(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 June 2024 (13.06.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/121709 A1

(51) International Patent Classification:

C07D 231/12 (2006.01)	*C07D 409/14* (2006.01)
C07D 401/04 (2006.01)	*C07D 417/10* (2006.01)
C07D 401/10 (2006.01)	*C07D 417/14* (2006.01)
C07D 401/12 (2006.01)	*C07D 471/08* (2006.01)
C07D 403/10 (2006.01)	*C07D 487/04* (2006.01)
C07D 403/12 (2006.01)	*A61P 31/12* (2006.01)
C07D 409/10 (2006.01)	*A61K 31/4164* (2006.01)

(21) International Application Number:
PCT/IB2023/062180

(22) International Filing Date:
04 December 2023 (04.12.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/386,740	09 December 2022 (09.12.2022)	US
63/495,808	13 April 2023 (13.04.2023)	US

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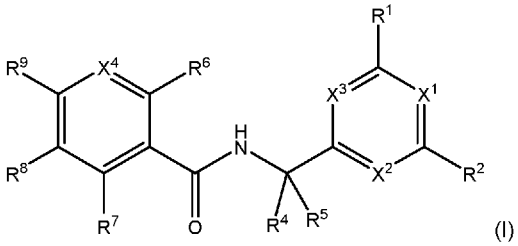
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: PAPAIN-LIKE PROTEASE (PLPRO) INHIBITORS



(I)

(57) Abstract: The invention relates to compounds of Formula (I) and pharmaceutically acceptable salts thereof as defined in the description; to their use in medicine; to compositions containing them; to processes for their preparation; and to intermediates used in such processes. The compounds of Formula (I) may inhibit the activity of papain-like protease (PLpro) and may be useful in the treatment of viral infections, in particular viral infections associated with with PLpro activity and/or expression such as coronaviruses infections.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

Papain-like protease (PLpro) inhibitors

BACKGROUND OF THE INVENTION

The present invention relates to novel compounds which are inhibitors of the papain-like protease (PLpro). The invention also relates to the preparation of these compounds and intermediates used in their preparation, compositions containing the compounds of the invention, and their use including their use to treat viral infections, in particular viral infections characterized with papain-like protease activity and/or expression such as coronavirus infections.

PLpro is a cysteine protease with a papain-like fold. PLpro is conserved across many coronaviruses, including SARS-CoV, MERS-CoV and SARS-CoV-2 (ACS Infect. Dis., 2020, 6, 8, 2099-2109). These viruses can cause severe acute respiratory tract infections, including the COVID-19 pandemic.

Viruses harboring PLpro, such as coronaviruses, are known in the literature to be causal agents of historic outbreaks and pandemics, for example the SARS outbreak in 2003 (N. Engl. J. Med., 2003; 349, 2431), the MERS-CoV outbreak in 2012 (Annu. Rev. Med. 2017. 68:387–99), and the COVID-19 pandemic beginning in 2020 (N. Engl. J. Med., 2020, 382, 727; Nat. Rev. Microbiol., 2022, 20, 270). They are also known in the literature to be likely to cause future pandemics (J. Infect. Dis., 2022, jiac296).

PLpro is responsible for processing cleavage sites in the viral polyproteins to produce functional units, which in turn assemble to execute RNA synthesis and other viral functions. PLpro also modulates host innate immune pathways, through deubiquitination and deISGylation activities. The enzymatic activity of PLpro is therefore essential to viral replication and evading host immune response (Nature, 2020, 587, 657-662). Numerous publications have evidenced that if PLpro can be selectively inhibited, it could prevent viral replication and be used in the treatment of viral infections (J. Med. Chem. 2022, 65, 4, 2940; Cell Chemical Biology, 2021, 28, 855–865; ACS Cent. Sci. 2021, 7, 7, 1245).

PLpro inhibitors have already been reported, for example in the aforementioned publications and in WO 2010/022355, WO 2022/192665, WO 2022/070048, WO 2022/169891 or WO 2022/189810. However, there remains a need for new compounds having an improved therapeutic profile as PLpro inhibitors, namely an improved activity.

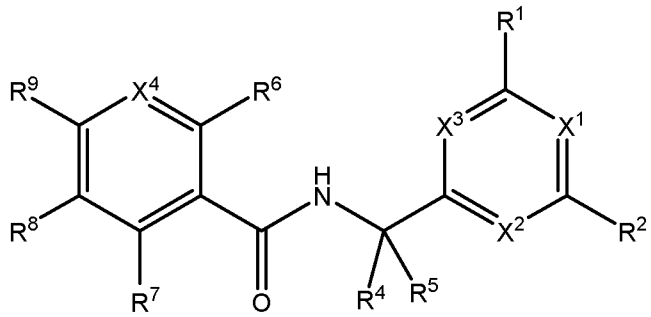
SUMMARY OF THE INVENTION

The present invention provides, in part, compounds of Formula (I) and pharmaceutically acceptable salts thereof. Such compounds may inhibit the activity of the papain-like protease (PLpro) and may be useful in the treatment, prevention, suppression and amelioration of viral infections, in particular viral infections characterized with PLpro activity and/or expression such as coronaviruses infections, and infections caused by other nidoviruses.

Also provided are pharmaceutical compositions, comprising the compounds or salts of the invention, alone or in combination with other therapeutic agents, which may provide greater clinical benefit. Such additional therapeutic agents include, but are not limited to, viral RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors or metabolism boosting agents that leads to reduction in virus replication or host response that may contribute to greater clinical benefit.

The present invention also provides, in part, methods for preparing such compounds, pharmaceutically acceptable salts and compositions of the invention, and methods of using the foregoing. This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used in isolation as an aid in determining the scope of the claimed subject matter.

According to an embodiment of the invention there is provided a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, and X^3 are each independently selected from N or CR^3, with the proviso that no more than two of X^1, X^2 and X^3 are N atoms;

X^4 is N or CH;

R^1 and R^2 are each independently selected from the group consisting of C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, C_3-C_8 cycloalkenyl and 3-8 membered heterocycloalkenyl, each optionally substituted by one, two or three R^{10};

Each R^3 is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy;

R^4 and R^5 are each independently selected from the group consisting of H and C_1-C_4 alkyl, C_1-C_4 aminoalkyl and C_1-C_4 alkoxy-C_1-C_4 alkyl, or alternatively R^4 and R^5 together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl optionally substituted by one R^{10} or a 4-8 membered heterocycloalkyl optionally substituted by one R^{10};

R^6 is selected from the group consisting of H, halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, -OR^{12}, -SR^{12}, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-oxiran-C(=O)-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-oxiran-C(=O)-OH and C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-N(R^{11})R^{12};

R^e and R^f are each independently selected from the group consisting of H and C_1-C_4 alkyl;

R^7 and R^8 are each independently selected from the group consisting of H, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl, -C_1-C_6 alkyl-$NR^{14}R^{15}$, -NHR^{16}, -N(R^{13})-C(=O)-R^{16} and -C(=O)-$NR^{14}R^{15}$, wherein any said 4-10 membered heterocycloalkyl is optionally substituted with one, two or three R^{10};

R^9 is selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkyl-C(=O)-OH, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-N(R^{11})R^{12}, -C(=O)-N(R^{11})-(CR^gR^h)-R^{12}, -(CR^gR^h)-N(R^{11})-(CR^gR^h)-R^{12}, -(CR^gR^h)-O-(CR^gR^h)-R^{12}, -(CR^gR^h)-S-(CR^gR^h)-R^{12}, -(CR^gR^h)-S(=O)-(CR^gR^h)-R^{12}, -(CR^gR^h)-SO_2-(CR^gR^h)-R^{12},-SO_2-N(R^{11})-(CR^gR^h)-R^{12} , -(CR^gR^h)-C(=O)-N(R^{11})R^{12}, -(CR^gR^h)-SO_2-N(R^{11})R^{12}, -C_1-C_3 alkyl-C(=O)-N(R^{11})-C_1-C_3 alkyl-R^{12}, -N(R^{11})R^{12}, -N(R^{11})-C_1-C_3 alkyl-R^{12}, -O-C_1-C_3 alkyl-R^{12}, -N(R^{11})-C(=O)-N(R^{13})-R^{12}, -C_1-C_3 alkyl-N(R^{11})R^{12}, -(CR^gR^h)-N(R^{11})-(CR^gR^h)-R^{12}, -C_1-C_3 alkyl-N(R^{11})-C(=O)-R^{12}, -(CR^gR^h)-N(R^{11})-C(=O)-R^{12} and -C_1-C_3 alkyl-N(R^{11})-C(=O)-C_1-C_3 alkyl-R^{12};

Each of R^g and R^h is independently selected from the group consisting of H, cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, -C_1-C_6 alkoxy-C_1-C_6 alkyl, or alternatively, R^g and R^h together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl or a 4-8 membered Heterocycloalkyl, each

optionally substituted by one R^{10};with the proviso that at least one of R^7, R^8 and R^9 is H and that R^6, R^7, R^8 and R^9 are not all H at the same time;

Each R^{10} is independently selected at each occurrence from the group consisting of cyano, nitro, oxo, 1-(1-cyanocyclopropyl)methyl, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -C_1-C_6 alkyl-R^{12}, C_1-C_6 alkoxy, -C_1-C_6 alkoxy-C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-8 membered heterocycloalkyl, -COOH, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-N(R^{11})R^{12}, -N(R^{11})R^{12}, -C_1-C_3 alkyl-N(R^{11})R^{12}, -N(R^{11})C(=O)R^{12}, -C_1-C_3 alkyl-N(R^{11})C(=O)R^{12}, -S(O)R^{12}, -$S(O)_2R^{12}$, -$S(O)_2$N(R^{11})R^{12}, -N(R^{13})$S(O)_2$N(R^{11})R^{12}, -N(R^{13})$S(O)_2R^{12}$, -OR^{12},-C_1-C_3 alkyl-OR^{12} and -SR^{12};

Each R^{11} is independently selected from H, -SO_2CH_3, -C(=O)CH_3 and C_1-C_6 alkyl;

Each R^{12} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl, C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl, wherein said C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl are each optionally substituted by one or two R^{17};

Or alternatively R^{11} and R^{12} together form a 4-8 membered heterocycloalkyl;

Each R^{13} is independently selected from H and C_1-C_6 alkyl;

Each R^{14} and R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -SO_2-C_1-C_6 alkyl and C_1-C_6 alkoxy-C_1-C_6 alkyl;

Each R^{16} is a 3-8 membered heterocycloalkyl optionally substituted with one, two or three R^{10}; and

Each R^{17} is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of the embodiments of the invention and the Examples included herein. It is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is to be also understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting.

E1 A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as defined above.

E2 A compound of embodiment E1 or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, and X^3 are each independently selected from N or CR^3, with the proviso that no more than two of X^1, X^2 and X^3 are N atoms;

X^4 is N or CH;

R^1 and R^2 are each independently selected from the group consisting of C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, C_3-C_8 cycloalkenyl and 3-8 membered heterocycloalkenyl, each optionally substituted by one, two or three R^{10};

Each R^3 is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy;

R^4 and R^5 are each independently selected from the group consisting of H and C_1-C_4 alkyl, C_1-C_4 aminoalkyl and C_1-C_4 alkoxy-C_1-C_4 alkyl, or alternatively R^4 and R^5 together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl optionally substituted by one R^{10} or a 4-8 membered heterocycloalkyl optionally substituted by one R^{10};

R^6 is selected from the group consisting of H, halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, -OR^{12}, -SR^{12}, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-O-C_1-C_6 alkyl and C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-N(R^{11})R^{12};

R^e and R^f are each independently selected from the group consisting of H and C_1-C_3 alkyl;

R^7 and R^8 are each independently selected from the group consisting of H, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl, -C_1-C_6 alkyl-$NR^{14}R^{15}$, -NHR^{16}, -N(R^{13})-C(=O)-R^{16} and -C(=O)-$NR^{14}R^{15}$, wherein any said 4-10 membered heterocycloalkyl is optionally substituted with one, two or three R^{10};

R^9 is selected from the group consisting of H, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-N(R^{11})R^{12}, -C(=O)-N(R^{11})-C_1-C_3 alkyl-R^{12}, -C_1-C_3 alkyl-C(=O)-N(R^{11})R^{12}, -C_1-C_3 alkyl-C(=O)-N(R^{11})-C_1-C_3 alkyl-R^{12}, -N(R^{11})R^{12}, -N(R^{11})-C_1-C_3 alkyl-R^{12}, -C_1-C_3 alkyl-N(R^{11})R^{12}, -C_1-C_3 alkyl-N(R^{11})-C_1-C_3 alkyl-R^{12}, -C_1-C_3 alkyl-N(R^{11})-C(=O)-R^{12} and -C_1-C_3 alkyl-N(R^{11})-C(=O)-C_1-C_3 alkyl-R^{12},

with the proviso that at least one of R^7, R^8 and R^9 is H and that R^6, R^7, R^8 and R^9 are not all H at the same time;

Each R^{10} is independently selected at each occurrence from the group consisting of cyano, nitro, oxo, 1-(1-cyanocyclopropyl)methyl, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -C_1-C_6 alkyl-R^{12}, C_1-C_6 alkoxy, -C_1-C_6 alkoxy-C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-8 membered heterocycloalkyl, -COOH, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-N(R^{11})R^{12}, -N(R^{11})R^{12}, -C_1-C_3 alkyl-N(R^{11})R^{12}, -N(R^{11})C(=O)R^{12}, -C_1-C_3 alkyl-N(R^{11})C(=O)R^{12}, -S(O)R^{12}, -S(O)$_2$$R^{12}$, -S(O)$_2$N($R^{11}$)$R^{12}$, -N($R^{13}$)S(O)$_2$N($R^{11}$)$R^{12}$, -N($R^{13}$)S(O)$_2$$R^{12}$, -O$R^{12}$,-$C_1$-$C_3$ alkyl-OR^{12} and -SR^{12};

Each R^{11} is independently selected from H and C_1-C_6 alkyl;

Each R^{12} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl, C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl, wherein said C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl are each optionally substituted by one or two R^{17};

Or alternatively R^{11} and R^{12} together form a 4-8 membered heterocycloalkyl;

Each R^{13} is independently selected from H and C_1-C_6 alkyl;

Each R^{14} and R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -SO_2-C_1-C_6 alkyl and C_1-C_6 alkoxy-C_1-C_6 alkyl;

Each R^{16} is a 3-8 membered heterocycloalkyl optionally substituted with one, two or three R^{10}; and

Each R^{17} is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy.

E3 A compound of any one of embodiments E1 to E2 or a pharmaceutically acceptable salt thereof, wherein X^4 is CH.

E4 A compound of any one of embodiments E1 to E3, or a pharmaceutically acceptable salt thereof, wherein X^2 and X^3 are both CH and X^1 is N.

E5 A compound of any one of embodiments E1 to E3, or a pharmaceutically acceptable salt thereof, wherein X^2 and X^3 are CH, and X^1 is CR^3.

E6 A compound of embodiment E5, or a pharmaceutically acceptable salt thereof, wherein X^1, X^2 and X^3 are CH.

E7 A compound of any one of embodiments E1 to E6, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each independently selected from the group consisting of H and C_1-C_4 alkyl or R^4 and R^5 together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl.

E8 A compound of embodiment E7, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are each independently selected from the group consisting of H and methyl or R^4 and R^5 together with the carbon atom to which they are attached form a cyclopropyl.

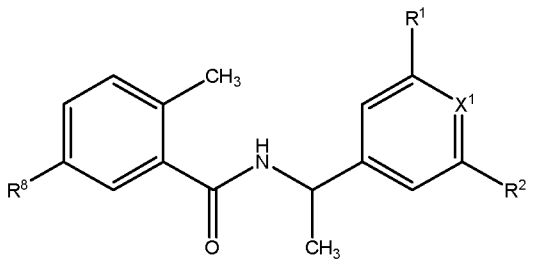
E9 A compound of embodiment E8, or a pharmaceutically acceptable salt thereof, wherein R^4 is H and R^5 is methyl.

E10 A compound of embodiment E8, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 together with the carbon atom to which they are attached form a cyclopropyl.

E11 A compound of any one of embodiments E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^6 is methyl and R^7 and R^9 are both H.

E12 A compound of any one of embodiments E1 to E10, or a pharmaceutically acceptable salt thereof, wherein R^6 is methyl and R^7 and R^8 are both H.

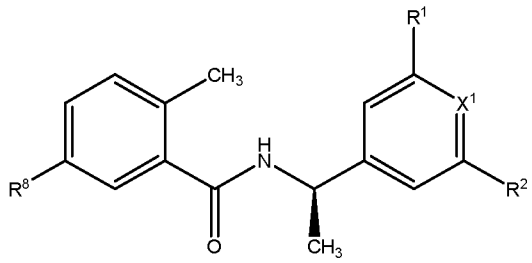
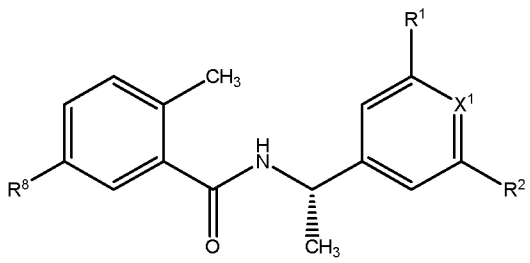
E13 A compound of any one of embodiments E1 to E2 having Formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^3 or N and R^3 is H or methoxy.

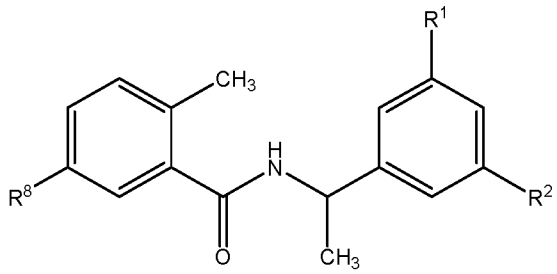
E14 A compound of embodiment E13 which is of formula:

or

or a pharmaceutically acceptable salt thereof.

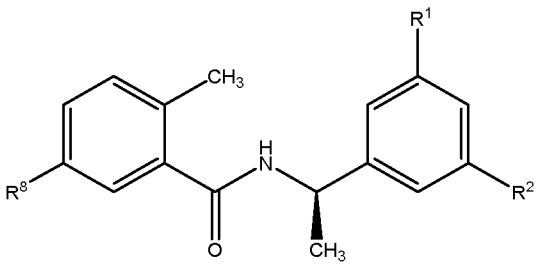
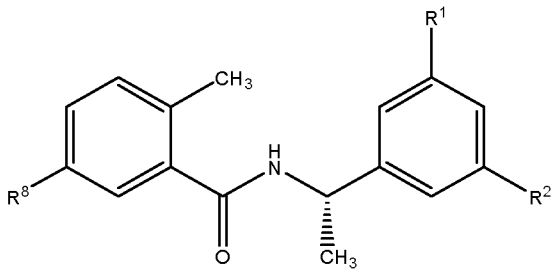
E15 A compound of embodiment E13 having the formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof.

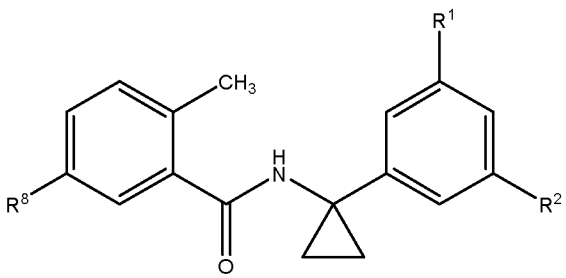
E16 A compound of embodiment E15 which is of formula:

or

or a pharmaceutically acceptable salt thereof.

