vlierberghe, H. The paradox of the unfolded protein response in cancer *Anticancer Res.* **2013**, 33, 4683– 4694
- Gao, Y.; Sartori, D. J.; Li, C.; Yu, Q.-C.; Kushner, J. A.; Simon, M. C.; Diehl, J. A. PERK is required in the adult pancreas and is essential for maintenance of glucose homeostasis *Mol. Cell. Biol.* **2012**, 32, 5129–5139
- 20 Bi, M.; Naczki, C.; Koritzinsky, M.; Fels, D.; Blais, J.; Hu, N.; Harding, H.; Novoa, I.; Varia, M.; Raleigh, J.; Scheuner, D.; Kaufman, R. J.; Bell, J.; Ron, D.; Wouters, B. G.; Koumenis, C. ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth *EMBO J.* **2005**, 24, 3470–3481
- 25 Kim, I.; Xu, W.; Reed, J. C. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities *Nat. Rev. Drug Discovery* **2008**, 7, 1013– 1030

Fels, D. R.; Koumenis, C. The PERK/eIF2 α /ATF4 module of the UPR in hypoxia resistance and tumor growth *Cancer Biol. Ther.* **2006**, 5, 723– 728

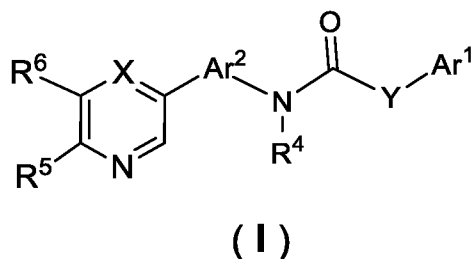
WO2018/194885

U.S. Publication No. 2017/0165259

5 U.S. Patent No. 8,598,156

What is claimed is:

1. A compound of the formula (I):



5 wherein:

Ar¹ is aryl, heteroaryl, or cycloalkyl, optionally substituted by one or more independent R¹ substituents;

Ar² is aryl or heteroaryl, optionally substituted by one or more independent R² substituents;

10 Y is C(R^{3a})(R^{3b})C₀₋₆alkyl, NR^{3a}, -O-, C(O), CF₂, CNOR^{3bb}, or a direct bond to Ar¹;

R^{3a} is H, alkyl, or cycloalkyl;

R^{3b} is H, alkyl, OR^{3c}, or NR^{3d}R^{3e};

R^{3bb} is H or alkyl;

R⁴ is H, alkyl, or OH;

15 X is CR⁷ or N;

R¹ is one or more independent H, deuterium, halo, CN, NO₂, alkyl, cycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, or C₀₋₆alkyl-O-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G¹ substituents;

20 R² is one or more independent H, deuterium, halo, CN, NO₂, alkyl, C₀₋₆alkylcycloalkyl, C₀₋₆alkyl-O-C₁₋₁₂alkyl, C₀₋₆alkyl-OH, or C₀₋₆alkyl-O-C₃₋₁₂cycloalkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H, alkyl, or cycloalkyl, optionally substituted by one or more independent G³ substituents;

R⁵ is H, CH₃, NHR⁹, or OR⁹;

25 R⁶ is H, alkyl, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H, CN, or alkyl, optionally substituted by one or more independent deuterium or halo;

R^{8a} and R^{8b} are each independently H, C₁₋₁₂alkyl, C₀₋₁₂alkyl-C₃₋₁₂cycloalkyl, or C₀₋₁₂alkyl-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G⁴

substituents; or

R^{8a} and R^{8b} taken together with the nitrogen to which they are attached form 5-10 membered heterocyclyl;

R^9 is H, alkyl, cycloalkyl, or heterocycloalkyl;

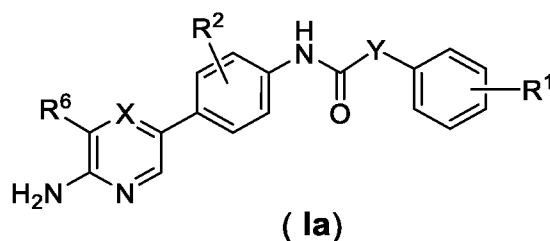
5 G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{0-12} alkyl- C_{3-12} cycloalkyl, C_{0-12} alkyl- C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent
10 H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