E17 A compound of any one of embodiments E1 to E2 having Formula (Ic):



(Ic)

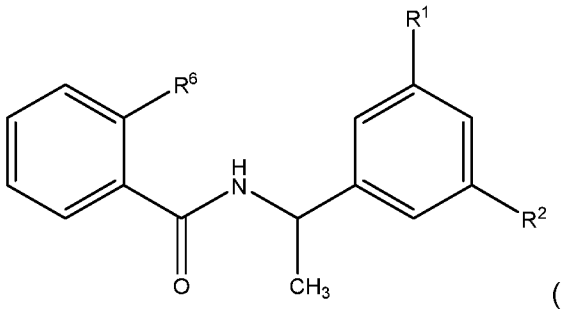
or a pharmaceutically acceptable salt thereof

E18 A compound of any one of embodiments E1 to E17, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of 4-10 membered heterocycloalkyl optionally substituted with one substituent selected from C_1-C_6 alkyl, C_1-C_6 alkyl-$NR^{14}R^{15}$, -NHR^{16} and -$N(R^{13})$-C(=O)-R^{16}.

E19 A compound of embodiment E18, or a pharmaceutically acceptable salt thereof, wherein R^{13} is H; each R^{14} and R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl; and R^{16} is a 4-6 membered heterocycloalkyl.

E20 A compound of embodiment E19, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of -CH_2-NH_2, -CH_2-NH-methyl, -CH_2-NH-SO_2-methyl, -NH-C(=O)-piperidinyl, -NH-azetidinyl, piperazin-1-yl, 4-methyl-piperazin-1-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl and 3,6-diazabicyclo[3.1.1]heptan-3-yl.

E21 A compound of any one of embodiments E1 to E2 having Formula (Id):

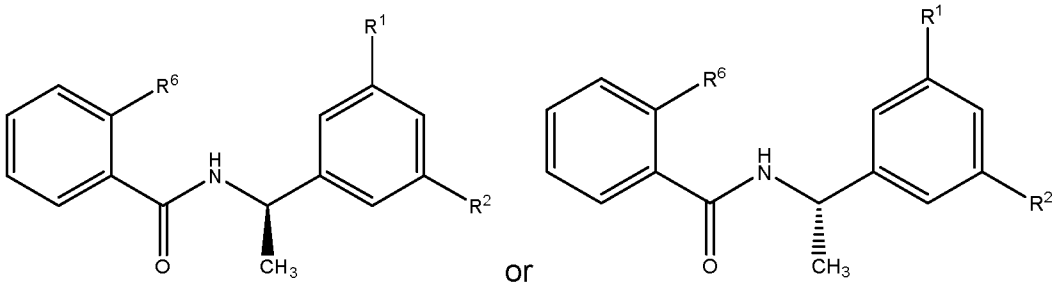


(Id)

or a pharmaceutically acceptable salt thereof, wherein R^6 is C_1-C_3 alkyl-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-O-C_1-C_6 alkyl or C_1-C_3 alkyl-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-$N(R^{11})R^{12}$; and R^{11} and R^{12} are each independently selected from H and C_1-C_6 alkyl.

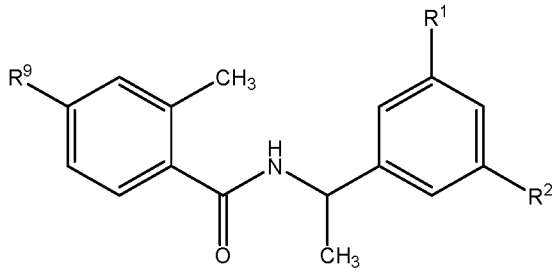
E22 A compound of embodiment E21, or a pharmaceutically acceptable salt thereof, wherein R^6 is -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-O-CH_3, -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-$NH(CH_3)$ or -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-NH_2.

E23 A compound of any one of embodiments E21 to E22 which is of formula:



or a pharmaceutically acceptable salt thereof.

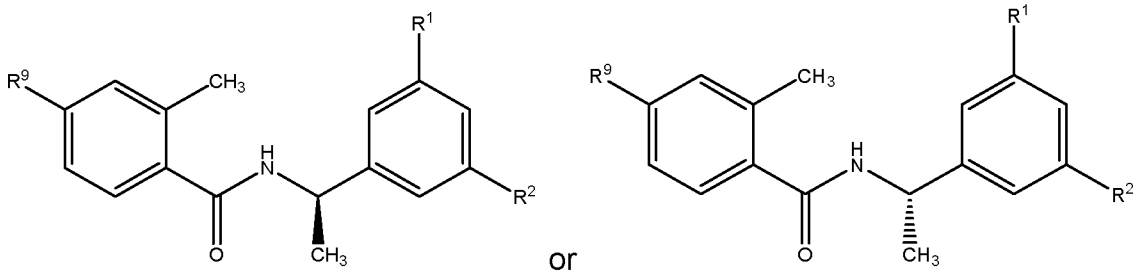
E24 A compound of any one of embodiments E1 to E2 having the formula (Ie):



(Ie)

or a pharmaceutically acceptable salt thereof.

E25 A compound of embodiment E24 which is of formula:



or a pharmaceutically acceptable salt thereof.

E26 A compound of any one of embodiments E24 to E25 or a pharmaceutically acceptable salt thereof, wherein R^9 is -C(=O)-NH-CH_2-R^{12} and R^{12} is a 5-6 membered heteroaryl.

E27 A compound of embodiment E26 or a pharmaceutically acceptable salt thereof, wherein said 5-6 membered heteroaryl is a thiazolyl.

E28 A compound of any one of embodiments E1 to E27, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered heteroaryl, each optionally substituted by one or two R^{10} group.

E29 A compound of embodiment E28, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from the group consisting of phenyl, pyridinyl, a 6-membered heterocycloalkenyl and 5-membered heteroaryl, each optionally substituted by one or two R^{10} group.

E30 A compound of embodiment E29, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from phenyl, pyridinyl, 3,6-dihydro-2H-pyranyl, pyrazolyl, pyrrolyl, thiazolyl, isothiazolyl, morpholinyl and thiophenyl, each optionally substituted by one or two R^{10} group.

E31 A compound of any one of embodiments E28 to E30, or a pharmaceutically acceptable salt thereof, wherein each said R^{10} is selected from the group consisting of halogen, cyano, amino, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, -C(=O)-O-C_1-C_6 alkyl, -COOH and -C(=O)-$N(R^{11})R^{12}$, -C_1-C_3 alkyl-$N(R^{11})R^{12}$, -C_1-C_3 alkyl-$N(R^{11})C(=O)R^{12}$, -$S(O)_2R^{12}$, -$S(O)_2N(R^{11})R^{12}$, -OR^{12} and -C_1-C_3 alkyl-OR^{12}; R^{11} is H or C_1-C_6 alkyl; and R^{12} is H, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or 4-8 membered heterocycloalkyl, wherein each said C_3-C_8 cycloalkyl and 4-8 membered heterocycloalkyl is optionally substituted by one hydroxy.

E32 A compound of embodiment E31, or a pharmaceutically acceptable salt thereof, wherein each said R^{10} is selected from the group consisting of methyl, cyano, amino, chloro, -COOH, -C(=O)-O-methyl, -C(=O)-NH_2, -C(=O)-NH-methyl, -C(=O)-$N(CH_3)_2$, -C(=O)-pyperidin-1-yl, -C(=O)-morpholin-4-yl, hydroxy, -CH_2-NH-(3-hydroxy-cyclopentyl), -CH_2-NH-(cyclopentyl), -CH_2-NH-(tetrahydrofuranyl), -CH_2-OH, -$S(O)_2$-CH_3, -CH_2-NH-C(=O)-CH_3, -$S(O)_2$-$N(CH_3)_2$, -CF_3 and -OCH_3.

E33 A compound of embodiment E1, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**1**);

(2R)-N-(3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**2**);

5-(azetidin-3-ylamino)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**3**);

methyl 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1H-pyrrole-3-carboxylate (**4**);

5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (**5**);

(2R)-N-(3-((1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**6**);

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-((methylamino)methyl)benzamide (**7**);

5-(azetidin-3-ylamino)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**8**);

N-(1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**9**);

(2R)-N-(3-((1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**10**);

(2R)-N-(3-((1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**11**);

N-(1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**12**);

5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (**13**);

(2R)-N-(3-((1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**14**);

5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide (**15**);

(2R)-N-(3-((1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**16**);

(2R)-N-(4-methyl-3-((1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide (**17**);

5-(aminomethyl)-N-(1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**18**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**19**);

(2R)-N-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide (**20**);

methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(thiophen-2-yl)phenyl)-1H-pyrrole-3-carboxylate (**22**);

rel-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1 (**23**);

rel-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-2 (**24**);

rel-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1 (**25**);

rel-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-2 (**26**);

(*R*)-*N*-(4-methyl-3-(((*R**)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1 (**27**);

(*R*)-*N*-(4-methyl-3-(((*R**)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2 (**28**);

methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (**29**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (**30**);

methyl 5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(methylsulfonamidomethyl)benzamido)ethyl)phenyl)thiophene-2-carboxylate (**31**);

(2R)-N-(3-((1-(3-(1H-pyrazol-5-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**32**);

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide (**33**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide (**34**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxamide (**35**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methylthiophene-2-carboxamide (**36**);

5-(aminomethyl)-N-(1-(3-(isothiazol-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**37**);

5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**38**);

methyl 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (**39**);

5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**40**);

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N,1-trimethyl-1H-pyrrole-2-carboxamide (**41**);

5-(aminomethyl)-N-(1-(4-methoxy-3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methylbenzamide (**42**);

5-(aminomethyl)-N-(1-(3-(5-cyanothiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**43**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl)ethyl)benzamide (**44**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)benzamide (**45**);

N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**46**); and

5-(aminomethyl)-N-(1-(3-(5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**47**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl) benzamide **(48)**;

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl)-5-(piperazin-1-yl)benzamide **(49)**;

5-(aminomethyl)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(50)**;

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methylthiophene-2-carboxamide **(51)**;

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido) ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide **(52)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid **(53)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(54)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N-methyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(55)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N,N-dimethyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(56)**;

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(57)**;

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(58)**;

methyl 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate **(59)**;

N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-((methylamino)methyl) benzamide **(60)**;

N-(1-(3-(1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(61)**;

(R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide **(62)**;

(R)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-4-(((thiazol-4-ylmethyl)amino)methyl)benzamide **(63)** ;

2-(aminomethyl)-6-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) benzamide **(64)**;

5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(5-(trifluoromethyl)thiophen-2-yl)pyridin-4-yl)ethyl)benzamide **(65)**;

5-(aminomethyl)-N-(1-(2-(5-chlorothiophen-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide **(66)**;

(R)-5-(aminomethyl)-N-(1-(3-(3,6-dihydro-2H-pyran-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(68)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl)benzamide **(69)**;

methyl (E)-4-(2-(3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoyl)hydrazineyl)-4-oxobut-2-enoate **(70)**;

(E)-2-(3-(2-(4-amino-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide **(71)** ;

(R,E)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-(3-(2-(4-(methylamino)-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)benzamide **(72)**;

N-(1-(3-(5-(acetamidomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(73)**;

N-(1-(3-(5-((cyclopentylamino)methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(74)**;

N-(1-(3-(5-((((1S,3R)-3-hydroxycyclopentyl)amino) methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl) benzamide **(75)**;

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(5-((((S)-tetrahydrofuran-3-yl)amino)methyl)thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl) benzamide **(76)**;

5-(aminomethyl)-N-(1-(3'-chloro-4'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(77)**;

5-(aminomethyl)-N-(1-(3'-chloro-5'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(78)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) benzamide **(79)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-methyl-1H-pyrazol-5-yl)phenyl)ethyl) benzamide **(80)**;

5-(aminomethyl)-N-(1-(3,5-bis(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(81)**;

5-(aminomethyl)-N-(1-(3-(5-(hydroxymethyl) thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(82)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide **(83)** ;

(R)-N,N-dimethyl-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxamide **(84)**;

methyl (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylate **(85)**;

(R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylic acid **(86)**;

(R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide **(87)**;

(R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide **(88)**;

2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide **(89)**;

2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide **(90)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(piperazin-1-yl)benzamide **(91)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamido methyl)benzamide **(92)**;

rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-1 **(93)**;

rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-2 **(94)**;

(R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1 **(95)**;

(R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2 **(96)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-1 **(97)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-2 **(98)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-1 **(99)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-2 **(100)**;

N-(1-(3-(5-cyanothiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl) cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide **(101)**;

N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide **(102)**; and

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl) cyclopropyl)-5-(piperazin-1-yl)benzamide **(103)**.

E34 A compound of embodiment E1, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

(R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide (**Example 62**);

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide (**Example 83**), and

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(piperazin-1-yl)benzamide (**Example 91**).

Any of the compounds described in embodiment E33 or E34, or pharmaceutically acceptable salts thereof, may be claimed individually or grouped together with one or more other compounds of embodiments E1 to E34, or pharmaceutically acceptable salts thereof.

E35 A pharmaceutical composition comprising a compound of any one of embodiments E1 to E34, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

E36 A method for treating a viral infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments E1 to E34, or a pharmaceutically acceptable salt thereof.

E37 A method for treating a viral infection of embodiment E36, wherein the compound of any one of embodiments E1 to E34, or a pharmaceutically acceptable salt thereof, is administered as a single agent.

E38 A method for treating a viral infection of embodiment E36, further comprising administering a therapeutically effective amount of an additional therapeutic agent selected from the list consisting of viral RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors and metabolism boosting agents.

E39 A method for treating a viral infection of any one of embodiments E36 to E38, wherein said viral infection is a coronavirus infection.

E40 A method for treating a viral infection of embodiment E39, wherein said coronavirus infection is COVID-19.

E41 A compound of any one of embodiments E1 to E34, for use as a medicament.

E42 A compound of any one embodiments E1 to E34, for use in the treatment of a viral infection.

E43 A compound for use of embodiment E42 wherein said viral infection is a coronavirus infection.

E44 A compound for use of embodiment E43 wherein said coronavirus infection is COVID-19.

E45 Use of a compound of any one of embodiments E1 to E34 for the manufacture of a medicament for the treatment of a viral infection.

E46 Use of a compound of embodiment E45 wherein said viral infection is a coronavirus infection.

E47 Use of a compound of embodiment E46 wherein said coronavirus infection is COVID-19.

E48 A method for the treatment of a disorder mediated by the papain-like protease in a subject, comprising administering to the subject in need thereof a compound of any one of embodiments E1 to E34, or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating the disorder.

Each of the embodiments described herein may be combined with any other embodiment(s) described herein not inconsistent with the embodiment(s) with which it is combined. In addition, any of the compounds described in the Examples, or pharmaceutically acceptable salts thereof, may be claimed individually or grouped together with one or more other compounds of the Examples, or pharmaceutically acceptable salts thereof, for any of the embodiment(s) described herein.

Furthermore, each of the embodiments described herein envisions within its scope pharmaceutically acceptable salts of the compounds described herein.

Definitions

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention have the meanings that are commonly understood by those of ordinary skill in the art.

The invention described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein.

One of ordinary skill in the art will appreciate that compounds of the present invention include conformational isomers (e.g., cis and trans isomers) and all optical isomers (e.g., enantiomers and diastereomers), racemic, diastereomeric and other mixtures of such isomers, and tautomers thereof, where they may exist. One of ordinary skill in the art will also appreciate that compounds of the invention include solvates, hydrates, isomorphs, polymorphs, esters, salt forms, prodrugs, and isotopically labelled versions thereof, where they may be formed.

As used herein, the term “about” when used to modify a numerically defined parameter means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter (± 10%). For example, a dose of about 5 mg means 5 mg ± 10%, i.e., it may vary between 4.5 mg and 5.5 mg.

If substituents are described as being “independently selected” from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

“Optional" or "optionally" means that the subsequently described event or circumstance may, but need not occur, and the description includes instances where the event or circumstance occurs and instances in which it does not.

The terms “optionally substituted” and “substituted or unsubstituted” are used interchangeably to indicate that the particular group being described may have no non-hydrogen substituents (i.e., unsubstituted), or the group may have one or more non-hydrogen substituents (i.e., substituted). If not otherwise specified, the total number of substituents that may be present is equal to the number of H atoms present on the unsubstituted form of the group being described. Where an optional substituent is attached via a double bond, such as an oxo (=O) substituent, the group occupies two available valences, so the total number of other substituents that are included is reduced by two. In the case where optional substituents are selected independently from a list of alternatives, the selected groups may be the same or different. Throughout the disclosure, it will be understood that the number and nature of optional substituent groups will be limited to the extent that such substitutions make chemical sense to one of ordinary skill in the art.

“Halogen” or “halo” refers to fluoro, chloro, bromo and iodo (F, Cl, Br, I).

“Cyano” refers to a substituent having a carbon atom joined to a nitrogen atom by a triple bond, i.e., -C≡N.

"Hydroxy" refers to an -OH group.

“Nitro” refers to a $-NO_2$ group.

“Oxo” refers to a double bonded oxygen (=O).

"Alkyl" refers to a saturated, monovalent aliphatic hydrocarbon radical that has a specified number of carbon atoms, including straight chain or branched chain groups. Alkyl groups may contain, but are not limited to, 1 to 6 carbon atoms (“C_1-C_6 alkyl”), 1 to 5 carbon atoms (“C_1-C_5 alkyl”), 1 to 4 carbon atoms (“C_1-C_4 alkyl”), 1 to 3 carbon atoms (“C_1-C_3 alkyl”), or 1 to 2 carbon atoms (“C_1-C_2 alkyl”). Examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-heptyl, n-octyl, and the like. Alkyl groups may be optionally substituted, unsubstituted or substituted, as further defined herein.

"Hydroxyalkyl" refers to an alkyl group, as defined above, wherein from one to all of the hydrogen atoms of the alkyl group are replaced by hydroxy groups. Examples include, but are not limited to, hydroxymethyl, dihydroxymethyl, hydroxyethyl and dihydroxyethyl.

"Fluoroalkyl" refers to an alkyl group, as defined herein, wherein from one to all of the hydrogen atoms of the alkyl group are replaced by fluoro atoms. Examples include, but are not limited to, fluoromethyl, difluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, and tetrafluoroethyl. Examples of fully substituted fluoroalkyl groups (also referred to as perfluoroalkyl groups) include trifluoromethyl ($-CF_3$) and pentafluoroethyl ($-C_2F_5$).

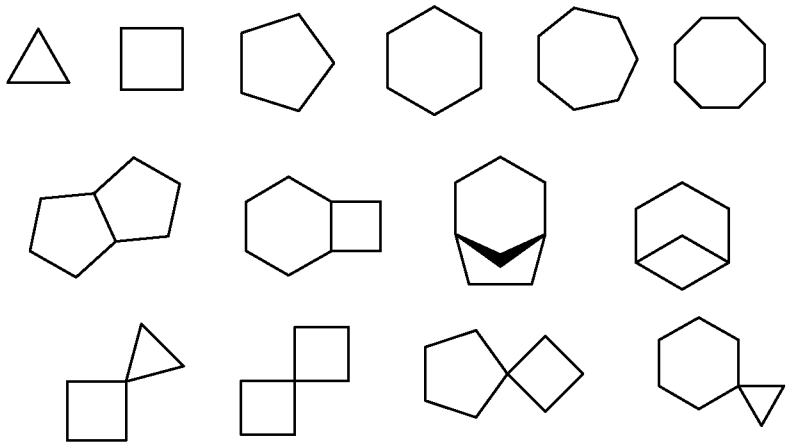
"Alkoxy" refers to an alkyl group, as defined herein, that is single bonded to an oxygen atom. The attachment point of an alkoxy radical to a molecule is through the oxygen atom. An alkoxy radical may be depicted as alkyl-O-. Alkoxy groups may contain, but are not limited to, 1 to 6 carbon atoms ("C_1-C_6 alkoxy"), 1 to 4 carbon atoms ("C_1-C_4 alkoxy"), or 1 to 3 carbon atoms ("C_1-C_3 alkoxy"). Alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isobutoxy, and the like.