15 or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 of the formula (Ia):



20

wherein:

Y is $CR^{3a}R^{3b}$;

R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or $NR^{3d}R^{3e}$;

25 R^1 is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C_{0-6} alkyl- O - C_{1-12} alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl- O - C_{3-12} cycloalkyl, optionally substituted by one or more independent G^1 substituents;

R^2 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkylcycloalkyl, C_{0-6} alkyl- O - C_{1-12} alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl- O - C_{3-12} cycloalkyl, optionally substituted by
30 one or more independent G^2 substituents;

R^{3c} , R^{3d} and R^{3e} are each independently H or alkyl, optionally substituted by one or more independent G^3 substituents;

X is CR^7 or N;

R^6 is H, alkyl, CO_2R^{8a} , or $CO(NR^{8a}R^{8b})$;

5 R^7 is H, CN, or alkyl, optionally substituted by one or more independent deuterium or halo;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, or C_{0-12} alkyl C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4 substituents;

10 G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, C_{0-12} alkyl C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(=O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more

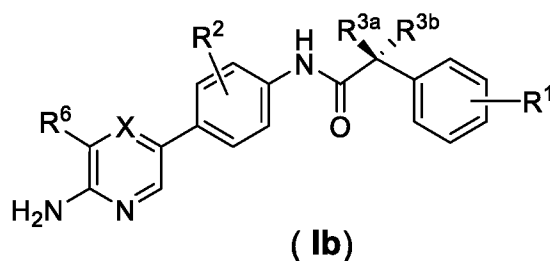
15 independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

20 or a pharmaceutically acceptable salt thereof.

3. The compound of any one of the preceding claims of the formula (Ib):



wherein:

25 X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C_{0-6} alkyl-O- C_{1-12} alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{3-12} cycloalkyl, optionally substituted by one or more independent G^1 substituents;

R^2 is one or more independent H, deuterium, halo, alkyl, cycloalkyl, C_{0-6} alkyl-O- C_{1-12}

$_{12}$ alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{3-12} cycloalkyl, optionally substituted by one or more independent G^2 substituents;

R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or $NR^{3d}R^{3e}$;

5 R^{3c} , R^{3d} and R^{3e} are each independently H or alkyl, optionally substituted by one or more independent G^3 substituents;

R^6 is CO_2R^{8a} or $CO(NR^{8a}R^{8b})$;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{3-12} cycloalkyl, or C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4 substituents;

10 G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more

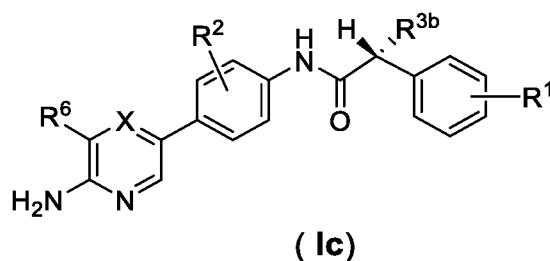
15 independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

20 or a pharmaceutically acceptable salt thereof.

4. The compound of any one of the preceding claims of the formula (**Ic**):



wherein:

25 X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent G^1 substituents;

R^2 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent G^2 substituents;

R^{3b} is OR^{3c} ;

R^{3c} is H or alkyl, optionally substituted by one or more independent G^3 substituents;

R^6 is $CO(NR^{8a}R^{8b})$;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{0-12} alkyl C_{3-12} cycloalkyl, or C_{0-12} alkyl C_{3-12} heterocycloalkyl, optionally substituted by one or more independent G^4

substituents;

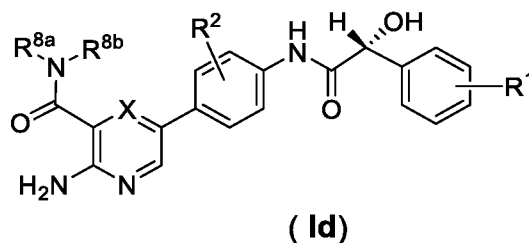
G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 , alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of the preceding claims of the formula (**Id**):



wherein:

X is CH or N;

R^1 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent H, deuterium, or halo;

R^2 is one or more independent H, deuterium, halo, alkyl, C_{0-6} alkyl-OH, or C_{0-6} alkyl-O- C_{1-12} alkyl, optionally substituted by one or more independent H, deuterium or halo;

R^{8a} and R^{8b} are each independently H, C_{1-12} alkyl, C_{3-12} cycloalkyl, or C_{3-12} heterocycloalkyl, optionally substituted by one or more independent H, deuterium, halo, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{3-12} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$,

$N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$,
5 $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$;

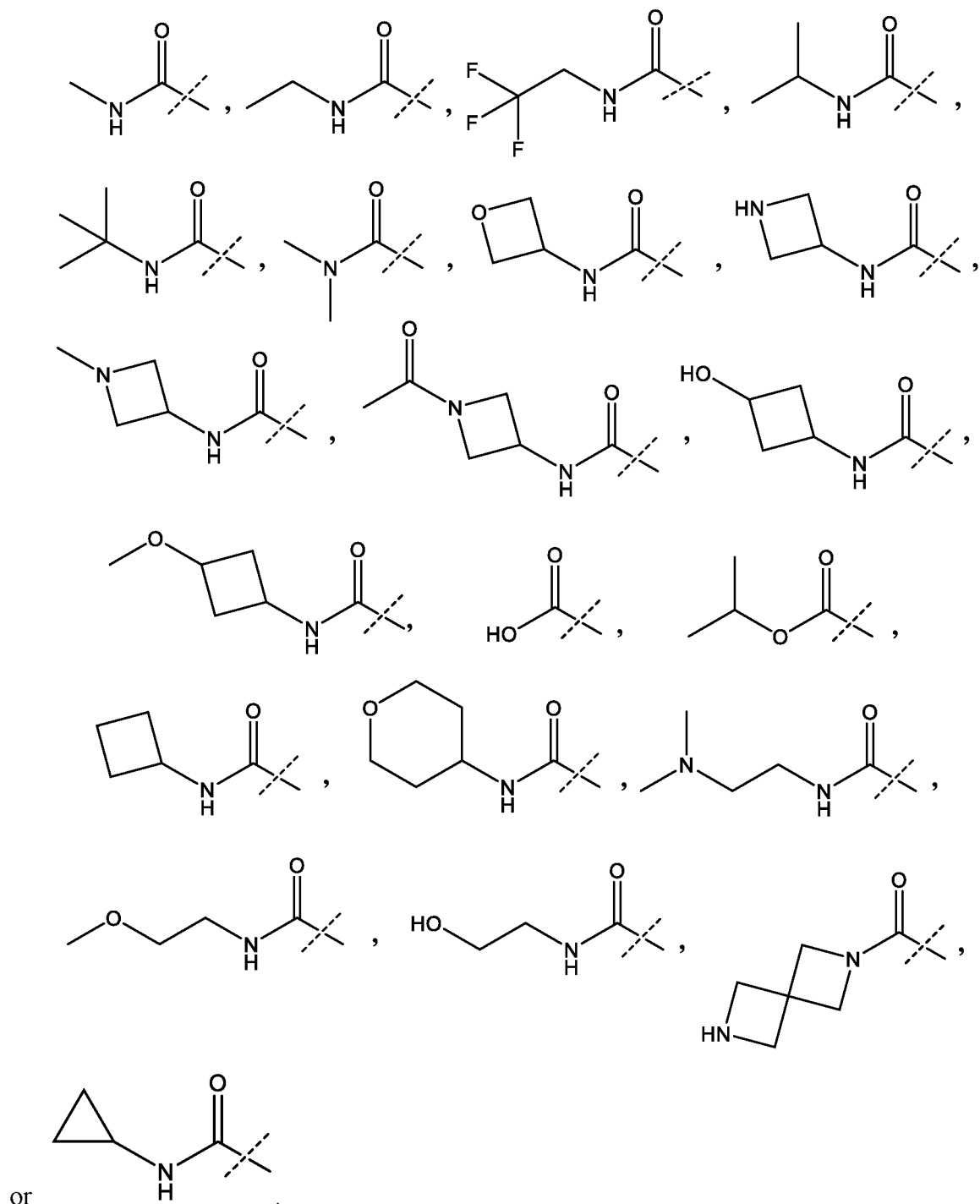
R^{10} , R^{11} , or R^{12} are each independently selected from H, deuterium, halo, CN, NO_2 ,
alkyl, cycloalkyl or heterocycloalkyl, optionally substituted by one or more independent H,