"Alkoxyalkyl" refers to an alkyl group, as defined herein, that is substituted by an alkoxy group, as defined herein. Examples include, but are not limited to, CH_3OCH_2- and $CH_3CH_2OCH_2$-.

"Alkenyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond. For example, as used herein, the term "C_2-C_6 alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 1-, 2-, or 3-butenyl, and the like.

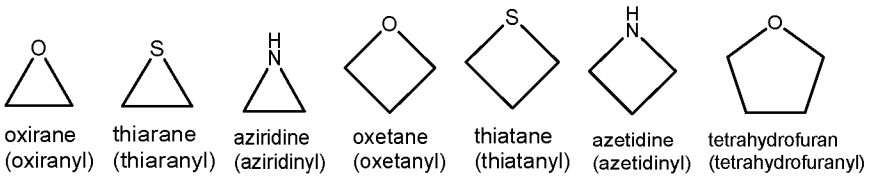
"Alkynyl" refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond. Examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-, 2-, or 3-butynyl, and the like.

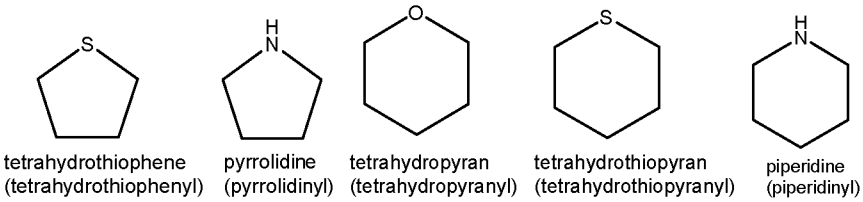
"Cycloalkyl" refers to a fully saturated hydrocarbon ring system that has the specified number of carbon atoms, which may be a monocyclic, bridged or fused bicyclic, spirocyclic or polycyclic ring system that is connected to the base molecule through a carbon atom of the cycloalkyl ring. Cycloalkyl groups may contain, but are not limited to, 3 to 8 carbon atoms ("C_3-C_8 cycloalkyl"), 3 to 6 carbon atoms ("C_3-C_6 cycloalkyl"), 3 to 5 carbon atoms ("C_3-C_5 cycloalkyl") or 3 to 4 carbon atoms ("C_3-C_4 cycloalkyl"). Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantanyl, and the like. Cycloalkyl groups may be optionally substituted, unsubstituted or substituted, as further defined herein. Illustrative examples of cycloalkyl rings include, but are not limited to, the following:

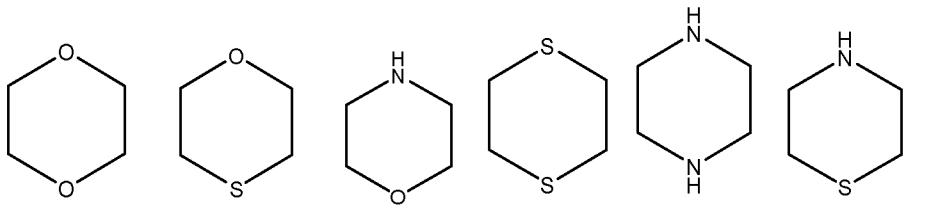


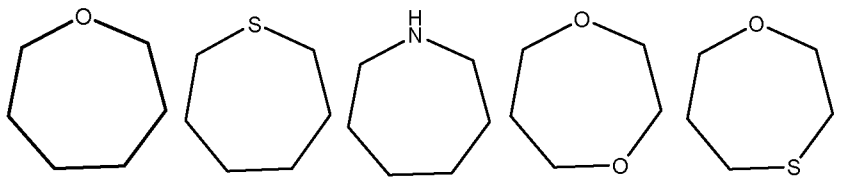
"Cycloalkenyl" refers to a cycloalkyl group, as defined herein, consisting of at least 3 carbon atoms and at least one carbon-carbon double bond. For example, as used herein, the term "C_3-C_8 cycloalkenyl" means a C_3-C_8 cycloalkenyl comprising at least 1 carbon-carbon double bond and which is not aromatic, including, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like.

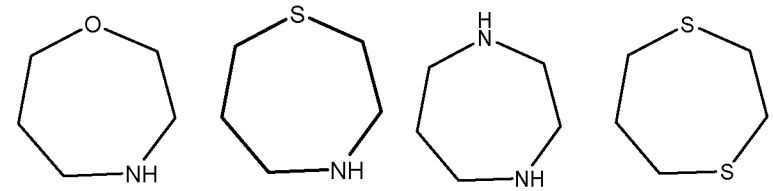
"Heterocycloalkyl" refers to a fully saturated ring system containing the specified number of ring atoms and containing at least one heteroatom selected from N, O and S as a ring member, where ring S atoms are optionally substituted by one or two oxo groups (i.e., $S(O)_q$, where q is 0, 1 or 2) and where the heterocycloalkyl ring is connected to the base molecule via a ring atom, which may be C or N. Heterocycloalkyl rings include rings which are spirocyclic, bridged, or fused to one or more other heterocycloalkyl or carbocyclic rings, where such spirocyclic, bridged, or fused rings may themselves be saturated, partially unsaturated or aromatic to the extent unsaturation or aromaticity makes chemical sense, provided the point of attachment to the base molecule is an atom of the heterocycloalkyl portion of the ring system. Heterocycloalkyl rings may contain 1 to 4 heteroatoms selected from N, O, and $S(O)_q$ as ring members, or 1 to 2 ring heteroatoms, provided that such heterocycloalkyl rings do not contain two contiguous oxygen or sulfur atoms. Heterocycloalkyl rings may be optionally substituted, unsubstituted or substituted, as further defined herein. Such substituents may be present on the heterocyclic ring attached to the base molecule, or on a spirocyclic, bridged or fused ring attached thereto. Heterocycloalkyl rings may include, but are not limited to, 3-10 membered heterocyclyl groups, for example 4-10, 3-8 or 4-8 membered heterocycloalkyl groups, in accordance with the definition herein. Illustrative examples of heterocycloalkyl rings include, but are not limited to a monovalent radical of:



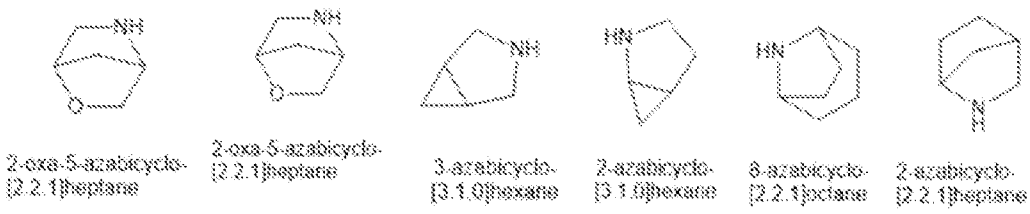


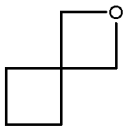




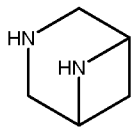


Illustrative examples of bridged and fused heterocycloalkyl groups include, but are not limited to a monovalent radical of:

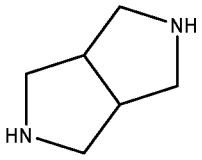




2-oxaspiro[3.3]heptane

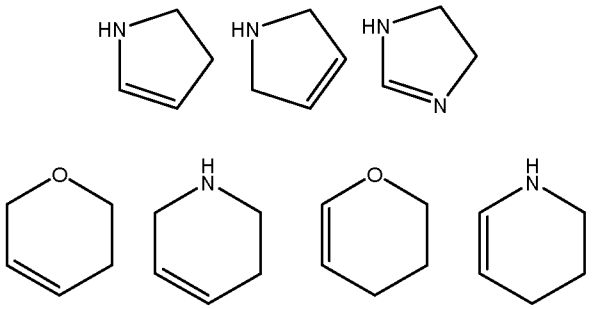


diazabicyclo[3.1.1]heptane



hexahydropyrrolo[3,4-c]pyrrole

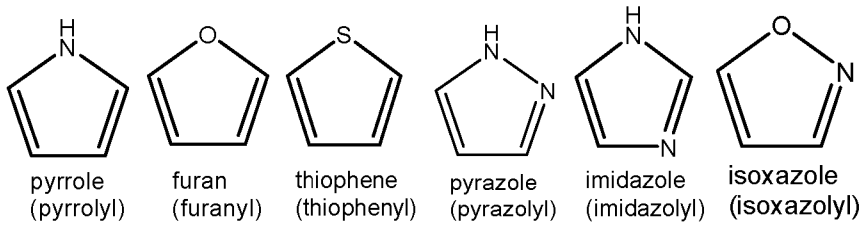
"Heterocycloalkenyl" refers to a heterocycloalkyl group, as defined herein, consisting of at least 3 carbon atoms and at least one carbon-carbon double bond. Heterocycloalkenyl rings may include, but are not limited to, 3-8 membered heterocycloalkenyl groups, for example 3-6 or 5-6 membered heterocycloalkenyl groups, in accordance with the definition herein. Illustrative examples of heterocycloalkenyl rings include, but are not limited to a monovalent radical of:

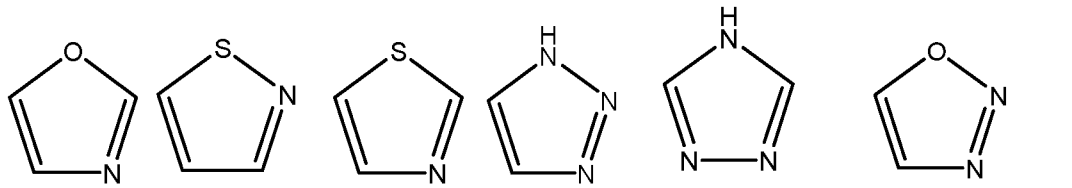


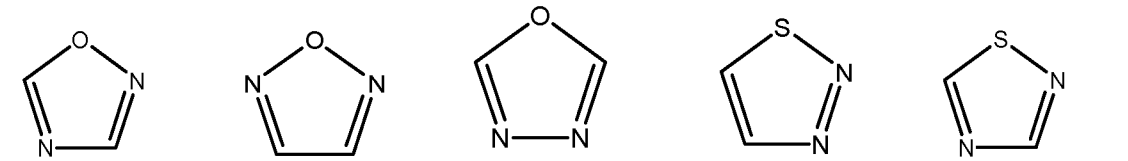
"Aryl" or "aromatic" refers to monocyclic, bicyclic (e.g., biaryl, fused) or polycyclic ring systems that contain the specified number of ring atoms, in which all carbon atoms in the ring are of sp^2 hybridization and in which the pi electrons are in conjugation. Aryl groups may contain, but are not limited to, 6 to 10 carbon atoms ("C_6-C_{10} aryl"). Fused aryl groups may include an aryl ring (e.g., a phenyl ring) fused to another aryl ring. Examples include, but are not limited to, phenyl, naphthyl, indanyl, and indenyl. Aryl groups may be optionally substituted, unsubstituted or substituted, as further defined herein.

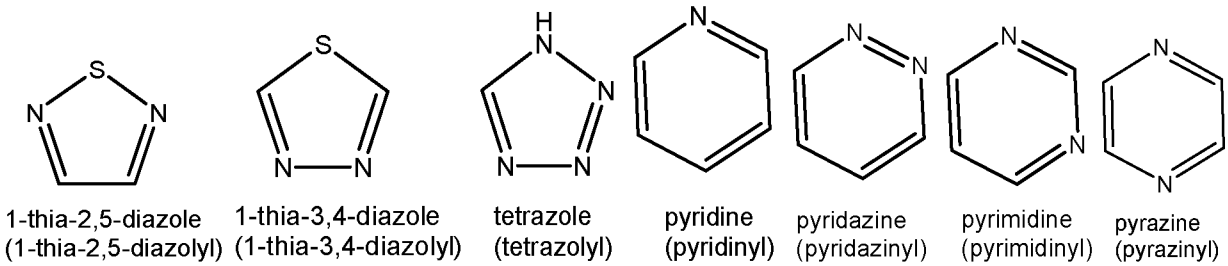
Similarly, "heteroaryl" or "heteroaromatic" refer to monocyclic, bicyclic (e.g., heterobiaryl, fused) or polycyclic ring systems that contain the specified number of ring atoms and include at least one heteroatom selected from N, O and S as a ring member in a ring in which all carbon atoms in the ring are of sp^2 hybridization and in which the pi electrons are in conjugation. Heteroaryl groups may contain, but are not limited to, 5 to 10 ring atoms ("5-10 membered heteroaryl"), 5 to 9 ring atoms ("5-9 membered heteroaryl"), or 5 to 6 ring atoms ("5-6 membered heteroaryl"). Heteroaryl rings are attached to the base molecule via a ring atom of the heteroaromatic ring. Thus, either 5- or 6-membered heteroaryl rings, alone or in a fused structure, may be attached to the base molecule via a ring C or N atom. Examples of

heteroaryl groups include, but are not limited to, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridizinyl, pyrimidinyl, pyrazinyl, benzofuranyl, benzothiophenyl, indolyl, benzamidazolyl, indazolyl, quinolinyl, isoquinolinyl, purinyl, triazinyl, naphthyridinyl, cinnolinyl, quinazolinyl and quinoxalinyl. Examples of 5- or 6-membered heteroaryl groups include, but are not limited to, pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl rings. Heteroaryl groups may be optionally substituted, unsubstituted or substituted, as further defined herein. Illustrative examples of monocyclic heteroaryl groups include, but are not limited to a monovalent radical of:

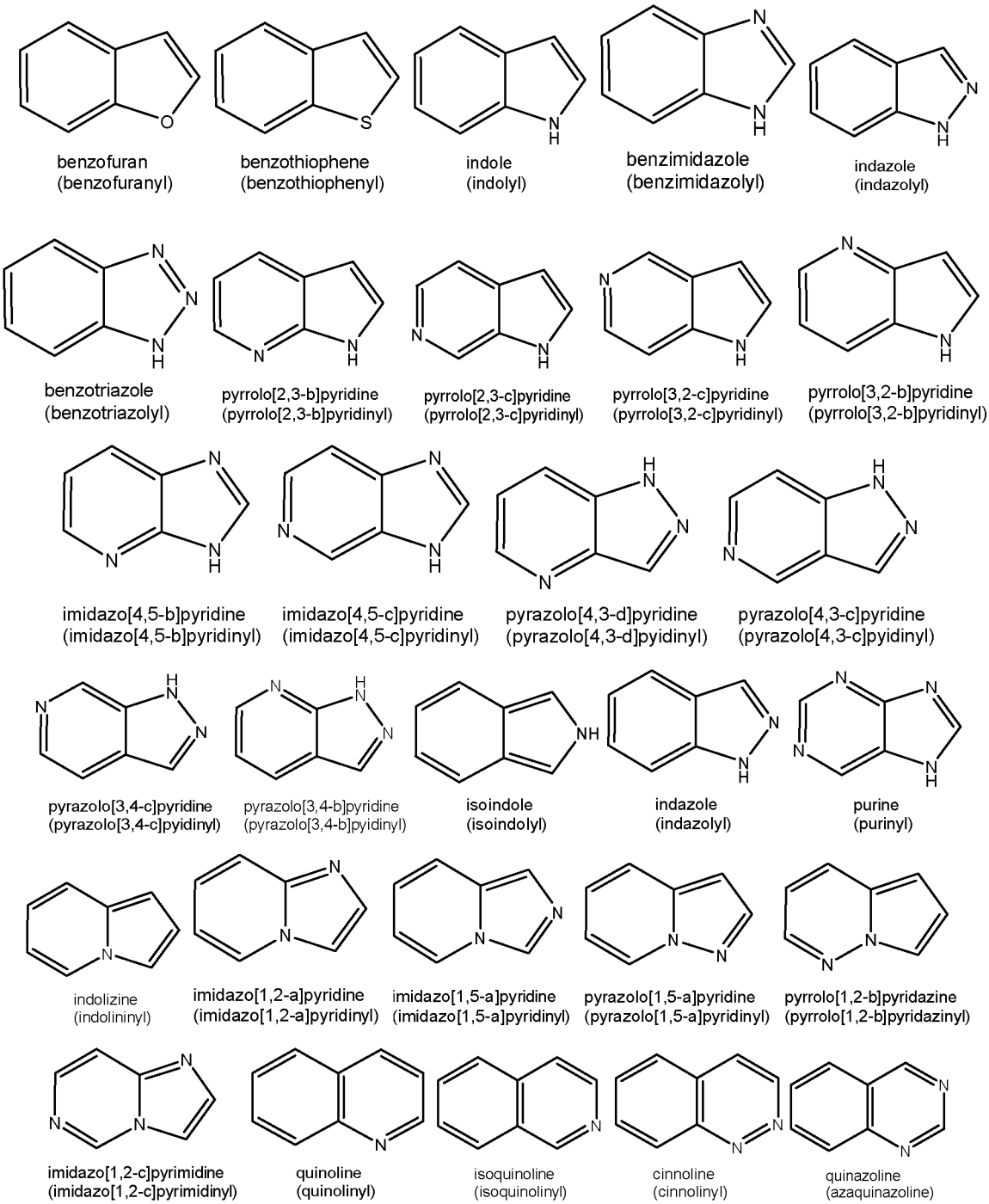


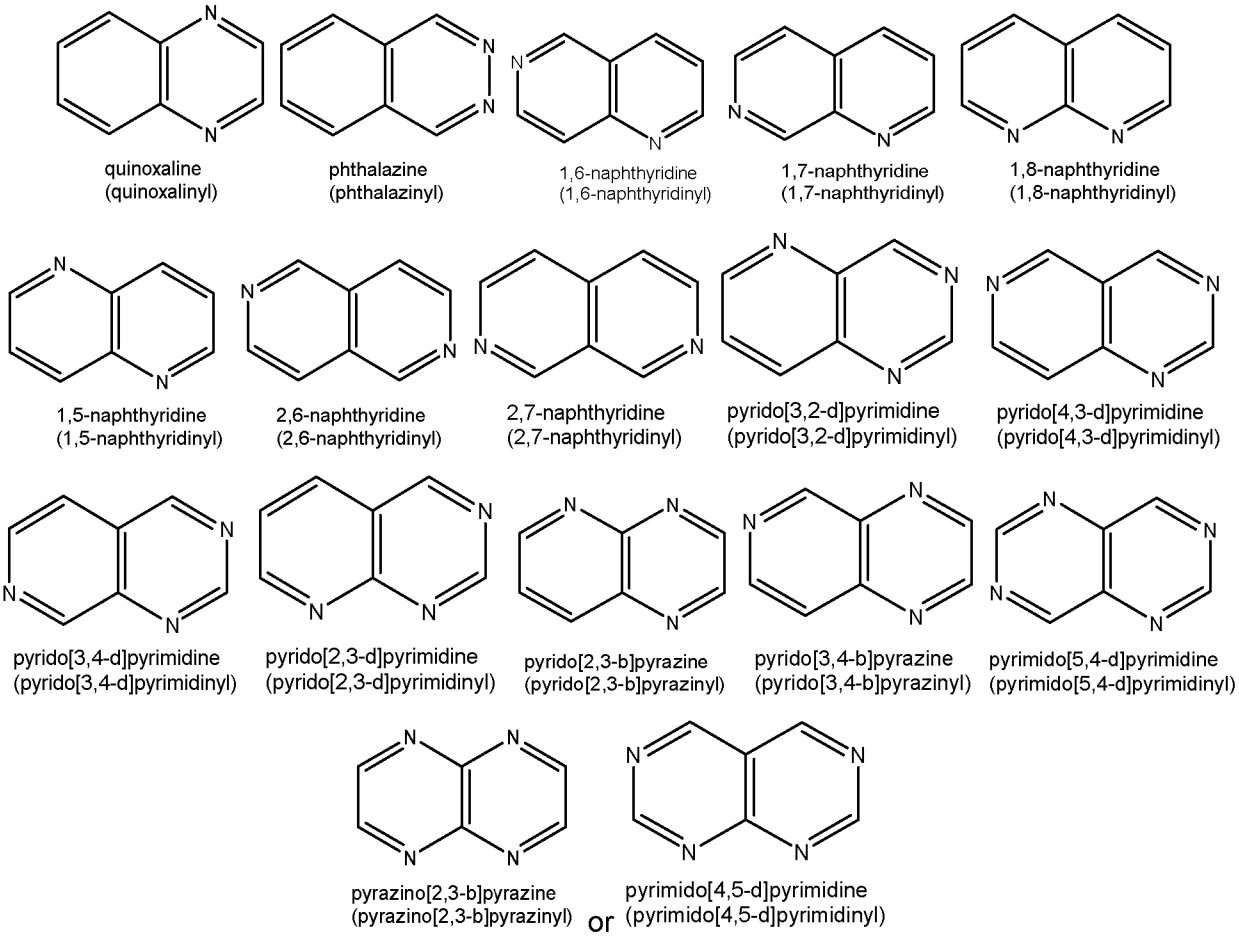






illustrative examples of fused ring heteroaryl groups include, but are not limited to:





"Amino" refers to a group $-NH_2$, which is unsubstituted. Where the amino is described as substituted or optionally substituted, the term includes groups of the form $-NR^xR^y$, where each of R^x and R^y is defined as further described herein. For example, "alkylamino" refers to a group $-NR^xR^y$, wherein one of R^x and R^y is an alkyl moiety and the other is H, and "dialkylamino" refers to $-NR^xR^y$ wherein both of R^x and R^y are alkyl moieties, where the alkyl moieties have the specified number of carbon atoms (e.g., $-NH(C_1\text{-}C_4$ alkyl) or $-N(C_1\text{-}C_4$ alkyl$)_2$).