5 deuterium, halo, OH, CN, or NO_2 ;

n is 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-4, wherein R⁶ is H,

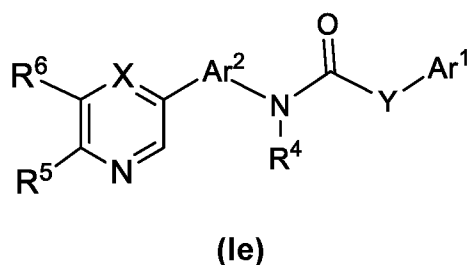


7. The compound of any one of claims 1-5, wherein X is CH.

8. The compound of any one of claims 1-5, wherein R¹ is H, methyl, ethyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, deuterium, CF₃, fluoro, or chloro.

9. The compound of any one of claims 1-5, wherein R^2 is H, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, fluoro, chloro, CF_3 or OCF_3 .
10. The compound of any one of claims 1-4, wherein R^{8a} and R^{8b} are each independently H, C_{1-6} alkyl, C_{0-6} alkyl C_{3-8} cycloalkyl, or C_{0-6} alkyl C_{3-8} heterocycloalkyl.
11. The compound of any one of claims 1-4, wherein R^{8a} and R^{8b} are each independently H, C_{1-3} alkyl, C_{0-3} alkyl C_{3-6} cycloalkyl, or C_{0-3} alkyl C_{3-6} heterocycloalkyl.
12. The compound of any one of claims 1-4, wherein R^{8a} and R^{8b} are each independently H, C_{1-3} alkyl, C_{3-6} cycloalkyl, or C_{3-6} heterocycloalkyl.
13. The compound of any one of claims 1-4, wherein G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 .
14. The compound of any one of claims 1-4, wherein G^1 , G^2 , G^3 , or G^4 are each independently H, deuterium, halo, CN, NO_2 , C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{3-6} heterocycloalkyl, OR^{10} , $NR^{10}R^{11}$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, $OC(O)R^{10}$, $OC(O)OR^{10}$, $OC(O)NR^{10}R^{11}$, $N(R^{12})C(O)R^{10}$, $N(R^{12})C(O)OR^{10}$, $N(R^{12})C(O)NR^{10}R^{11}$, $S(O)_nR^{10}$, $S(O)_nOR^{10}$, $S(O)_nNR^{10}R^{11}$, $N(R^{12})S(O)_nR^{10}$, $N(R^{12})S(O)_nOR^{10}$, or $N(R^{12})S(O)_nNR^{10}R^{11}$, optionally substituted by one or more independent H, deuterium, halo, OH, CN, or NO_2 .

15. The compound of claim 1 of the formula (Ie):



wherein:

5 Ar¹ is aryl, heteroaryl, or cycloalkyl, optionally substituted by one or more independent R¹ substituents;

Ar² is aryl or heteroaryl, optionally substituted by one or more independent R² substituents;

Y is C(R^{3a})(R^{3b})C₀₋₆alkyl, NR^{3a}, -O-, C(O), CF₂, or a direct bond to Ar¹;

10 R^{3a} is H or alkyl;

R^{3b} is OR^{3c} or NR^{3d}R^{3e};

R⁴ is H or OH;

X is CR⁷ or N;

15 R¹ is one or more independent halo, alkyl, or C₀₋₆alkyl-O-C₁₋₁₂alkyl, optionally substituted by one or more independent G¹ substituents;

R² is one or more independent halo, alkyl, or C₀₋₆alkyl-O-C₁₋₁₂alkyl, optionally substituted by one or more independent G² substituents;

R^{3c}, R^{3d} and R^{3e} are each independently H or alkyl;

R⁵ is H, CH₃, NH₂, or NHCH₃;

20 R⁶ is H, CO₂R^{8a}, or CO(NR^{8a}R^{8b});

R⁷ is H or alkyl;

R^{8a} and R^{8b} are each independently H, C₁₋₁₂alkyl, C₀₋₁₂alkyl-C₃₋₁₂cycloalkyl, or C₀₋₁₂alkyl-C₃₋₁₂heterocycloalkyl, optionally substituted by one or more independent G⁴ substituents; or

25 R^{8a} and R^{8b} taken together with the nitrogen to which they are attached form 5-10 membered heterocyclyl;

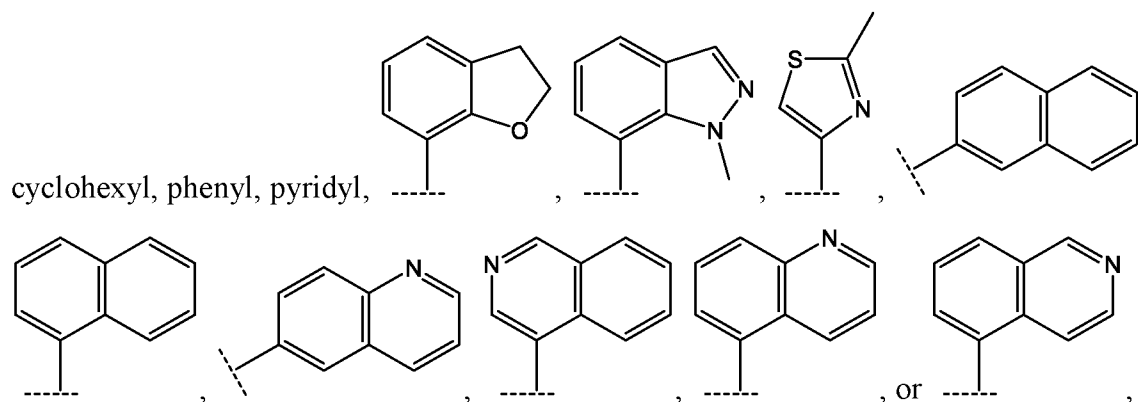
G¹, G², G³, or G⁴ are each independently halo, OR¹⁰, NR¹⁰R¹¹, C(O)R¹⁰; and

R¹⁰ or R¹¹ are each independently selected from H, or alkyl;

or a pharmaceutically acceptable salt thereof.

30

16. The compound of claim 15, wherein Ar¹ is cyclopropyl, cyclobutyl, cyclopentyl,



optionally substituted by one or more independent R¹ substituents.

5

17. The compound of claim 15 or 16, wherein R¹, for each occurrence, is independently chloro, fluoro, methyl, ethyl, methoxy, or CF₃.

18. The compound of any one of claims 15-17, wherein Y is -C(H)(OH)-, -C(CH₃)(OH)-, -C(H)(OCH₃)-, -C(H)(NH₂)-, CF₂, C(O), CH₂, -CH₂CH₂-, N(CH₃), -O-, or a direct bond to Ar¹.

19. The compound of any one of claims 15-18, wherein R⁴ is H.

20. The compound of any one of claims 15-18, wherein R⁴ is OH.

21. The compound of any one of claims 15-20, wherein Ar² is phenyl or pyridyl, optionally substituted by one or more independent R² substituents.