"Aminoalkyl" refers to an alkyl group, as defined above, that is substituted by 1, 2, or 3 amino groups, as defined herein.

The term "pharmaceutically acceptable" means the substance (e.g., the compounds described herein) and any salt thereof, or composition containing the substance or salt of the invention is suitable for administration to a subject or patient.

Salts

Salts encompassed within the term “pharmaceutically acceptable salts” refer to the compounds of this invention which are generally prepared by reacting the free base or free acid with a suitable organic or inorganic acid, or a suitable organic or inorganic base, respectively, to provide a salt of the compound of the invention that is suitable for administration to a subject or patient.

In addition, the compounds of Formula I may also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, which may be useful as intermediates for one or more of the following: 1) preparing compounds of Formula I; 2) purifying compounds of Formula I; 3) separating enantiomers of compounds of Formula I; or 4) separating diastereomers of compounds of Formula I.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include, but are not limited to, acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate, 1,5-naphathalenedisulfonic acid and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include, but are not limited to aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

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

For a review on suitable salts, see Paulekun, G. S. et al., Trends in Active Pharmaceutical Ingredient Salt Selection Based on Analysis of the Orange Book Database, J. Med. Chem. 2007; 50(26), 6665-6672.

Pharmaceutically acceptable salts of compounds of the invention may be prepared by methods well known to one skilled in the art, including but not limited to the following procedures

(i) by reacting a compound of the invention with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of a compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of a compound of the invention to another. This may be accomplished by reaction with an appropriate acid or base or by means of a suitable ion exchange procedure.

These procedures are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent.

Solvates

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

In addition, the compounds of Formula I may also include other solvates of such compounds which are not necessarily pharmaceutically acceptable solvates, which may be useful as intermediates for one or more of the following: 1) preparing compounds of Formula I; 2) purifying compounds of Formula I; 3) separating enantiomers of compounds of Formula I; or 4) separating diastereomers of compounds of Formula I.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates (Polymorphism in Pharmaceutical Solids by K. R. Morris, Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex may have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content may be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Complexes

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, for example, hydrogen bonded complex (cocrystal) may be formed with either a neutral molecule or with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together (Chem Commun, 17;1889-1896, by O. Almarsson and M. J. Zaworotko, 2004). A general review of multi-component complexes is available in J. Pharm. Sci., 64(8), 1269-1288, by Haleblian (August 1975).

Solid form

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically, such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution) and consists of two-dimensional order on the molecular level. Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-COO^-Na^+$, $-COO^-K^+$, or $-SO_3^-Na^+$) or non-ionic (such

as -$N^-N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Stereoisomers

Compounds of the invention may exist as two or more stereoisomers. Stereoisomers of the compounds may include *cis* and *trans* isomers (geometric isomers), optical isomers such as *R* and *S* enantiomers, diastereomers, rotational isomers, atropisomers, and conformational isomers. For example, compounds of the invention containing one or more asymmetric carbon atoms may exist as two or more stereoisomers. Where a compound of the invention contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Cis/trans isomers may also exist for saturated rings.

The pharmaceutically acceptable salts of compounds of the invention may also contain a counterion which is optically active (e.g., d-lactate or l-lysine) or racemic (e.g., dl-tartrate or dl-arginine).

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, a chiral sulfinamide or, in the case where a compound of the invention contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography, fractional crystallization, or by using both of said techniques, and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person. Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC Concentration of the eluate affords the enriched mixture. Chiral chromatography using sub-and supercritical fluids may be employed. Methods for chiral chromatography useful in some embodiments of the present invention are known in the art (see, for example, Smith, Roger M., Loughborough University, Loughborough, UK; Chromatographic Science Series (1998), 75 (Supercritical Fluid Chromatography with Packed Columns), pp. 223-249 and references cited therein).

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two crystal forms are produced in equimolar amounts each comprising a single enantiomer. While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, 1994).

Tautomerism

Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') may occur. This may take the form of proton tautomerism in compounds of the invention containing, for example, an imino/amino, keto/enol, or oxime/nitroso group, lactam/lactim or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

It must be emphasized that while, for conciseness, the compounds of the invention have been drawn herein in a single tautomeric form, all possible tautomeric forms are included within the scope of the invention.

Isotopes

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention may include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in one or both of drug or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are

particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention may generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g., D_2O, d_6-acetone, d_6-DMSO.

Prodrugs

A compound of the invention may be administered in the form of a prodrug. Thus, certain derivatives of a compound of the invention which may have little or no pharmacological activity themselves may, when administered into or onto the body, be converted into a compound of the invention having the desired activity, for example by hydrolytic cleavage, particularly hydrolytic cleavage promoted by an esterase or peptidase enzyme. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'The Expanding Role of Prodrugs in Contemporary Drug Design and Development, Nature Reviews Drug Discovery, 17, 559-587 (2018) (J. Rautio et al.).

Prodrugs in accordance with the invention may, for example, be produced by replacing appropriate functionalities present in compounds of the invention with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in 'Design of Prodrugs' by H. Bundgaard (Elsevier, 1985).

Thus, a prodrug in accordance with the invention may be (a) an ester or amide derivative of a carboxylic acid when present in a compound of the invention; (b) an ester, carbonate, carbamate, phosphate or ether derivative of a hydroxyl group when present in a compound of the invention; (c) an amide, imine, carbamate or amine derivative of an amino group when present in a compound of the invention; (d) a thioester, thiocarbonate, thiocarbamate or sulfide derivatives

of a thiol group when present in a compound of the invention; or (e) an oxime or imine derivative of a carbonyl group when present in a compound of the invention.

Some specific examples of prodrugs in accordance with the invention include:

(i) when a compound of the invention contains a carboxylic acid functionality (-COOH), an ester thereof, such as a compound wherein the hydrogen of the carboxylic acid functionality of the compound is replaced by C_1-C_8 alkyl (e.g., ethyl) or (C_1-C_8 alkyl)C(=O)OCH_2- (e.g., ^{t}BuC(=O)OCH_2-);

(ii) when a compound of the invention contains an alcohol functionality (-OH), an ester thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by –CO(C_1-C_8 alkyl) (e.g., methylcarbonyl) or the alcohol is esterified with an amino acid;

(iii) when a compound of the invention contains an alcohol functionality (-OH), an ether thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by (C_1-C_8 alkyl)C(=O)OCH_2- or –$CH_2OP(=O)(OH)_2$;

(iv) when a compound of the invention contains an alcohol functionality (-OH), a phosphate thereof, such as a compound wherein the hydrogen of the alcohol functionality of the compound is replaced by –$P(=O)(OH)_2$ or –$P(=O)(O^-Na^+)_2$ or –$P(=O)(O^-)_2Ca^{2+}$;

(v) when a compound of the invention contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound is/are replaced by C_1-C_{10} alkanoyl, –$COCH_2NH_2$ or the amino group is derivatized with an amino acid;

(vi) when a compound of the invention contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amine thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound is/are replaced by –$CH_2OP(=O)(OH)_2$.

Certain compounds of the invention may themselves act as prodrugs of other compounds the invention It is also possible for two compounds of the invention to be joined together in the form of a prodrug. In certain circumstances, a prodrug of a compound of the invention may be created by internally linking two functional groups in a compound of the invention, for instance by forming a lactone.

Metabolites

Also included within the scope of the invention are active metabolites of compounds of the invention, that is, compounds formed in vivo upon administration of the drug, often by oxidation or dealkylation. Some examples of metabolites in accordance with the invention include, but are not limited to,

(i) where the compound of the invention contains an alkyl group, a hydroxyalkyl derivative thereof (-CH → -COH):

(ii) where the compound of the invention contains an alkoxy group, a hydroxy derivative thereof (-OR → -OH);

(iii) where the compound of the invention contains a tertiary amino group, a secondary amino derivative thereof (-NRR' → -NHR or –NHR');

(iv) where the compound of the invention contains a secondary amino group, a primary derivative thereof (-NHR → $-NH_2$);

(v) where the compound of the invention contains a phenyl moiety, a phenol derivative thereof (-Ph → -PhOH);

(vi) where the compound of the invention contains an amide group, a carboxylic acid derivative thereof ($-RCONH_2$ → RCOOH);

(vii) where the compound of the invention contains an amide group, an amine derivative thereof (-RCONR' → NH2R'); and

(viii) where the compound of the invention contains an alkyl-substituted pyrazole, the dealkylated pyrazole derivative thereof; and

(vii) where the compound contains a hydroxy or carboxylic acid group, the compound may be metabolized by conjugation, for example with glucuronic acid to form a glucuronide. Other routes of conjugative metabolism exist. These pathways are frequently known as Phase 2 metabolism and include, for example, sulfation or acetylation. Other functional groups, such as NH groups, may also be subject to conjugation.

Pharmaceutical Compositions

In another embodiment, the invention comprises pharmaceutical compositions.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds of the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient and at least one pharmaceutically acceptable excipient.

The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors

such as the mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

As used herein, "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, carriers, diluents and the like that are physiologically compatible. Examples of excipients include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof, and may include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol, or sorbitol in the composition. Examples of excipients also include various organic solvents (such as hydrates and solvates). The pharmaceutical compositions may, if desired, contain additional excipients such as flavorings, binders/binding agents, lubricating agents, disintegrants, sweetening or flavoring agents, coloring matters or dyes, and the like. For example, for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Non-limiting examples of excipients, therefore, also include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with additional excipients such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Examples of excipients also include pharmaceutically acceptable substances such as wetting agents or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives, or buffers, which enhance the shelf life or effectiveness of the compound.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, capsules, pills, powders, liposomes and suppositories. The form depends on the intended mode of administration and therapeutic application.

Typical compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with antibodies in general. One mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In another embodiment, the compound is administered by intravenous infusion or injection. In yet another embodiment, the compound is administered by intramuscular or subcutaneous injection.

Oral administration of a solid dosage form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dosage form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the invention are ordinarily combined with one or more adjuvants. Such capsules or tablets may comprise a controlled release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dosage form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also may comprise adjuvants, such as one or more of wetting, emulsifying, suspending, flavoring (e.g., sweetening), or perfuming agents.

In another embodiment, the invention comprises a parenteral dosage form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneally, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using one or more of suitable dispersing, wetting agents, or suspending agents.

In another embodiment, the invention comprises a topical dosage form. "Topical administration" includes, for example, dermal and transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of this invention are administered by a transdermal

device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical excipients include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, B. C. Finnin and T. M. Morgan, J. Pharm. Sci., vol. 88, pp. 955-958, 1999.

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of this invention is dissolved or suspended in a suitable excipient. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (i.e., absorbable gel sponges, collagen) and non-biodegradable (i.e., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methylcellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration, the compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the invention comprises a rectal dosage form. Such rectal dosage form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other excipients and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

Acceptable excipients are nontoxic to subjects at the dosages and concentrations employed, and may comprise one or more of the following: 1) buffers such as phosphate, citrate, or other organic acids; 2) salts such as sodium chloride; 3) antioxidants such as ascorbic acid or methionine; 4) preservatives such as octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride, benzethonium chloride, phenol, butyl or benzyl alcohol; 5) alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, or m-cresol; 6) low molecular weight (less than about 10 residues) polypeptides; 7) proteins such as serum albumin, gelatin, or immunoglobulins; 8) hydrophilic polymers such as polyvinylpyrrolidone; 9) amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; 10) monosaccharides, disaccharides, or other carbohydrates including glucose, mannose, or dextrins; 11) chelating agents such as EDTA; 12) sugars such as sucrose, mannitol, trehalose or sorbitol; 13) salt-forming counter-ions such as sodium, metal complexes (e.g., Zn-protein complexes), or 14) non-ionic surfactants such as polysorbates (e.g., polysorbate 20 or polysorbate 80), poloxamers or polyethylene glycol (PEG).

For oral administration, the compositions may be provided in the form of tablets or capsules containing 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250 or 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient. A medicament typically contains from about 1.0 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1.0 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion.

Liposome containing compounds of the invention may be prepared by methods known in the art (See, for example, Chang, H.I.; Yeh, M.K.; Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy; Int J Nanomedicine 2012; 7; 49-60). Particularly useful liposomes may be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

Compounds of the invention may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy, 20th Ed., Mack Publishing (2000).

Sustained-release preparations may also be used. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing a compound of the invention, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or 'poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as those used in leuprolide acetate for depot suspension (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for intravenous administration must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Compounds of the invention are generally placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Suitable emulsions may be prepared using commercially available fat emulsions, such as a lipid emulsion comprising soybean oil, a fat emulsion for intravenous administration (e.g., comprising safflower oil, soybean oil, egg phosphatides and glycerin in water), emulsions containing soya bean oil and medium-chain triglycerides, and lipid emulsions of cottonseed oil. The active ingredient may be either dissolved in a pre-mixed emulsion composition or

alternatively it may be dissolved in an oil (e.g., soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g., egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion may comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

For example, the emulsion compositions may be those prepared by mixing a compound of the invention with a lipid emulsion comprising soybean oil or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulized by use of gases. Nebulized solutions may be breathed directly from the nebulizing device, or the nebulizing device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

A drug product intermediate (DPI) is a partly processed material that must undergo further processing steps before it becomes bulk drug product. Compounds of the invention may be formulated into drug product intermediate DPI containing the active ingredient in a higher free energy form than the crystalline form. One reason to use a DPI is to improve oral absorption characteristics due to low solubility, slow dissolution, improved mass transport through the mucus layer adjacent to the epithelial cells, and in some cases, limitations due to biological barriers such as metabolism and transporters. Other reasons may include improved solid-state stability and downstream manufacturability. In one embodiment, the drug product intermediate contains a compound of the invention isolated and stabilized in the amorphous state (for example, amorphous solid dispersions (ASDs)). There are many techniques known in the art to manufacture ASD's that produce material suitable for integration into a bulk drug product, for example, spray dried dispersions (SDD's), melt extrudates (often referred to as HME's), co-precipitates, amorphous drug nanoparticles, and nano-adsorbates. In one

embodiment amorphous solid dispersions comprise a compound of the invention and a polymer excipient. Other excipients as well as concentrations of said excipients and the compound of the invention are well known in the art and are described in standard textbooks. See, for example, "*Amorphous Solid Dispersions Theory and Practice*" by Navnit Shah et al.

Administration and Dosing

The term "treating", "treat" or "treatment" as used herein embraces both prophylactic and palliative treatment i.e., treatment relieving, alleviating or slowing the progression of the patient's disease (or condition) or any tissue damage associated with the disease.

As used herein, the terms, "subject, "individual" or "patient," used interchangeably, refer to any animal, including mammals. Mammals according to the invention include canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, humans and the like, and also encompass mammals in utero. Preferably, said animal is a human. Human subjects may be of any gender and at any stage of development.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which may include one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting (or slowing) further development of the pathology or symptomatology or both);

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology or symptomatology or both); and

(4) clearing out latent viral reservoirs in the body that exist following initial infection and may or may not be contributing to prolonged pathology or symptomatology of the disease, condition or disorder in individuals.

Typically, a compound of the invention is administered in an amount effective to treat a condition as described herein. The compounds of the invention may be administered as

compound per se, or alternatively, as a pharmaceutically acceptable salt. For administration and dosing purposes, the compound per se or pharmaceutically acceptable salt thereof will simply be referred to as the compounds of the invention.

The compounds of the invention are administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds of the invention may be administered orally, rectally, vaginally, parenterally, topically, intranasally, or by inhalation.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

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

In another embodiment, the compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. In another embodiment, the compounds of the invention may also be administered intranasally or by inhalation. In another embodiment, the compounds of the invention may be administered rectally or vaginally. In another embodiment, the compounds of the invention may also be administered directly to the eye or ear.

The dosage regimen for the compounds of the invention or compositions containing said compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus, the dosage regimen may vary widely. In one embodiment, the total daily dose of a compound of the invention is typically from about 0.01 to about 100 mg/kg (i.e., mg compound of the invention per kg body weight) for the treatment of the indicated conditions discussed herein. In another embodiment, total daily dose of the compound of the invention is from about 0.1 to about 50 mg/kg, and in another embodiment, from about 0.5 to about 30 mg/kg. It is not uncommon that the administration of the compounds

of the invention will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

Therapeutic Methods and Uses

The compounds of the invention inhibit the activity of the papain-like protease and may thus be useful in the treatment, prevention, suppression, and amelioration of diseases, disorders and conditions mediated by the papain-like protease, in particular viral infections such as coronaviruses infections.

Examples of such coronavirus infections include, but are not limited to, diseases or conditions in which coronaviruses are implicated like common cold, Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) or COVID-19 (Coronavirus disease 2019).

Co-administration

The compounds of the invention may be used alone, or in combination with one or more other therapeutic agents. The invention provides any of the uses, methods or compositions as defined herein wherein the compound of the invention, or pharmaceutically acceptable salt thereof, is used in combination with one or more other therapeutic agent discussed herein.

The administration of two or more compounds “in combination” means that all of the compounds are administered closely enough in time to affect treatment of the subject. The two or more compounds may be administered simultaneously or sequentially, via the same or different routes of administration, on same or different administration schedules and with or without specific time limits depending on the treatment regimen. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but as separate dosage forms at the same or different site of administration. Examples of “in combination” include, but are not limited to, “concurrent administration,” “co-administration,” “simultaneous administration,” “sequential administration” and “administered simultaneously”.

A compound of the invention and the one or more other therapeutic agents may be administered as a fixed or non-fixed combination of the active ingredients. The term "fixed combination" means a compound of the invention, or a pharmaceutically acceptable salt thereof, and the one or more therapeutic agents, are both administered to a subject simultaneously in a single composition or dosage. The term "non-fixed combination" means

that a compound of the invention, or a pharmaceutically acceptable salt thereof, and the one or more therapeutic agents are formulated as separate compositions or dosages such that they may be administered to a subject in need thereof simultaneously or at different times with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the subject.

In one embodiment, the compounds of this invention may be administered in combination with other therapeutic agents, which may provide greater clinical benefit. Such additional therapeutic agents include, but are not limited to, vital RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors and metabolism boosting agents that leads to reduction in virus replication or host response and may thus contribute to greater clinical benefit. An example of viral RNA polymerase inhibitor is remdesivir. Examples of MPro inhibitors include, but are not limited to, nirmatrelvir (also known as “PF-07321332”), PBI-0451, bofutrelvir (also known as “FB2001”), EDP-235, ensitrelvir (also known as “S-217622”) and ALG-097111.

Additional metabolism boosting agents such as ritonavir may also be used in combination with the compounds of the present invention or with combinations of the compounds of the present invention with other therapeutic agents as indicated above, in order to increase the therapeutic effect.

Examples of greater clinical benefits includes, but are not limited to, a larger reduction in symptoms, a faster time to alleviation of symptoms, reduced lung pathology, a larger reduction in the amount of coronavirus in the patient (viral load), and decreased disease severity or mortality.

These agents and compounds of the invention may be combined with pharmaceutically acceptable vehicles such as saline, Ringer’s solution, dextrose solution, and the like. The particular dosage regimen, i.e., dose, timing and repetition, will depend on the particular individual and that individual’s medical history.

Kits

Another aspect of the invention provides kits comprising the compound of the invention or pharmaceutical compositions comprising the compound of the invention. A kit may include, in addition to the compound of the invention or pharmaceutical composition thereof, diagnostic or therapeutic agents. A kit may also include instructions for use in a diagnostic or therapeutic method. In some embodiments, the kit includes the compound or a pharmaceutical composition

thereof and a diagnostic agent or rapid test. In other embodiments, the kit includes the compound or a pharmaceutical composition thereof, one or more therapeutic agents, such as a viral RNA polymerase inhibitor – e.g., remdesivir -, a MPro inhibitor – e.g., nirmatrelvir, PBI-0451, bofutrelvir, EDP-235, ensitrelvir and ALG-097111 - a nucleoside inhibitor, a host factor inhibitor, another PLpro inhibitor or a metabolism boosting agent, and optionally a diagnostic agent or rapid test. In yet another embodiment, the invention comprises kits that are suitable for use in performing the methods of treatment described herein. In one embodiment, the kit contains a first dosage form comprising one or more of the compounds of the invention in quantities sufficient to carry out the methods of the invention. In another embodiment, the kit comprises one or more compounds of the invention in quantities sufficient to carry out the methods of the invention and a container for the dosage.

Synthetic Methods

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources or may be prepared using methods well known to those skilled in the art. Many of the compounds used herein, are related to, or may be derived from compounds in which one or more of the scientific interest or commercial need has occurred. Accordingly, such compounds may be one or more of 1) commercially available; 2) reported in the literature or 3) prepared from other commonly available substances by one skilled in the art using materials which have been reported in the literature.

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the present invention. Although specific starting materials and reagents are discussed below, other starting materials and reagents may be substituted to provide one or more of a variety of derivatives or reaction conditions. In addition, many of the compounds prepared by the methods described below may be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

The skilled person will appreciate that the experimental conditions set forth in the schemes that follow are illustrative of suitable conditions for effecting the transformations

shown, and that it may be necessary or desirable to vary the precise conditions employed for the preparation of compounds of the invention. It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention.

In the preparation of compounds of the invention it is noted that some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., a primary amine, secondary amine, carboxyl, etc. in a precursor of a compound of the invention). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art. The use of such protection and deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure 8th Edition.

For example, if a compound contains an amine or carboxylic acid functionality, such functionality may interfere with reactions at other sites of the molecule if left unprotected. Accordingly, such functionalities may be protected by an appropriate protecting group (PG) which may be removed in a subsequent step. Suitable protecting groups for amine and carboxylic acid protection include those protecting groups commonly used in peptide synthesis (such as *N*-t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and 9-fluorenylmethylenoxycarbonyl (Fmoc) for amines and lower alkyl or benzyl esters for carboxylic acids) which are generally not chemically reactive under the reaction conditions described and may typically be removed without chemically altering other functionality in a compound of the invention.

GENERAL EXPERIMENTAL DETAILS

In the non-limiting Examples and Preparations that illustrate the invention and that are set out in the description, and in the following General Schemes, the following abbreviations, definitions and analytical procedures may be referred to:

Abbreviations

°2θ is degrees 2-theta;

AcCl is acetyl chloride;

AcOH is acetic acid;

ADH-101 is alcohol dehydrogenase 101;

APCI is atmospheric pressure chemical ionization;

aq is aqueous;

$BF_3.OEt_2$ is boron trifluoride diethyl etherate;

BH_3Me_2S is (dimethyl sulphide)trihydroboron;

BINAP is 1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine;

Bn is benzyl;

Boc is *tert*-butoxycarbonyl;

Boc_2O is di-*tert*-butyl dicarbonate;

B_2Pin_2 is Bis(pinacolato)diboron
br is broad;

tBu is *tert*-butyl;

tBuOH is *tert*-butanol;

tBuOK is potassium *tert*-butoxide;

tBuXPhos is 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl;

tBuXPhos-Pd Gen-3 is [(2-di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate;

°C is degrees celcius;

Cbz is benzyloxycarbonyl;

$CDCl_3$ is deutero-chloroform;

CDI is 1,1'-carbonyldiimidazole;

δ is chemical shift;

d is doublet;

dd is doublet of doublets;

ddd is doublet of doublet of doublets;

dt is doublet of triplets;

DCE is 1,2-dichloroethane;

DCM is dichloromethane (also known as methylene chloride);

DIAD is diisopropyl azodicarboxylate;

(-)-DIP-Chloride™ is (-)-B-chlorodiisopinocampheylborane;

DIPEA or DIEA is N-ethyldiisopropylamine, also known as N,N-diisopropylethylamine;

DMA is N,N-dimethylacetamide;

DME is 1,2-dimethoxyethane;

DMAP is 4-dimethylaminopyridine;
DMF is N,N-dimethylformamide;
DMSO is dimethyl sulfoxide;
DMSO-d_6 is deuterodimethylsulfoxide;
DPPP is 1,3-bis(diphenylphosphino)propane;
EA is ethyl acetate
EDC is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide;
EDC.HCl is N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride;
EI is electron impact ionization;
eq. is equivalent
ES is electron scatter;
ESI is electrospray ionization;
Et_2O is diethyl ether;
EtOAc is ethyl acetate;
EtOH is ethanol;
Et_3N is triethylamine;
g is gram;
GCMS is gas chromatography-mass spectrometry;
HATU is 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate;
HPLC is high performance liquid chromatography;
HOAc is acetic acid;
HOBt is 1-hydroxybenzotriazole hydrate;
hr(s) is hour(s);
IPA is isopropyl alcohol;
iPrOAc is isopropyl acetate;
Ir[dF(CF_3)ppy]$_2$(dtbpy)PF_6 is [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]iridium(III) hexafluorophosphate;
KOAc is Potassium acetate;
KRED101 is ketoreductase 101 enzyme;
L is liter;
LCMS is liquid chromatography mass spectrometry;
LG is leaving group;

m is multiplet;
M is molar;
m-CPBA is 3-chloroperbenzoic acid;
Me is methyl;
MeCN is acetonitrile;
MeMgBr is methylmagnesium bromide;
MeNHOMe HCl is N,O-dimethylhydroxylamine hydrochloride;
MeOD_d_4 is deuterated methanol;
MeOH is methanol;
MeI is methyl iodide;
2-MeTHF is 2-methyl tetrahydrofuran;
mg is milligram;
MHz is mega Hertz;
min(s) is minute(s);
mL is milliliter;
mmol is millimole;
mol is mole;
MS (m/z) is mass spectrum peak;
MsCl is mesyl chloride;
MTBE is *tert*-butyl methyl ether;
NADP+ is nicotinamide adenine dinucleotide phosphate;
$NiCl_2$•glyme is nickel (II) chloride ethylene glycol dimethyl ether complex;
NMR is nuclear magnetic resonance;
ODS is octadecyl-silica;
ORTEP is Oak Ridge Thermal Ellipsoid Plot;
$Pd(tBu_3P)_2$ is bis(tri-*tert*-butylphosphine)palladium(0);
Pd/C is palladium on carbon;
$Pd_2(dba)_3$ is palladium tris(dibenzylideneacetone)dipalladium(0);
$Pd(dppf)Cl_2$ is [1,1'-bis(diphenylphophino)ferrocene]dichloropalladium(II);
$Pd(OAc)_2$ is palladium(II) acetate;
$Pd(PPh_3)_4$ is tetrakis(triphenylphosphine)palladium(0);
PE is Petroleum ether

Pet. ether is the petroleum fraction consisting of aliphatic hydrocarbons and boiling in the range 35–60°C;

PG is protecting group;

PMB is para-methoxybenzyl;

$PMB\text{-}NH_2$ is para-methoxybenzylamine;

Polycat 5 ® is bis(2-dimethylaminoethyl)(methyl)amine

PPh_3 is triphenylphosphine;

pH is power of hydrogen;

ppm is parts per million;

PSD is position sensitive detector;

psi is pounds per square inch;

PXRD is powder X-ray diffraction;

q is quartet;

rpm is rotation per minute;

rt is room temperature;

RT is retention time;

Ru-phos is 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl;
s is singlet;

sat. is saturated;

SEM-Cl is 2-(trimethylsilyl)ethoxymethyl chloride;

SFC is supercritical fluid chromatography;

t is triplet;

T_3P is propylphosphonic anhydride;

TBAF is *tert*-butyl ammonium fluoride;

TBDMSCl is *tert*-butyldimethylsilyl chloride;

TEA is Triethylamine;

TFA is trifluoroacetic acid;

THF is tetrahydrofuran;

$Ti(O\text{-}iPr)_4$ is titanium(IV) isopropoxide

TLC is thin layer chromatography;

TMEDA is *N,N,N'N'*-tetramethylethylenediamine;

TMSCl is trimethylsilyl chloride;

TMSCN is trimethylsilyl cyanide;

$TMSCHN_2$ is (diazomethyl)trimethylsilane;

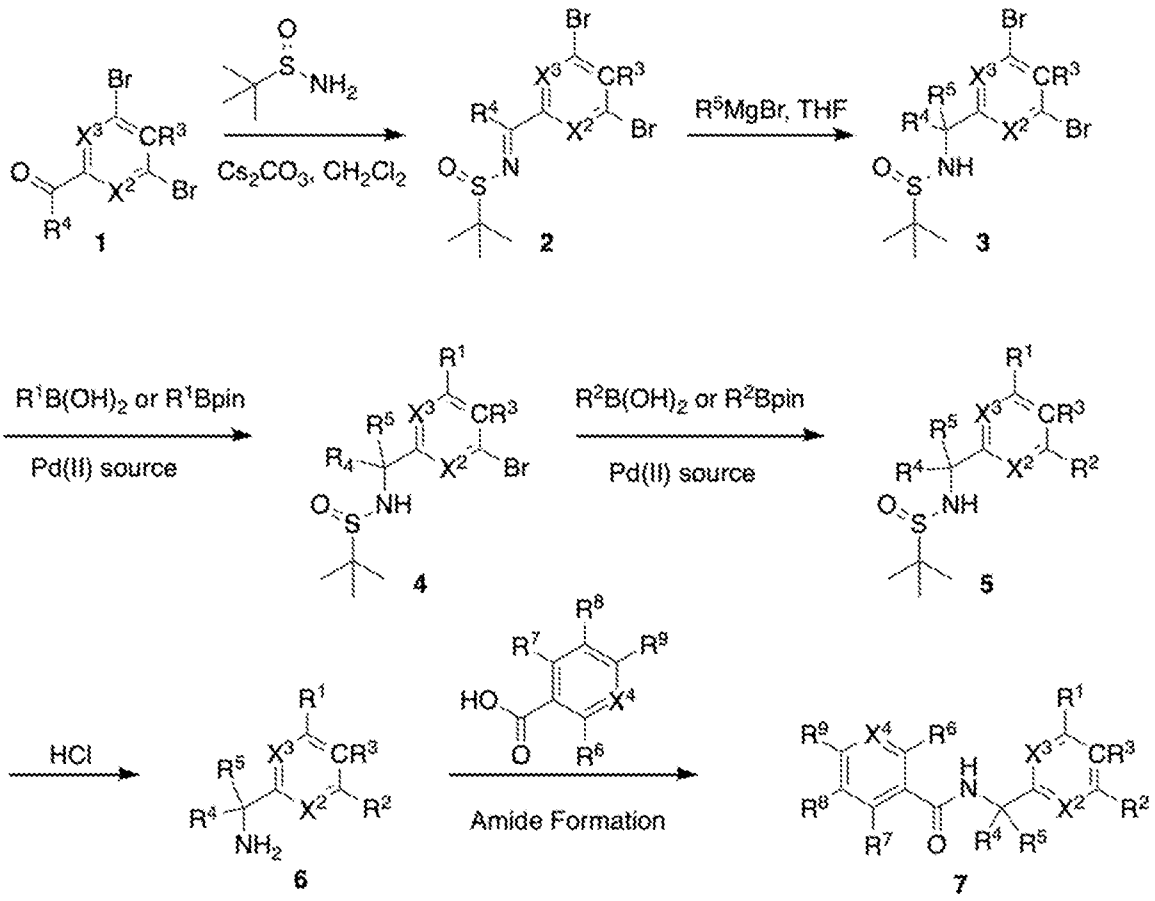
TsCl is p-toluenesulfonyl chloride;
Ts_2O is p-toluenesulfonic anhydride;
UPLC is ultra-performance liquid chromatography;
µL is microliter;
µmol is micromole;
wt is weight; and
Xantphos is 4,5-bis(diphenylphosphno)-9,9-dimethylxanthene

General Methods:

The Schemes described below are intended to provide a general description of the methodology employed in the preparation of the compounds of the present invention. Some of the compounds of the present invention contain a single chiral center. In the following Schemes, the general methods for the preparation of the compounds are shown either in racemic or enantioenriched form. It will be apparent to one skilled in the art that all of the synthetic transformations may be conducted in a precisely similar manner whether the materials are enantioenriched or racemic. Moreover, the resolution to the desired optically active material may take place at any desired point in the sequence using well known methods such as described herein and in the chemistry literature.

Unless stated otherwise, the variables in General Schemes 1 and 2 (GS1 and GS2) below have the same meanings as defined herein.

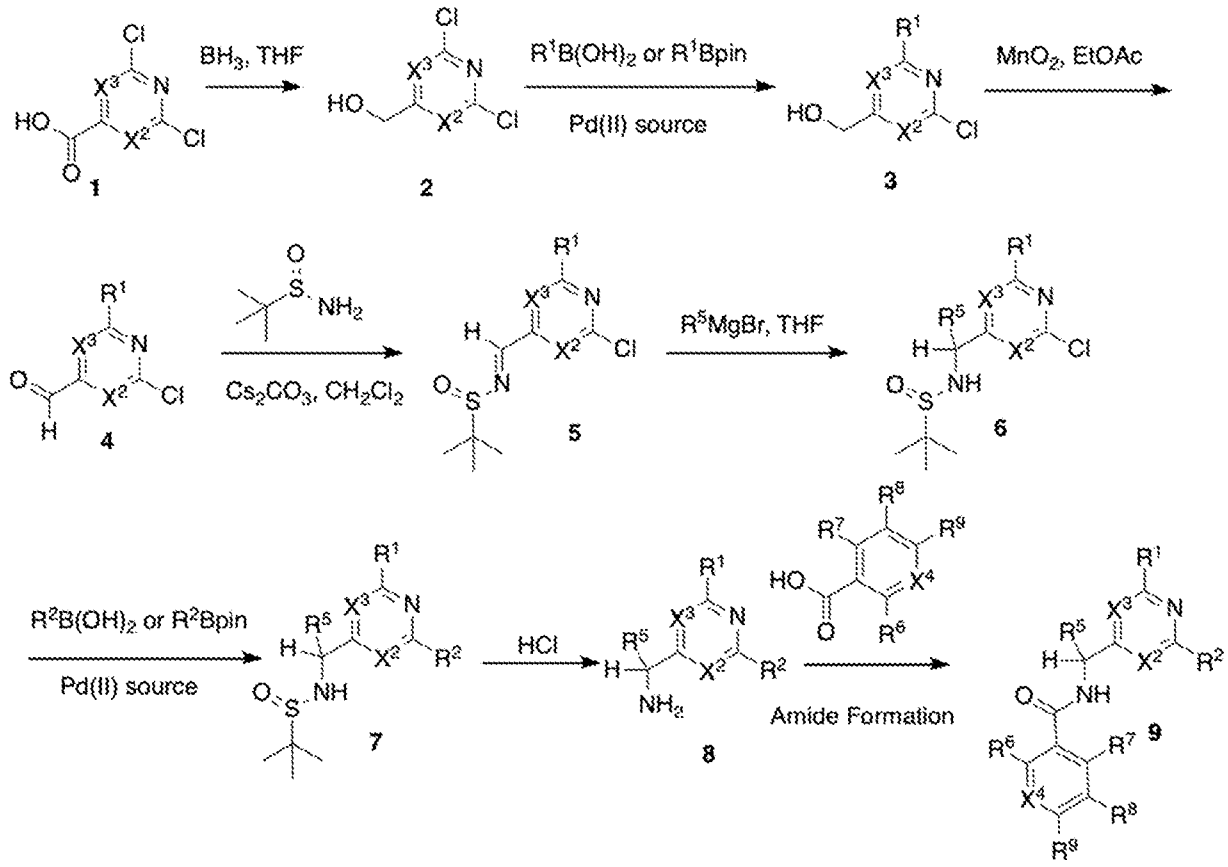
General Scheme 1 (GS1):



General Scheme 1 describes a general method for preparing compound 7, wherein R^1 to R^9 are as defined in Embodiment 1. A starting material such as commercially available 3,5-dibromobenzaldehyde (compound 1) may be treated with either a racemic or chiral sulfinamide, and subsequently reacted with a relevant Grignard reagent to provide the protected amine (compound 3). Two subsequent couplings with the appropriate boronates and a Palladium catalyst under Suzuki conditions provide the di-substituted compound 5. Compound 5 is then deprotected to the amine (compound 6), which is then in turn coupled with a relevant carboxylic acid to provide compound 7. The carboxylic acids of interest are either readily commercially available or synthesizable using straightforward techniques familiar to those skilled in the art. For example, such acids may be prepared using conditions described in WO 2005/102389 or US 4,182,775. This amide formation reaction can be accomplished through standard amide coupling conditions using coupling reagents such as 1,1'-carbonyldiimidazole, 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or others. In certain cases, the substituents

R^1 to R^9 may contain a protecting group which may be appended or removed by additional steps in the synthetic sequence using conditions known in the art (March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure 8th Edition or *Protecting Groups*, 10 Georg Thieme Verlag, 1994). In cases where R^4 and R^5 connect to form a cycle, the above scheme may need to be adapted in order to access compound 3 using techniques familiar to those of ordinary skill in the art, for example as described in WO 2015/19325.