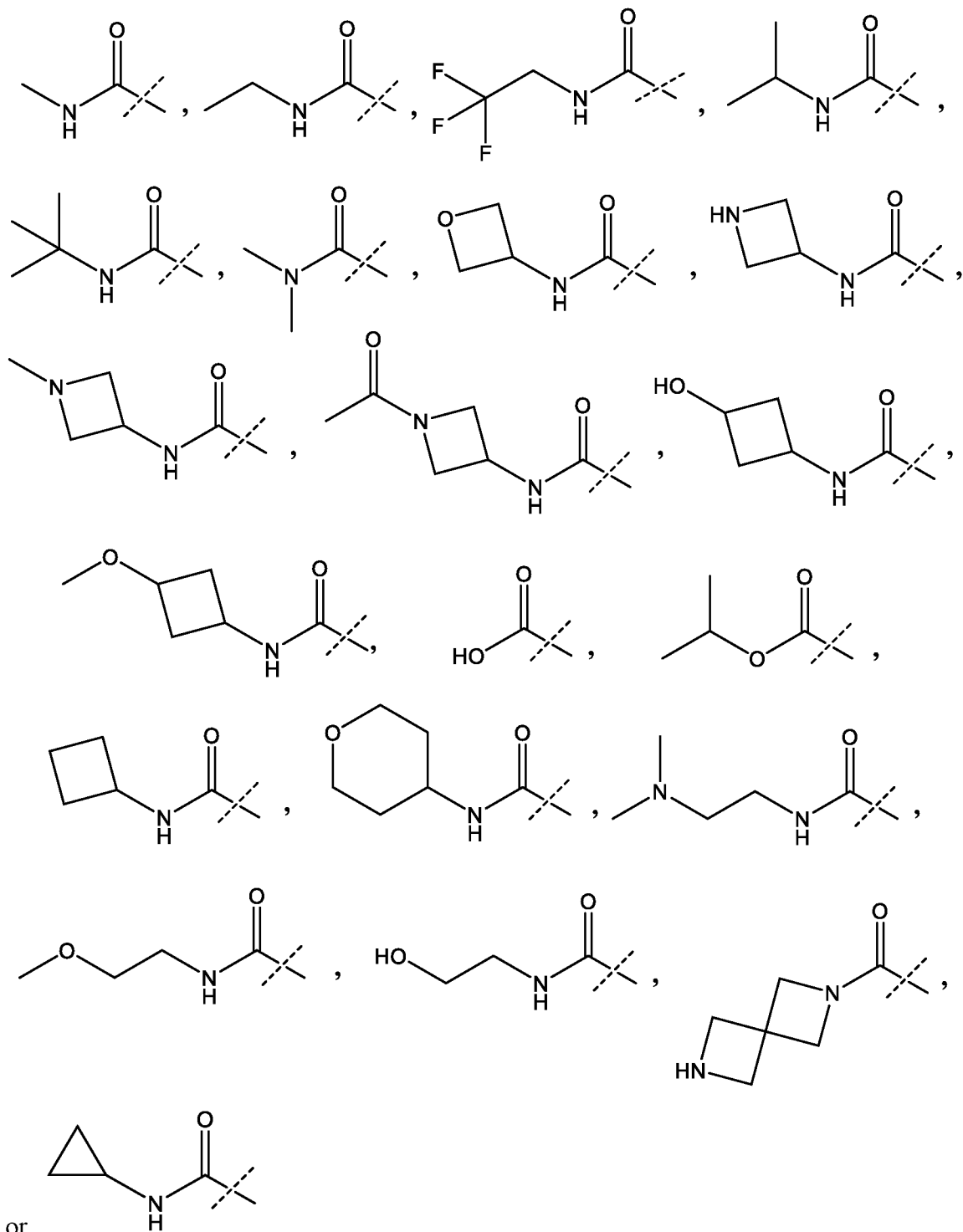
22. The compound of any one of claims 15-21, wherein R², for each occurrence, is independently methyl, ethyl, methoxy, fluoro, chloro, CF₃, or OCF₃.

23. The compound of any one of claims 15-22, wherein X is CR⁷.

24. The compound of any one of claims 15-23, wherein R⁷ is H.

25. The compound of any one of claims 15-22, wherein X is N.

26. The compound of any one of claims 15-25, wherein R^5 is H, methyl, NH_2 , or $NHCH_3$.
27. The compound of any one of claims 15-26, wherein R^6 is H,



28. A compound selected from the group consisting of:
2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;

- (*R*)-2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-hydroxy-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 5 (*R*)-2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-hydroxy-2-phenylpropanamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- 10 (*R*)-2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- (*S*)-2-amino-*N*-isopropyl-5-(4-(2-methoxy-2-phenylacetamido)-2-methylphenyl)nicotinamide;
- 2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 15 (*R*)-2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-amino-2-phenylacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 20 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylnicotinamide;
- 25 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethylnicotinamide;
- 30 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-ethylnicotinamide;

- 2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*R*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
5 (*S*)-2-amino-*N*-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*R*)-2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
10 (*S*)-2-amino-*N*-(*tert*-butyl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-trifluoroethyl)nicotinamide;
15 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-trifluoroethyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(2,2,2-trifluoroethyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-
20 isobutylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isobutylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-isobutylnicotinamide;
25 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-dimethylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-dimethylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N,N*-
30 dimethylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-3-yl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-3-yl)nicotinamide;

- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(oxetan-3-yl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;
- 5 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-hydroxycyclobutyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-
- 10 methoxycyclobutyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-methoxycyclobutyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-(3-methoxycyclobutyl)nicotinamide,
- 15 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylpyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-methylpyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-*N*-
- 20 methylpyrazine-2-carboxamide;
3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*R*)-3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
- 25 (*S*)-3-amino-*N*-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
- 30 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinic acid;
isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate;
(*R*)-isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-