General Scheme 2 (GS2):



General Scheme 2 describes a general method for preparing compound 9, wherein R^1 to R^3 and R^5 to R^9 are as defined in Embodiment 1 and R^4 is H. A starting material such as commercially available 2,6-dichloroisonicotinic acid is first converted to the primary alcohol, which is then subjected to cross coupling under Suzuki conditions with a boronic acid or boronic ester to provide compound 3. Oxidation of the primary alcohol of compound 3 to the aldehyde (compound 4) then allows for reaction with either a racemic or chiral sulfinamide to provide compound 5. Compound 5 is subsequently reacted with a Grignard reagent to provide the

protected amine (compound 6). Compound 6 is then subjected to cross coupling under Suzuki conditions with a boronic acid or boronic ester to provide compound 7. Compound 7 is then deprotected to provide the corresponding amine (compound 8), which is subsequently coupled with a relevant carboxylic acid using standard amidation conditions to provide compound 9. As with GS1, the carboxylic acids of interest are either readily commercially available or made using techniques generally known in the art. In certain cases, R^1 to R^3 and R^5 to R^9 may contain a protecting group which may be appended or removed by additional steps in the synthetic sequence using conditions known in the art (March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure 8th Edition or *Protecting Groups*, 10 Georg Thieme Verlag, 1994).

For both general schemes GS1 and GS2, as will be clear to those familiar in the art, the individual reaction steps may be rearranged to carry out the multiple-step transformation in various orders. An extra separation step may also be added to isolate the desired stereochemical form if a chiral sulfinamide or other chiral auxiliary of interest is utilized. Additionally, that chiral form can be employed for any subsequent steps if the enantiopure product is desired rather than the racemic form shown in the schemes. If the final product of such schemes is racemic, the mixture of enantiomers or diastereomers formed may be separated using supercritical fluid or reversed-phase chromatography with a chiral column. Compounds at every step may also be purified by standard techniques, such as column chromatography, crystallization, or reverse phase SFC or HPLC.

EXAMPLES

In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art. All starting materials in these Preparations and Examples are either commercially available or can be prepared by methods known in the art or as described herein.

Reactions were performed in air or, when oxygen- or moisture-sensitive reagents or intermediates were employed, under an inert atmosphere (nitrogen or argon). When appropriate, reaction apparatuses were dried under dynamic vacuum using a heat gun, and anhydrous solvents (Sure-SealTM products from Aldrich Chemical Company, Milwaukee,

Wisconsin or DriSolvTM products from EMD Chemicals, Gibbstown, NJ) were employed. In some cases, commercial solvents were passed through columns packed with 4Å molecular sieves, until the following QC standards for water were attained: a) <100 ppm for dichloromethane, toluene, N,N-dimethylformamide, and tetrahydrofuran; b) <180 ppm for methanol, ethanol, 1,4-dioxane, and diisopropylamine. For very sensitive reactions, solvents were further treated with metallic sodium, calcium hydride, or molecular sieves, and distilled just prior to use. Other commercial solvents and reagents were used without further purification. For syntheses referencing procedures in other Examples or Methods, reaction conditions (reaction time and temperature) may vary. Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing.

When indicated, reactions were heated by microwave irradiation using Biotage Initiator or Personal Chemistry Emrys Optimizer microwaves. Reaction progress was monitored using thin-layer chromatography (TLC), liquid chromatography-mass spectrometry (LCMS), high-performance liquid chromatography (HPLC), and/or gas chromatography-mass spectrometry (GCMS) analyses. TLC was performed on pre-coated silica gel plates with a fluorescence indicator (254 nm excitation wavelength) and visualized under UV light and/or with iodine, potassium permanganate, cobalt(II) chloride, phosphomolybdic acid, and/or ceric ammonium molybdate stains. LCMS data were acquired on an Agilent 1100 Series instrument with a Leap Technologies autosampler, Gemini C18 columns, acetonitrile/water gradients, and either trifluoroacetic acid, formic acid, or ammonium hydroxide modifiers. The column eluent was analyzed using a Waters ZQ mass spectrometer scanning in both positive and negative ion modes from 100 to 1200 Da. Other similar instruments were also used. HPLC data were generally acquired on an Agilent 1100 Series instrument, using the columns indicated, acetonitrile/water gradients, and either trifluoroacetic acid or ammonium hydroxide modifiers. GCMS data were acquired using a Hewlett Packard 6890 oven with an HP 6890 injector, HP-1 column (12 m x 0.2 mm x 0.33 μm), and helium carrier gas. The sample was analyzed on an HP 5973 mass selective detector scanning from 50 to 550 Da using electron ionization. Purifications were performed by medium performance liquid chromatography (MPLC) using Isco CombiFlash Companion, AnaLogix IntelliFlash 280, Biotage SP1, or Biotage Isolera One instruments and pre-packed Isco RediSep or Biotage Snap silica cartridges. Chiral purifications were performed by chiral supercritical fluid chromatography (SFC), generally using Berger or Thar instruments; columns such as ChiralPAK-AD, -AS, -IC, Chiralcel-OD, or -OJ columns; and CO_2 mixtures with methanol, ethanol, 2-propanol, or acetonitrile, alone or modified using

trifluoroacetic acid or propan-2-amine. UV detection was used to trigger fraction collection. For syntheses referencing procedures in other Examples or Methods, purifications may vary: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate Rfs or retention times.

Mass spectrometry data are reported from LCMS analyses. Mass spectrometry (MS) was performed via atmospheric pressure chemical ionization (APCI), electrospray Ionization (ESI), electron impact ionization (EI) or electron scatter (ES) ionization sources.

Proton nuclear magnetic spectroscopy (^{1}H NMR) chemical shifts are given in parts per million downfield from tetramethylsilane and were recorded on 300, 400, 500, or 600 MHz Varian, Bruker, or Jeol spectrometers. Chemical shifts are expressed in parts per million (ppm, δ) referenced to the deuterated solvent residual peaks (chloroform, 7.26 ppm; CD_2HOD, 3.31 ppm; acetonitrile-d2, 1.94 ppm; dimethyl sulfoxide-d5, 2.50 ppm; DHO, 4.79 ppm). The peak shapes are described as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br s, broad singlet; app, apparent. Analytical SFC data were generally acquired on a Berger analytical instrument as described above. Optical rotation data were acquired on a PerkinElmer model 343 polarimeter using a 1 dm cell. Microanalyses were performed by Quantitative Technologies Inc. and were within 0.4% of the calculated values. The ^{1}H NMR spectra of many of the compounds herein indicate a mixture of rotamers, due to the presence of amide and/or carbamate functionality, and have been tabulated to reflect the presence of more than one rotamer.

Unless otherwise noted, chemical reactions were performed at room temperature (about 23°C).

Unless noted otherwise, all reactants were obtained commercially and used without further purification or were prepared using methods known in the literature.

The terms “concentrated”, “evaporated” and “concentrated in vacuo” refer to the removal of solvent at reduced pressure on a rotary evaporator with a bath temperature less than 60°C. The term “room temperature or ambient temperature” means a temperature between 18 to 25°C.

Hydrogenation may be performed in a Parr shaker under pressurized hydrogen gas, or in Thales-nano H-Cube flow hydrogenation apparatus at full hydrogen and a flow rate between 1-2 mL/min at specified temperature.

HPLC, UPLC, LCMS, GCMS, and SFC retention times were measured using the methods noted in the procedures.

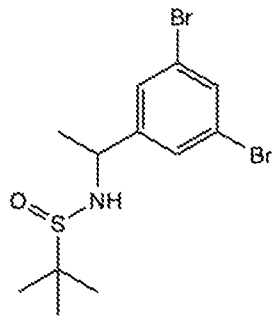
In some examples, chiral separations were carried out to separate enantiomers or diastereomers of certain compounds of the invention (in some examples, the separated enantiomers are designated as ENT-1 and ENT-2, according to their order of elution; similarly, separated diastereomers are designated as DIAST-1 and DIAST-2, according to their order of elution). In some examples, the optical rotation of an enantiomer was measured using a polarimeter. According to its observed rotation data (or its specific rotation data), an enantiomer with a clockwise rotation was designated as the (+)-enantiomer and an enantiomer with a counter-clockwise rotation was designated as the (-)-enantiomer. Racemic compounds are indicated either by the absence of drawn or described stereochemistry, or by the presence of (+/-) adjacent to the structure, or the presence of the text "OR1"; in this latter case, the indicated stereochemistry represents just one of the two enantiomers that make up the racemic mixture.

The compounds and intermediates described below were named using the naming conventions provided with ACD/ChemSketch 2017.2.1, File Version C40H41, Build 99535 (Advanced Chemistry Development, Inc., Toronto, Ontario, Canada) or with ChemDraw 21.0.0 The naming conventions provided with ACD/ChemSketch 2017.2.1 and ChemDraw 21.0.0 are well known by those skilled in the art and it is believed that the naming convention provided with ACD/ChemSketch 2017.2.1 generally comports with the IUPAC (International Union for Pure and Applied Chemistry) recommendations on Nomenclature of Organic Chemistry and the CAS Index rules.

Preparations

The following describe preparations of some starting materials or intermediates used for preparation of certain compounds of the invention.

Preparation P1: N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide



(**P1**)

Step 1. Preparation of (E)-N-(3,5-dibromobenzylidene)-2-methylpropane-2-sulfinamide

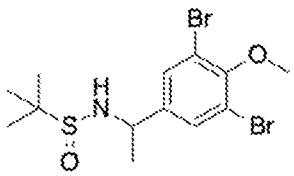
To a solution of 3,5-dibromobenzaldehyde (3000.0 mg, 11.37 mmol) in CH_2Cl_2 (100.0 mL) were added 2-methylpropane-2-sulfinamide (4130 mg, 34.1 mmol) and Cs_2CO_3 (5560 mg, 17.1 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was then purified by silica gel chromatography via Biotage (80 g silica column, PE:EA = 1:0 to 0:1) to afford (E)-N-(3,5-dibromobenzylidene)-2-methylpropane-2-sulfinamide (4170 mg, 99.9% yield) as a white solid. LCMS (ESI): m/z = 366 $[M+H]^+$.

Step 2. Preparation of N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide

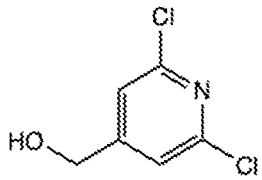
To a solution of (E)-N-(3,5-dibromobenzylidene)-2-methylpropane-2-sulfinamide (4000.0 mg, 10.90 mmol) in THF (80 mL) under N_2 was added MeMgBr (11.0 mL, 3M, 33 mmol) at 0 °C. The reaction mixture was stirred at 20 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was then quenched with 6 mL sat. aq. NH_4Cl at 0 °C, then partitioned between EA/H_2O (100/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford the crude product N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide (3760 mg, 90.1% yield) as a yellow oil. LCMS (ESI): m/z = 382 $[M+H]^+$.

Preparation 10: N-(1-(3,5-dibromo-4-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide

The intermediate P10 was prepared in a similar manner to the N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide (**P1**).

Example Number	Structure; Compound Name	Analogous method, reactants	Characterizing Data
P10	 N-(1-(3,5-dibromo-4-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide	Preparation of **P1**, Step 1,3,5-dibromo-4-methoxybenzaldehyde; Preparation of **P1**, Step 2.	^{1}H NMR (400 MHz, CHLOROFORM-d) δ (ppm) = 7.48-7.43 (m, 2H), 4.52-4.40 (m, 1H), 3.90-3.84 (m, 3H), 3.46-3.27 (m, 1H), 1.49 (d, *J*=6.6 Hz, 3H), 1.23-1.20 (m, 9H). m/z = 413.8 $[M+H]^+$

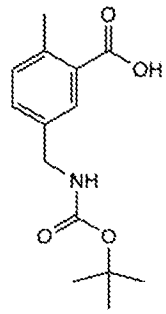
Preparation P2: (2,6-dichloropyridin-4-yl)methanol



(**P2**)

To a mixture of BH_3/THF (13.40 g, 156 mmol, 1M, 156 mL) in THF (20 mL) under ice-water bath temperature and N_2 was added 2,6-dichloroisonicotinic acid (10.00 g, 52.08 mmol) in THF (100 mL) dropwise and the reaction was stirred at 25 °C for 16 hours. The reaction mixture was then treated with methanol and concentrated to dryness. The residue was redissolved in EtOAc (100 mL), washed with water (100 mL), dried over Na_2SO_4, and concentrated to dryness. The residue was then purified by silica gel chromatography eluting with PE/EA (0-30%) to obtain (2,6-dichloropyridin-4-yl)methanol (5360 mg, 57.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.52-4.63 (m, 2H) 5.67 (t, *J*=5.81 Hz, 1H) 7.39-7.52 (m, 2H). LCMS (ESI): m/z = 178 $[M+H]^+$.

Preparation P3: 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid



(**P3**)

Step 1. Preparation of methyl 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoate

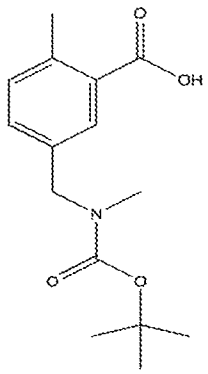
To a solution of methyl 5-cyano-2-methylbenzoate (300.0 mg, 1.71 mmol) in CH_3OH (10 mL) were added $(Boc)_2O$ (448 mg, 2.05 mmol), $NaBH_4$ (140 mg 3.70 mmol), and $NiCl_2$ (444 mg, 3.42 mmol) at 0 °C. The reaction was maintained at 0 °C for 30 minutes then stirred at 25 °C for 12 hours. LCMS showed a product with the desired mass. TLC (PE/EA = 10/1, UV) showed that a new spot was exposed. The reaction was then quenched by sat. aq. NH_4Cl (5 mL). The mixture was extracted with EA (30 mL x 3), dried by Na_2SO_4, and concentrated to give a residue. The residue was purified by silica gel chromatography (PE:EA = 100:0 to 90:10) to give

methyl 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoate (300 mg, 62.7%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ (ppm) = 7.87-7.80 (s, 1H), 7.39-7.29 (d, 1H), 7.25-7.20 (d, 1H), 4.97-4.77 (s, 1H), 4.39-4.25 (d, 2H), 3.92-3.88 (s, 3H), 2.61-2.58 (s, 3H), 1.48 (s, 9H). LCMS (ESI): m/z = 301.9 $[M+Na]^+$.

Step 2. Preparation of 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid

To a solution of methyl 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoate (2500.0 mg, 8.950 mmol) in THF (18.0 mL), MeOH (12.0 mL) and H_2O (6.0 mL) was added $LiOH.H_2O$ (1500 mg, 35.8 mmol). The reaction was stirred at 25 °C for 12 hours. LCMS showed the starting material was consumed, and a desired mass was found. MeOH was removed in vacuo, and the aqueous residue was acidified to pH = 6 with HCl (2N). The precipitate was filtered and dried in vacuo to give 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (2300 mg, 96.9 % yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD, 297 K) δ (ppm) = 7.85 (s, 1H), 7.37-7.32 (m, 1H), 7.27-7.20 (m, 1H), 4.28-4.21 (m, 2H), 2.58-2.56 (m, 1H), 2.56 (s, 3H), 1.47 (s, 9H). LCMS (ESI): m/z = 288.1 $[M+Na]^+$.

Preparation P4: 5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoic acid



(**P4**)

Step 1. Preparation of methyl 5-((((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoate

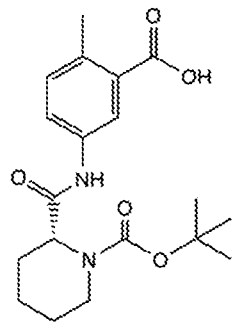
To a solution of methyl 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoate (500 mg, 1.79 mmol) in THF (12 mL) was added tBuOK (301 mg, 2.68 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h, then a solution of MeI (381 mg, 2.68 mmol) in THF (3.0 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 0.5 hour. TLC (PE/EA = 10/1, UV) showed the starting material was consumed, and one main new spot was observed. The reaction mixture was poured into ice water (20 mL) then extracted with EA (20 mL x 2). The combined organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to give

methyl 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoate (450 mg, 85.7%) as a yellow gum, which was used in the next step directly.

Step 2. Preparation of 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoic acid

To a solution of methyl 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoate (450 mg, 1.53 mmol) in THF (6.0 mL) and H_2O (2.0 mL) was added NaOH (184 mg, 4.60 mmol) at 25 °C. The mixture was stirred at 25 °C for 40 hours. TLC (PE/EA = 10/1, UV) showed most of the starting material remained. Additional NaOH (184 mg, 4.60 mmol) was added to the reaction at 25 °C, and the reaction was stirred at 50 °C for 16 hours. TLC (PE/EA = 10/1, UV) showed some of the starting material remained and one new spot on baseline was observed. The reaction mixture was stirred at 70 °C for another 5 hours. TLC (PE/EA = 10/1, UV) showed the starting material was consumed. The reaction mixture was then concentrated under vacuo to remove solvent. The residue was then dissolved in H_2O (10 mL) and extracted with EA (20 mL x 2). The organic layer was discarded. The aqueous phase was acidized with aq. HCl (1N) to pH = 4-5 and extracted with EA (20 mL x 3). The organic extracts were combined and dried with Na_2SO_4, filtered, and concentrated in vacuo to give 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoic acid (390 mg, 91.0%) as a yellow gum. ^{1}H NMR (400MHz, MeOD-d_4) δ (ppm) = 7.73 (br s, 1H), 7.25-7.12 (m, 2H), 4.33 (s, 2H), 2.74 (br s, 3H), 2.47 (s, 3H), 1.38 (br s, 9H).

Preparation P5: (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid



(**P5**)

Step 1. Preparation of *tert*-butyl (*R*)-2-((3-(methoxycarbonyl)-4-methylphenyl)carbamoyl) piperidine-1-carboxylate

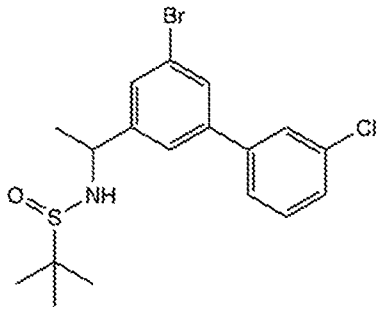
To a solution of (2R)-1-[(2-methylpropan-2-yl)oxycarbonyl]piperidine-2-carboxylic acid (1000 mg, 4.37 mmol) in DMF (15 mL) were added methyl 5-amino-2-methylbenzoate (720 mg, 4.36 mmol), HATU (1990 mg, 5.24 mmol), and DIPEA (1690 mg, 13.1 mmol). The reaction was

stirred at 25 °C for 12 hours. LCMS showed that a desired mass was produced, and TLC (PE/EA = 5/1) showed a new spot was exposed. The mixture was treated with 100 mL H_2O then extracted by EA (20 mL x 3). The organic phase was dried by Na_2SO_4, concentrated, and purified by silica gel chromatography (PE:EA = 100:0 to 80:20) to give *tert*-butyl (*R*)-2-((3-(methoxycarbonyl)-4-methylphenyl)carbamoyl)piperidine-1-carboxylate (1.4 g, 85.3%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ (ppm) = 8.01 (d, *J*=2.2 Hz, 1H), 7.68-7.58 (d, 1H), 7.26-7.16 (d, 1H), 5.32 (s, 1H), 4.88 (br s, 1H), 4.18-4.02 (s, 1H), 3.93-3.82 (s, 3H), 2.94-2.79 (m, 1H), 2.56 (s, 3H), 2.42-2.31 (m, 1H), 1.75-1.60 (m, 4H), 1.54 (s, 9H). LCMS (ESI): m/z = 399.2 $[M+Na]^+$.

Step 2. Preparation of (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid

To a solution of *tert*-butyl (*R*)-2-((3-(methoxycarbonyl)-4-methylphenyl)carbamoyl)piperidine-1-carboxylate (1400.0 mg, 3.719 mmol) in THF (6.0 mL), MeOH (4.0 mL) and H_2O (2.0 mL) was added $LiOH.H_2O$ (624 mg, 14.9 mmol). The reaction was stirred at 25 °C for 12 hours. LCMS showed the starting material was consumed, and a desired mass was found. MeOH was removed in vacuo, and the aqueous residue was acidified to pH = 6 with 2N HCl. The precipitate was filtered and dried in vacuo to give (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (1100 mg, 81.6%) as a white solid. LCMS (ESI): m/z = 385.1 $[M+Na]^+$.

Preparation P6: N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide



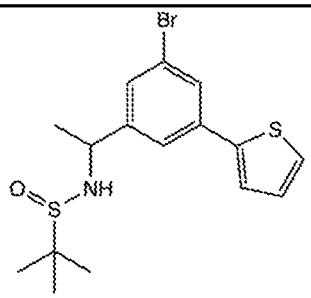
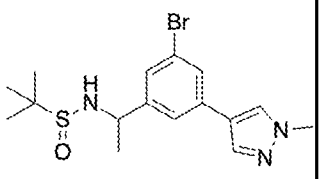
(**P6**)

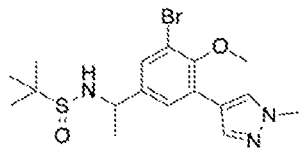
To a solution of N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide (**P1**) (1000.0 mg, 2.610 mmol) in dioxane (20.0 mL) under N_2, was added sat. aq. Na_2CO_3 (2.0 mL) and $Pd(dppf)_2Cl_2$ (191 mg, 0.261 mmol) and (3-chlorophenyl)boronic acid (408 mg, 2.61 mmol) at 20 °C. The reaction mixture was stirred at 100 °C under N_2 for 15 hours. LCMS showed a mass

peak of the desired product. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was then purified by silica gel chromatography via Biotage (80 g silica column, PE:EA = 1:0 to 0:1) to afford the crude product **P6** (515 mg, 47.6%) as a yellow oil. LCMS (ESI): m/z = 414 $[M+H]^+$.

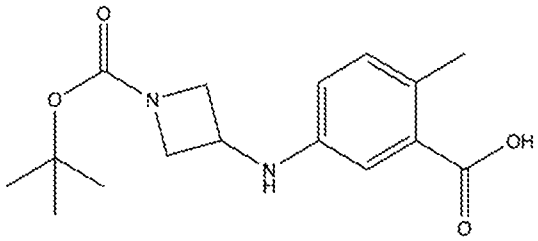
Preparations P7, P9 and P11

The following intermediates were prepared in a similar manner to the N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**) using N-(1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide (**P1**) and an appropriate boronic acid or boronic ester.

Example Number	Structure; Compound Name	Analogous method, reactants	Characterizing Data
P7	 N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide	Preparation **P6**, thiophen-2-ylboronic acid	LCMS (ESI): m/z = 386 $[M+H]^+$.
P9	 N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-	Preparation **P6**, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm) = 8.05-7.96 (m, 1H), 7.86-7.83 (m, 1H), 7.69-7.60 (m, 1H), 7.57-7.48 (m, 1H), 7.39 (s, 1H), 4.57-4.45 (m, 1H), 3.99-3.89 (m, 3H), 1.62-1.51 (m, 3H), 1.33-1.18 (m, 9H).

	methylpropane-2-sulfinamide		LCMS (ESI): m/z = 385.9 $[M+H]^+$.
P11	 *N*-(1-(3-bromo-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide	Preparation **P6**, *N*-(1-(3,5-dibromo-4-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide (**P10**) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole	^{1}H NMR (400 MHz, CHLOROFORM-d) δ (ppm) = 7.89-7.81 (m, 2H), 7.42-7.35 (m, 2H), 4.13 (q, *J*=7.3 Hz, 1H), 3.97 (s, 3H), 3.75-3.68 (m, 3H), 2.05 (s, 1H), 1.53 (d, *J*=6.8 Hz, 3H), 1.26-1.20 (m, 9H). LCMS (ESI): m/z = 414.1 $[M+H]^+$

Preparation P8: 5-((1-(tert-butoxycarbonyl)azetidin-3-yl)amino)-2-methylbenzoic acid



(**P8**)

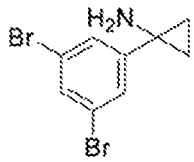
Step 1: Preparation of tert-butyl 3-((3-(methoxycarbonyl)-4-methylphenyl)amino)azetidine-1-carboxylate

To a solution of methyl 5-amino-2-methylbenzoate (1000.0 mg, 6.054 mmol) and tert-butyl 3-oxoazetidine-1-carboxylate (1040 mg, 6.05 mmol) in MeOH (50.0 mL) was added HOAc (1.0 mL) and $NaBH_3CN$ (761mg, 12.1 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was partitioned between EA/sat. aq. $NaHCO_3$ (100/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography via Biotage (20 g silica column, PE: EA= 1:0 to 0:1) to afford *tert*-butyl 3-((3-(methoxycarbonyl)-4-methylphenyl)amino)azetidine-1-carboxylate (1532 mg, 79%) as a yellow oil. LCMS (ESI): m/z = 321 $[M+H]^+$.

Step 2: Preparation of 5-((1-(tert-butoxycarbonyl)azetidin-3-yl)amino)-2-methylbenzoic acid

To a solution of tert-butyl 3-((3-(methoxycarbonyl)-4-methylphenyl)amino)azetidine-1-carboxylate (1500mg, 4.682 mmol) in MeOH (50 mL) was added 10% NaOH (8 mL) at 20 °C. The reaction mixture was stirred at 60 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was acidified with 1N HCl at 0 °C and partitioned between EA/H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to afford 5-((1-(tert-butoxycarbonyl)azetidin-3-yl)amino)-2-methylbenzoic acid (1230 mg, 85.8%) as a yellow solid. LCMS (ESI): m/z = 307 $[M+H]^+$.

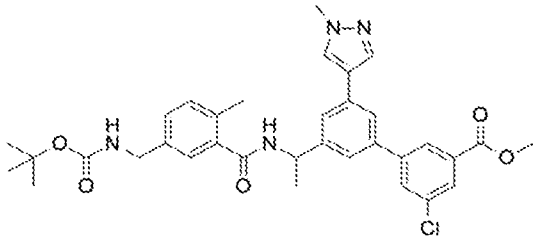
Preparation of P12: 1-(3,5-dibromophenyl)cyclopropan-1-amine



(**P12**)

To a stirred solution of 3,5-dibromobenzonitrile (4000.0 mg, 15.33 mmol) and $Ti(O\text{-}iPr)_4$ (4790 mg, 16.9 mmol) in Et_2O (80 mL) was added ethylmagnesium bromide (11.2 mL, 3M, 33.7 mmol) dropwise at -78°C. After that, the mixture was kept at 20°C for 1 h before adding $BF_3.OEt_2$ (4350 mg, 30.7 mmol) to it at 20°C. The mixture was then stirred for 0.5 h. The reaction was quenched by adding HCl (20 mL, 1N) to it, followed by stirring at 20°C for an additional 0.5 h. The mixture was then extracted with MTBE (100 mL x 2) after adding sat. aq. NaOH (20 mL) to it. The combined organic layer was evaporated in vacuo to give a residue, which was purified by silica gel chromatography via Biotage (40 g silicon column, PE: EA= 1:0 to 0/1) to afford 1-(3,5-dibromophenyl)cyclopropan-1-amine (2.5 g, 56%) as a yellow solid. LCMS (ESI): m/z = 291.9 $[M+H]^+$.

Preparation of P13: methyl 3'-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate

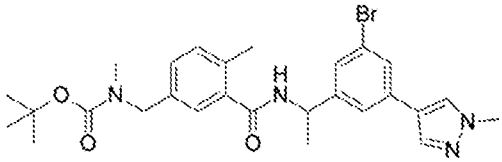


(**P13**)

Methyl 3'-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate was prepared using protocols analogous to the protocols described in Example 4 Step 1-3 with N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**) in step 1, 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) in step 2, (3-chloro-5-(methoxycarbonyl)phenyl)boronic acid in step 3, and then purification by chromatography on silica gel (4.0 g, EA/PE = 0~100%).

LCMS (ESI): m/z = 639.0 $[M+Na]^+$.

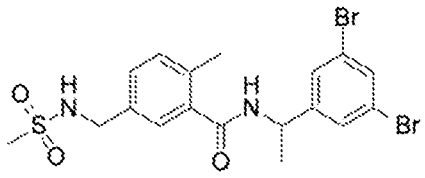
Preparation of P14: tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)(methyl)carbamate



(**P14**)

Tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)(methyl)carbamate was prepared using protocols analogous to the protocols described in Example 33 Step 1-2 with 5-(((tert-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoic acid (**P4**) and 1-(3,5-dibromophenyl)ethan-1-amine in step 1, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in step 2, and then purification by silica gel chromatography via Biotage (4 g silicon column, PE: EA= 1:2). LCMS (ESI): m/z = 441.3 $[M+H-Boc]^+$.

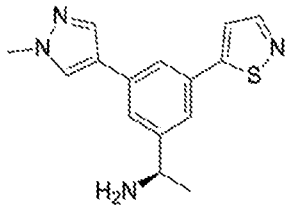
Preparation of P15: N-(1-(3,5-dibromophenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl) benzamide



(**P15**)

Using a protocol similar to Step 1 of Example 33 and 2-methyl-5-(methylsulfonamidomethyl) benzoic acid and 1-(3,5-dibromophenyl)ethan-1-amine as the reactants affords N-(1-(3,5-dibromophenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.59-1.61 (m, 3H) 2.44 (s, 3H) 2.91-2.99 (m, 3H) 4.27-4.36 (m, 2H) 5.21-5.29 (m, 1H) 7.23-7.27 (m, 2H) 7.32-7.38 (m, 2H) 7.45-7.53 (m, 2H) 7.58-7.65 (m, 1H). LCMS (ESI): m/z = 505.1 $[M+H]^+$.

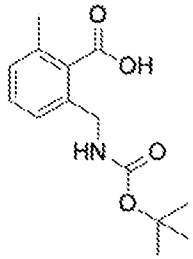
Preparation of P16: (R)-1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethan-1-amine



(P16)

(R)-1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethan-1-amine was prepared in a similar manner to Step 1-2 of Example 1 using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole as the reactants. LCMS (ESI): m/z = 268.0 $[M+H-NH_3]^+$.

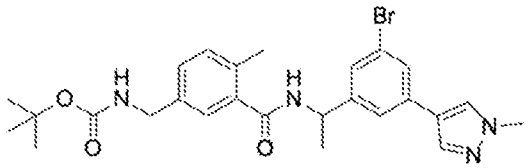
Preparation of P17: 2-(((tert-butoxycarbonyl)amino)methyl)-6-methylbenzoic acid



(P17)

2-(((tert-butoxycarbonyl)amino)methyl)-6-methylbenzoic acid was prepared in a similar manner to 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) using methyl 2-cyano-6-methylbenzoate as the starting material. ^{1}H NMR (400 MHz, MeOD-d4) δ = 7.35-7.26 (m, 1H), 7.24-7.15 (m, 2H), 4.30 (s, 2H), 2.38 (s, 3H), 1.50-1.39 (m, 9H).

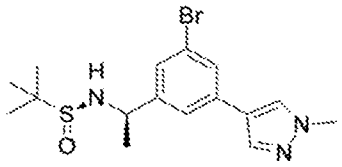
Preparation of P18: tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate



(P18)

tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate was prepared in a similar manner to Step 1-2 of Example 4 using N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**) as the starting material in Step 1 and 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) as the acid in Step 2. ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.01 (s, 1H), 7.84 (s, 1H), 7.63 (t, *J* = 1.6 Hz, 1H), 7.57 (s, 1H), 7.42 (t, *J* = 1.4 Hz, 1H), 7.28-7.22 (m, 2H), 7.22-7.17 (m, 1H), 5.18 (q, *J* = 7.0 Hz, 1H), 4.20 (s, 2H), 3.93 (s, 3H), 2.81 (s, 2H), 2.32 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.42 (s, 9H). LCMS (ESI): m/z = 527.2 $[M+H]^+$.

Preparation of P19: (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide



(P19)

Step 1. Preparation of (S,E)-N-(1-(3,5-dibromophenyl)ethylidene)-2-methylpropane-2-sulfinamide

To a solution of 1-(3,5-dibromophenyl)ethan-1-one (30000 mg, 107.94 mmol) in THF (500 mL) under N_2 were added (S)-2-methylpropane-2-sulfinamide (26200 mg, 216 mmol) and Ti(O-iPr)$_4$ (123000 mg, 432 mmol) at 15°C. The reaction mixture was stirred at 70°C under N_2 for 15 h then cooled to 20°C and poured into H_2O (500 mL), and filtered. The cake was washed with

ethyl acetate (500 mL x 5), the filtrate was evaporated in vacuo to give a crude, which was purified by flash chromatography (220 g silica gel column, EA/PE from 0 to 30%) to give (S,E)-N-(1-(3,5-dibromophenyl)ethylidene)-2-methylpropane-2-sulfinamide (30 g, 72.9%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.91 (d, *J* = 1.3 Hz, 2H), 7.78 (t, *J* = 1.5 Hz, 1H), 2.73 (s, 3H), 1.33 (s, 9H). LCMS (ESI): m/z = 381.9 $[M+H]^+$.

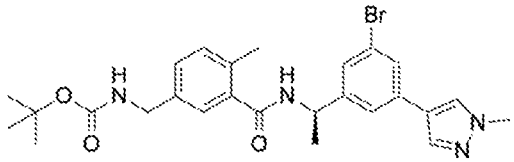
Step 2. Preparation of (S)-N-((R)-1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of (S,E)-N-(1-(3,5-dibromophenyl)ethylidene)-2-methylpropane-2-sulfinamide (20000 mg, 52.476 mmol) in THF (525 mL) under N_2 was added L- selectride (18000 mg, 94.5 mmol) dropwise at -78°C. The reaction mixture was stirred at -78°C for 3 h then poured into aq. sat. NH_4Cl (300 mL) at 0°C and extracted with ethyl acetate (500 mL x 5). The combined organic layer was evaporated in vacuo to give a crude, which was purified by flash chromatography (330 g silica gel column, EA/PE from 0 to 30%) to give (S)-N-((R)-1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide (20000 mg, 99.5%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.57 (t, *J* = 1.7 Hz, 1H), 7.41 (d, *J* = 1.5 Hz, 2H), 4.51 (d, *J* = 6.6 Hz, 1H), 3.30 (s, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.22 (s, 9H). ^{1}H NMR ($CDCl_3$) showed it was consistent with the desired product. LCMS (ESI): m/z = 383.9 $[M+H]^+$.

Step 3. Preparation of (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide

(S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide was prepared in a similar manner to **P6** using (S)-N-((R)-1-(3,5-dibromophenyl)ethyl)-2-methylpropane-2-sulfinamide and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 7.73 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.33 (d, *J* = 9.7 Hz, 2H), 4.55 (q, *J* = 6.5 Hz, 1H), 3.95 (s, 3H), 3.33 (s, 1H), 1.53 (d, *J* = 6.6 Hz, 3H), 1.22 (s, 9H). LCMS (ESI): m/z = 386.2 $[M+H]^+$.

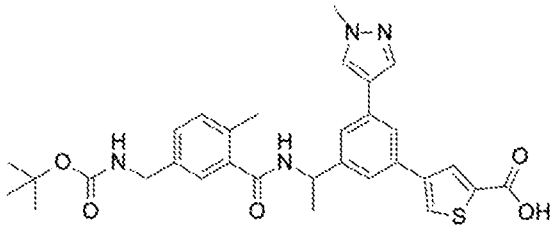
Preparation of P20: tert-butyl (R)-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate



(P20)

tert-butyl (R)-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate was prepared in a similar manner to Step 1-2 of Example 4 using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) as the starting material in Step 1 and 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) as the acid in Step 2.

Preparation of P21: 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid



(P21)

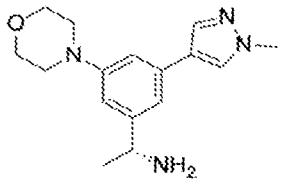
Step 1. Preparation of methyl 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate

Methyl 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate was prepared following a procedure analogous to Example 1, Step 1-3, starting from *N*-(1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate. ^{1}H NMR (400MHz, $CDCl_3$-d) δ = 8.10 (d, *J* = 1.5 Hz, 1H), 7.81 (s, 1H), 7.75-7.68 (m, 2H), 7.60-7.56 (m, 1H), 7.47-7.43 (m, 2H), 7.30 (s, 1H), 7.25-7.20 (m, 1H), 7.19-7.15 (m, 1H), 6.26 (br d, *J* = 6.8 Hz, 1H), 6.07 (br s, 1H), 5.01 (br s, 1H), 4.27 (br d, *J* = 5.1 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.41 (s, 3H), 2.05 (s, 3H), 1.42 (s, 9H). LCMS (ESI): m/z = 589.3 $[M+H]^+$.

Step 2. Preparation of 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid

To a solution of methyl 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido) ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (200.0 mg, 0.423 mmol) in MeOH (4.0 mL) was added NaOH (2 mL, 2M) at 20°C, The reaction mixture was stirred at 20°C for 12 h, at which time, LCMS showed no starting material remained and the formation of a major peak. The reaction mixture was then evaporated in vacuo to give crude, which was dissolved in H_2O (50 mL). The solution was then acidified by citric acid aqueous solution (5%, 6.0 mL) to pH = 6~7 and extracted by ethyl acetate (50 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to give 4-(3-(1-(5-(((tert-butoxycarbonyl)amino) methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (130 mg 53.5%) as a white solid. ^{1}H NMR (400MHz, MeOD-d4) δ = 8.17 (d, *J* = 1.5 Hz, 1H), 8.07 (s, 1H), 8.02 (d, *J* = 1.5 Hz, 1H), 7.92 (s, 1H), 7.77 (s, 1H), 7.58 (br d, *J* = 8.2 Hz, 2H), 7.25 (br d, *J* = 8.3 Hz, 2H), 7.22-7.18 (m, 1H), 5.28 (br t, *J* = 7.3 Hz, 1H), 4.20 (s, 2H), 3.95 (s, 3H), 2.33 (s, 3H), 1.60 (d, *J* = 7.0 Hz, 3H), 1.39 (s, 9H). LCMS (ESI): m/z = 575.3 $[M+H]^+$.

Preparation of P22: (R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethan-1-amine



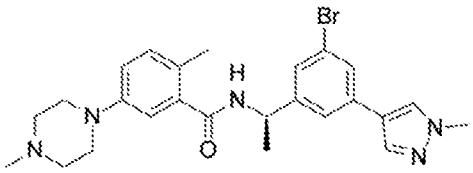
(P22)

Step 1. Preparation of (S)-2-methyl-N-((R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl) ethyl)propane-2-sulfinamide

To a mixture of (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) (250 mg, 0.650 mmol) in 1,4-dioxane (5.0 mL) were added sat. aq. K_2CO_3 (270 mg, 1.95 mmol), morpholine (170 mg, 1.95 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (31.0 mg, 0.0650 mmol), and $Pd_2(dba)_3$ (59.6 mg, 0.0650 mmol) at 20°C. The reaction mixture was stirred at 100°C under N_2 for 15 h. After that, the reaction mixture was diluted with H_2O (10 mL) and extracted by ethyl acetate (20 mL x 3). The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated in vacuo to give a residue, which was then purified by silica gel chromatography via Biotage (4 g silicon column, PE: EA= 1:0 to 0:1) to afford (S)-2-methyl-N-((R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl)propane-2-sulfinamide (200 mg, 98.4%) as a yellow solid. LCMS (ESI): m/z = 391.0 $[M+H]^+$.