- methylphenyl)nicotinate;
(*S*)-isopropyl 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinate;
2-amino-N-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
5 (*R*)-2-amino-N-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*S*)-2-amino-N-(azetidin-3-yl)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
10 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(1-methylazetidin-3-yl)nicotinamide;
15 2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
(*R*)-2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
20 (*S*)-2-amino-N-cyclobutyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
30 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)nicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-

- methoxyethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)nicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)nicotinamide;
5 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
10 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)nicotinamide;
N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*R*)-N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-
15 2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*S*)-N-(4-(6-amino-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-
20 isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(*o*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-
25 isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(*m*-tolyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
30 (*R*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-

- isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
5 isopropylnicotinamide;
2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
10 (*S*)-2-amino-5-(4-(2-(3-ethylphenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
15 (*S*)-2-amino-5-(4-(2-(2,3-dihydrobenzofuran-7-yl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
20 (*R*)-2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(1-methyl-1H-indazol-7-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
25 (*R*)-2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-hydroxy-2-(2-methylthiazol-4-yl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
30 5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-(methylamino)nicotinamide;
(*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-(methylamino)nicotinamide;
(*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-

- (methylamino)nicotinamide;
5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-methylnicotinamide;
(*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-methylnicotinamide;
5 (*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropyl-2-methylnicotinamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
10 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-N,2-dihydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
15 (*R*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
(*S*)-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
20 2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
(*R*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
(*S*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-(methylamino)pyridin-3-yl)phenyl)acetamide;
25 N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*R*)-N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
(*S*)-N-(4-(6-aminopyridin-3-yl)-3-methylphenyl)-2-(3,5-difluorophenyl)-2-hydroxyacetamide;
30 2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide;
(*R*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-yl)phenyl)acetamide;
(*S*)-2-(3,5-difluorophenyl)-2-hydroxy-N-(3-methyl-4-(6-methylpyridin-3-

- yl)phenyl)acetamide;
2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-
- 5 isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-
- 10 ethylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-ethylnicotinamide;
2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-
- 15 cyclopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylnicotinamide;
- 20 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-
- 25 trifluoroethyl)nicotinamide;
2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
- 30 (*S*)-2-amino-5-(2-chloro-4-(2-(3-chlorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;

- (*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
5 (*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
10 (*R*)-2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
15 (*R*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-chloro-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
20 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylnicotinamide;
25 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
30 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)nicotinamide;
2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide;
(*R*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-

- ethylphenyl)nicotinamide;
(*S*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)nicotinamide;
2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
5 (*R*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(*o*-tolyl)acetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
10 (*S*)-2-amino-5-(2-ethyl-4-(2-(3-ethylphenyl)-2-hydroxyacetamido)phenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylnicotinamide;
15 (*S*)-2-amino-5-(4-(2-(3-chlorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylnicotinamide;
2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
20 (*R*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(2-ethyl-4-(2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-N-isopropylnicotinamide;
25 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
(*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methoxyphenyl)-N-isopropylnicotinamide;
30 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-N-isopropylnicotinamide;
(*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-N-isopropylnicotinamide;

- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-(trifluoromethoxy)phenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 5 (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-
- 10 ethylnicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-ethylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-ethylnicotinamide;
- 15 2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)nicotinamide;
- (*R*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)nicotinamide;
- (*S*)-2-amino-N-cyclopropyl-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-
- 20 methylphenyl)nicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- 25 (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluoro-2-methylphenyl)-N-(oxetan-3-yl)nicotinamide;
- 2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-isopropylnicotinamide;
- (*R*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-
- 30 isopropylnicotinamide;
- (*S*)-2-amino-5-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-3-fluorophenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;

- (*R*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- (*S*)-2-amino-5-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-5-fluoro-2-methylphenyl)-N-isopropylnicotinamide;
- 5 2-amino-5-(4-(2,2-difluoro-2-phenylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3,5-difluorophenyl)-2-oxoacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(6-methylpyridin-2-yl)acetamido)phenyl)nicotinamide;
- 10 2-amino-5-(4-(2-(3,5-difluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-phenylacetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(3-phenylpropanamido)phenyl)nicotinamide;
- 2-amino-5-(4-(2-(2-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 15 2-amino-5-(4-(2-(4-fluorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(2-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(3-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(4-(2-(4-methoxyphenyl)acetamido)-2-methylphenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*o*-tolyl)acetamido)phenyl)nicotinamide;
- 20 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*m*-tolyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(*p*-tolyl)acetamido)phenyl)nicotinamide;
- 2-amino-5-(4-(2-(2-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(4-chlorophenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 25 2-amino-N-isopropyl-5-(2-methyl-4-(2-(2-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(4-(trifluoromethyl)phenyl)acetamido)phenyl)nicotinamide;
- 30 2-amino-5-(4-(2-(2-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(3-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-5-(4-(2-(4-ethylphenyl)acetamido)-2-methylphenyl)-N-isopropylnicotinamide;
- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(naphthalen-1-yl)acetamido)phenyl)nicotinamide;

- 2-amino-N-isopropyl-5-(2-methyl-4-(2-(naphthalen-2-yl)acetamido)phenyl)nicotinamide;
2-amino-N-isopropyl-5-(2-methyl-4-(2-(quinolin-6-yl)acetamido)phenyl)nicotinamide;
2-amino-N-isopropyl-5-(4-(2-(isoquinolin-4-yl)acetamido)-2-methylphenyl)nicotinamide;
2-amino-N-isopropyl-5-(4-(2-(isoquinolin-5-yl)acetamido)-2-methylphenyl)nicotinamide;
5 2-amino-N-isopropyl-5-(2-methyl-4-(2-(quinolin-5-yl)acetamido)phenyl)nicotinamide;
2-amino-5-(4-(2-cyclopropylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclobutylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclopentylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-5-(4-(2-cyclohexylacetamido)-2-methylphenyl)-N-isopropylnicotinamide;
10 2-amino-5-(4-benzamido-2-methylphenyl)-N-isopropylnicotinamide;
2-amino-N-isopropyl-5-(2-methyl-4-(3-methyl-3-phenylureido)phenyl)nicotinamide;
phenyl (4-(6-amino-5-(isopropylcarbamoyl)pyridin-3-yl)-3-methylphenyl)carbamate;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
15 (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-methylpyrazine-2-carboxamide;
3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-
20 trifluoroethyl)pyrazine-2-carboxamide;
(*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
(*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
25 3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*R*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*S*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
30 3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
(*R*)-3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;

- (*S*)-3-amino-N-cyclobutyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- 5 (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-
- 10 2H-pyran-4-yl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide;
- 15 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-(dimethylamino)ethyl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-
- 20 (dimethylamino)ethyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
- 25 (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-methoxyethyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-
- 30 hydroxyethyl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-methylphenyl)-N-(2-hydroxyethyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;

- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-isopropylpyrazine-2-carboxamide;
- 5 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-ethylpyrazine-2-carboxamide;
- 10 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
- 15 3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- (*R*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- 20 (*S*)-3-amino-N-cyclopropyl-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)pyrazine-2-carboxamide;
- 3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- (*R*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- (*S*)-3-amino-6-(4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)-2-ethylphenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
- 25 3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
- (*R*)-3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
- (*S*)-3-amino-6-(2-ethyl-4-(2-hydroxy-2-(*m*-tolyl)acetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
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- 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 5 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-isopropylpyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 10 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 15 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-cyclopropylpyrazine-2-carboxamide;
 3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 20 (R)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 (S)-3-amino-6-(2-chloro-4-(2-(3,5-difluorophenyl)-2-hydroxyacetamido)phenyl)-N-(oxetan-3-yl)pyrazine-2-carboxamide;
 25 or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition, comprising a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-28 with one or more pharmaceutically acceptable carriers, diluents, or excipients.

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30. A method of treating cancer in a patient comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1-28, or a pharmaceutical composition of claim 29, or a pharmaceutically acceptable salt thereof.

31. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-28 for use in therapy.

5 32. A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-28, or a pharmaceutical composition of claim 29 for use in the treatment of cancer.

33. A method of treating a disease in a patient in need of such treatment, said method comprising administering a PERK kinase modulating compound according to any one of claims 1-28, or a pharmaceutically acceptable salt thereof, wherein the disease is cancer.