Step 2. Preparation of (R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethan-1-amine
To a flask of (S)-2-methyl-N-((R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl) propane-2-sulfinamide (250 mg, 0.640 mmol) was added HCl/CH_3OH (5.0 mL, 4M). The solution was stirred at 25°C for 1 h. LCMS showed the reaction was completed. Then the solution was evaporated in vacuo to give (R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethan-1-amine (207 mg, 100%) as a yellow solid. LCMS (ESI): m/z = 269.9 $[M+H-NH_3]^+$.

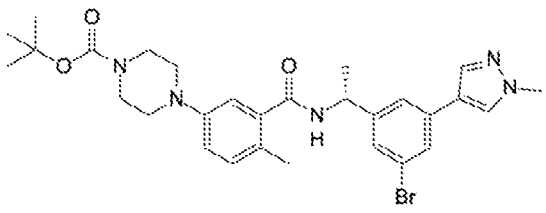
Preparation of P23: (R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide



(P23)

(R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide was prepared in a similar manner to Step 1-2 of Example 4 using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) as the starting material in Step 1 and 2-methyl-5-(4-methylpiperazin-1-yl)benzoic acid as the acid in Step 2. LCMS (ESI): m/z = 496.0 $[M+H]^+$.

Preparation of P24: tert-butyl (R)-4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylphenyl)piperazine-1-carboxylate

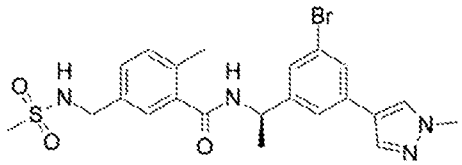


(P24)

Tert-butyl (R)-4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate was prepared in a similar manner to Step 1-2 of Example 4 using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) as the starting material in Step 1 and 5-(4-(tert-

butoxycarbonyl)piperazin-1-yl)-2-methylbenzoic acid in Step 2. LCMS (ESI): m/z = 528.0 [M+H-tBu]+; 584.2 $[M+H]^+$.

Preparation of P25: (R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

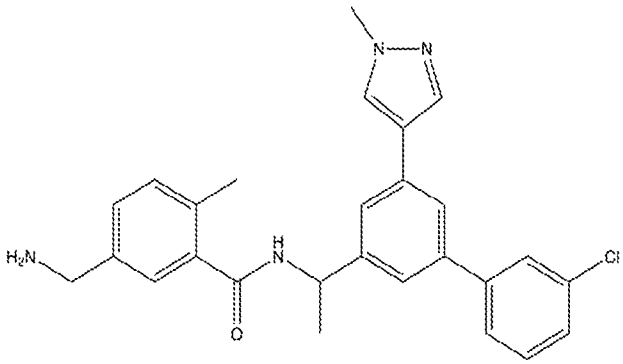


(P25)

(R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide was prepared in a similar manner to Step 1-2 of Example 4 using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) as the starting material in Step 1 and 2-methyl-5-(methylsulfonamidomethyl)benzoic acid in Step 2. LCMS (ESI): m/z = 505.0 $[M+H]^+$.

Examples

Example 1: 5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide



(1)

Step 1: Preparation of N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**) (500.0 mg, 1.21 mmol) in dioxane (20.0 mL) under N_2, were added sat. aq. Na_2CO_3 (2.0 mL), $Pd(dppf)_2Cl_2$ (88.2 mg, 0.121 mmol), and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (502 mg, 2.41 mmol) at 20 °C. The reaction mixture was stirred at 100 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. The

reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was then purified by silica gel chromatography via Biotage (20 g silica column, PE: EA= 1:0 to 0:1) to afford the crude product N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (365 mg, 72.8%) as a yellow oil. LCMS (ESI): m/z = 416 $[M+H]^+$.

Step 2: Preparation of 1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethan-1-amine

To a solution of N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (350 mg, 0.841 mmol) in MeOH (20 mL) was added HCl (3 mL, conc.) at 0 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. Then the reaction mixture was concentrated in vacuo and partitioned between EA and sat. aq. Na_2CO_3 (100/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EA (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to afford 1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethan-1-amine (262 mg) as a yellow solid. LCMS (ESI): m/z = 312 $[M+H]^+$.

Step 3: Preparation of tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To a solution of 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) (119 mg, 0.449 mmol) in DMF (10.0 mL) were added HATU (256 mg, 0.673 mmol), TEA (136 mg, 1.35 mmol), and 1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethan-1-amine (140.0mg, 0.449 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was partitioned between EA/H_2O (100/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4 , and evaporated in vacuo to afford the crude product tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (251 mg, 100%) as the yellow solid. LCMS (ESI): m/z = 559 $[M+H]^+$.

Step 4: Preparation of 5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide

To a solution of tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (250 mg, 0.447 mmol) in CH_2Cl_2 (10 mL) was added HCl (4 mL, 4M) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h. LCMS showed a mass peak of the desired product. The reaction mixture was evaporated in vacuo followed by the addition of MeOH (8 mL) and basified with $NH_3.H_2O$ (3 mL) at 0 °C. After that, the mixture was evaporated in vacuo to afford a crude. The crude was dissolved in 5 mL DMF and purified by prep-HPLC to afford 5-(aminomethyl)-*N*-(1-(3'-chloro-5-(1-methyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (39 mg, 17%) as a white solid after solvent removal and lyophilization. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.55 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.73-7.70 (m, 2H), 7.67-7.61 (m, 2H), 7.55 (s, 1H), 7.50-7.45 (m, 1H), 7.45-7.37 (m, 3H), 7.37-7.33 (m, 1H), 5.34 (q, *J*=7.0 Hz, 1H), 4.07 (s, 2H), 3.97 (s, 3H), 2.40 (s, 3H), 1.64 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 459 $[M+H]^+$.

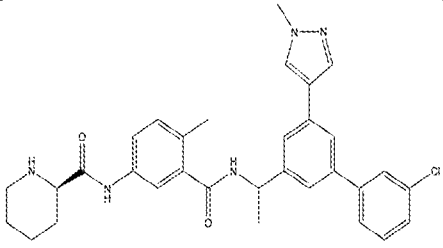
Prep-HPLC condition:

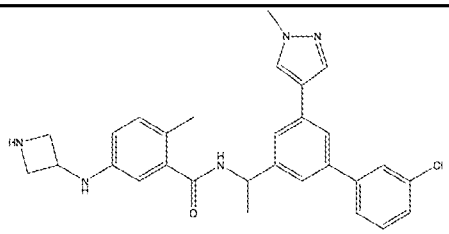
Column: C18-1 150*30mm*5μM;

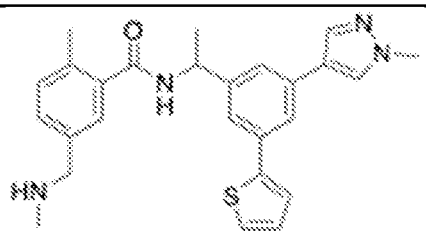
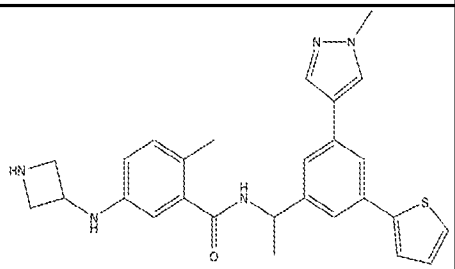
Mobile phase: water (FA)-MeCN; B%: 7%-47%,

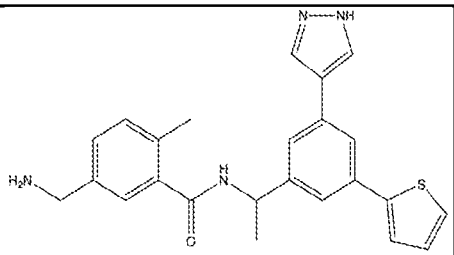
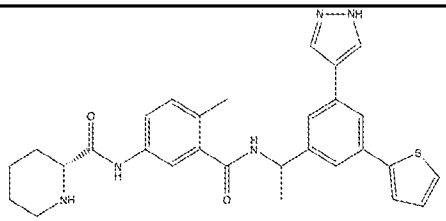
Flow Rate (mL/min): 30 mL/min

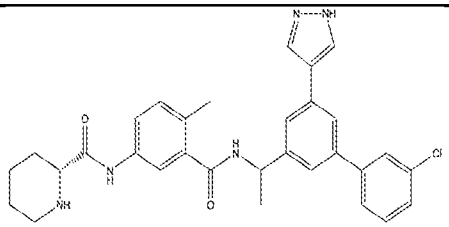
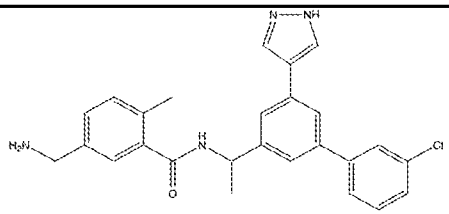
The following examples were prepared in a similar manner to the 5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**Example 1**), using an appropriate halide plus boronic acid or boronic ester (in Step 1) and an appropriate carboxylic acid (in Step 3).

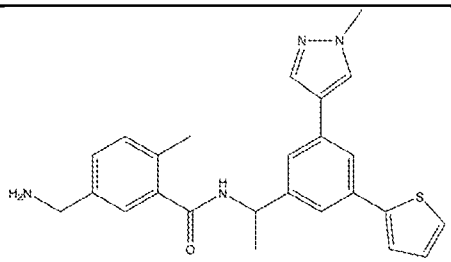
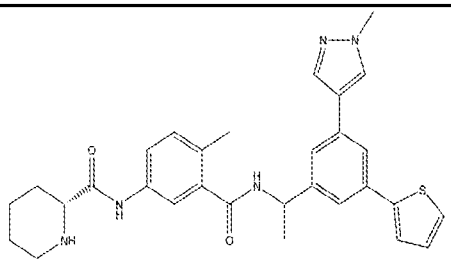
Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
2	 (R)-N-(3-(((RS)-1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-	Example 1, Step 1-2; Then Example 1, Step 3, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.56 (s, 1H), 8.10 (s, 1H), 8.01-7.94 (m, 1H), 7.75-7.68 (m, 3H), 7.68-7.61 (m, 2H), 7.57-7.37 (m, 4H), 7.25 (d, J=8.3 Hz, 1H), 5.31 (q, J=7.0 Hz, 1H), 3.97

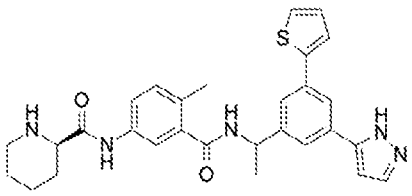
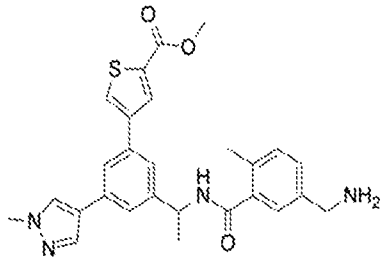
	4-methylphenyl)piperidine-2-carboxamide		(s, 3H), 3.80-3.73 (m, 1H), 3.42-3.35 (m, 1H), 3.05-2.92 (m, 1H), 2.35 (s, 3H), 2.22 (br d, J=12.6 Hz, 1H), 1.99 (br s, 1H), 1.92-1.80 (m, 1H), 1.76-1.65 (m, 3H), 1.62 (d, J=7.1 Hz, 3H). LCMS (ESI): m/z = 556 $[M+H]^+$.
3	 5-(azetidin-3-ylamino)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 1, Steps 1-2; then Example 1, Step 3, 5-((1-(tert-butoxycarbonyl)azetidin-3-yl)amino)-2-methylbenzoic acid (**P8**); then Example 1, Step 4, TFA/CH_2Cl_2	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.10-8.06 (m, 1H), 7.94-7.91 (m, 1H), 7.70 (q, J=1.8 Hz, 2H), 7.68-7.60 (m, 2H), 7.53 (s, 1H), 7.47 (t, J=7.8 Hz, 1H), 7.42-7.37 (m, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.60-6.54 (m, 2H), 5.29 (q, J=7.2 Hz, 1H), 4.40 (quin, J=7.1 Hz, 1H), 4.09-4.00 (m, 2H), 3.97 (s, 3H), 3.68 (dd, J=7.2, 9.8 Hz, 2H), 2.23 (s, 3H), 1.61 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 500 $[M+H]^+$.

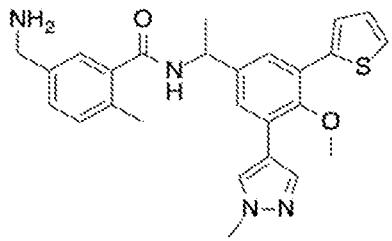
7	 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-((methylamino)methyl) benzamide	Example 1, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, 5-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-2-methylbenzoic acid (**P4**); Then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.06 (s, 1H), 7.90 (s, 1H), 7.74-7.72 (m, 1H), 7.57 (d, *J*=10.5 Hz, 2H), 7.49 (d, *J*=3.8 Hz, 1H), 7.42 (d, *J*=5.3 Hz, 1H), 7.36-7.30 (m, 2H), 7.26-7.22 (m, 1H), 7.13 (t, *J*=4.5 Hz, 1H), 5.28 (q, *J*=6.9 Hz, 1H), 3.97 (s, 3H), 3.72 (s, 2H), 2.38 (d, *J*=8.8 Hz, 6H), 1.62 (d, *J*=7.3 Hz, 3H). LCMS (ESI): m/z = 445 $[M+H]^+$.
8	 5-(azetidin-3-ylamino)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide	Example 1, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, 5-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)amino)-2-methylbenzoic acid (**P8**); Then Example 1, Step 4, TFA/CH_2Cl_2	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.06 (s, 1H), 7.90 (s, 1H), 7.75-7.69 (m, 1H), 7.58-7.46 (m, 3H), 7.42 (d, *J*=5.3 Hz, 1H), 7.14 (t, *J*=4.6 Hz, 1H), 7.04 (d, *J*=8.3 Hz, 1H), 6.61-6.53 (m, 2H), 5.29-5.00 (m, 1H), 4.42 (quin, *J*=7.0 Hz, 1H), 4.14-4.06 (m, 2H), 3.97 (s, 3H), 3.76-3.67 (m, 2H), 2.24 (s, 3H), 1.60 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 472 $[M+H]^+$.

9	 N-(1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide	Example 1, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**) and 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**); then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.06 (s, 2H), 7.77 (s, 1H), 7.60-7.57 (m, 2H), 7.50 (d, *J*=3.8 Hz, 1H), 7.42 (d, *J*=5.2 Hz, 1H), 7.36 (s, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.25 (d, *J*=7.5 Hz, 1H), 7.14 (t, *J*=4.5 Hz, 1H), 5.29 (q, *J*=7.0 Hz, 1H), 3.83 (s, 2H), 2.37 (s, 3H), 1.63 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 417 $[M+H]^+$.
10	 (R)-N-(3-(((RS)-1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	Example 1, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**) and 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.09 (s, 2H), 7.77 (s, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.60 (s, 1H), 7.57 (s, 1H), 7.52-7.41 (m, 2H), 7.25 (d, J=8.4 Hz, 1H), 7.14 (t, J=4.5 Hz, 1H), 5.28 (q, J=7.0 Hz, 1H), 3.76-3.71 (m, 1H), 3.38 (br s, 1H), 3.01-2.91 (m, 1H), 2.35 (s, 3H), 2.20 (br d, J=11.6 Hz, 1H), 1.98 (br d, J=6.9 Hz, 1H), 1.88-1.80 (m, 1H), 1.77-1.64 (m, 3H), 1.61 (d, J=7.0 Hz, 3H).

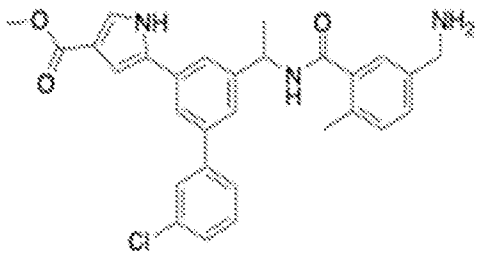
			LCMS (ESI): m/z = 514, $[M+H]^+$.
11	 (R)-N-(3-(((RS)-1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	Example 1, Step 1, N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**) and 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid **(P5)**; then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm) = 8.11 (br s, 2H), 7.76-7.63 (m, 5H), 7.55-7.37 (m, 4H), 7.23 (d, J=7.9 Hz, 1H), 5.31 (q, J=7.0 Hz, 1H), 3.48 (dd, J=3.0, 10.7 Hz, 1H), 3.20 (br d, J=12.8 Hz, 1H), 2.81-2.72 (m, 1H), 2.34 (s, 3H), 2.08-1.98 (m, 1H), 1.93 (br s, 1H), 1.71 (br d, J=9.9 Hz, 1H), 1.63 (d, J=7.0 Hz, 3H), 1.61-1.52 (m, 3H). LCMS (ESI): m/z = 542 $[M+H]^+$.
18	 (R)-5-(aminomethyl)-N-(1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 1, Step 3, 1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethan-1-amine (as prepared in Example 11); then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.09 (s, 2H), 7.80-7.61 (m, 4H), 7.55 (s, 1H), 7.50-7.31 (m, 4H), 7.29-7.21 (m, 1H), 5.33 (q, J=6.8 Hz, 1H), 3.83 (s, 2H), 2.37 (s, 3H), 1.64 (d, J=7.1 Hz, 3H). LCMS (ESI): m/z = 445 $[M+H]^+$.

19	 5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide	Example 1, Step 3, 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine (as prepared in Example 7) and 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**); then Example 1, Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.06 (s, 1H), 7.90 (s, 1H), 7.73 (s, 1H), 7.57 (d, J=10.5 Hz, 2H), 7.49 (d, J=3.8 Hz, 1H), 7.41 (d, J=5.2 Hz, 1H), 7.37-7.32 (m, 2H), 7.27-7.23 (m, 1H), 7.13 (t, J=4.5 Hz, 1H), 5.28 (q, J=7.0 Hz, 1H), 3.97 (s, 3H), 3.83 (s, 2H), 2.37 (s, 3H), 1.62 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 431 $[M+H]^+$.
20	 (R)-N-(4-methyl-3-(((RS)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide	Example 1 step 3, 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine (as prepared in Example 7) and (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 1 Step 4	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.07 (s, 1H), 7.97-7.92 (m, 1H), 7.76-7.68 (m, 2H), 7.56 (s, 2H), 7.53-7.44 (m, 2H), 7.42 (dd, J=1.0, 5.1 Hz, 1H), 7.25 (d, J=8.3 Hz, 1H), 7.14 (t, J=4.7 Hz, 1H), 5.27 (q, J=7.1 Hz, 1H), 3.97 (s, 3H), 3.81-3.75 (m, 1H), 3.42-3.36 (m, 1H), 3.06-2.93 (m, 1H), 2.35 (s, 3H), 2.23 (br d, J=11.6 Hz, 1H), 2.00 (br s, 1H), 1.91-1.81

			(m, 1H), 1.77-1.64 (m, 3H), 1.64-1.55 (m, 3H). LCMS (ESI): m/z = 528 $[M+H]^+$.
32	 (2*R*)-*N*-(3-((1-(3-(1*H*-pyrazol-5-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	Example 1, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**) and 1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 1, Step 2; then Example 1, Step 3, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 1, Step 4	^{1}H NMR (400 MHz, CD_3OD, 298 K) δ (ppm) = 8.10-7.89 (m, 1H), 7.80-7.59 (m, 4H), 7.55-7.47 (m, 2H), 7.45-7.35 (m, 1H), 7.22 (d, J=8.3 Hz, 1H), 7.15 (dd, J=3.6, 5.0 Hz, 1H), 6.83-6.73 (m, 1H), 5.37-5.25 (m, 1H), 3.41-3.34 (m, 1H), 3.23-3.04 (m, 1H), 2.77-2.59 (m, 1H), 2.32 (s, 3H), 2.04-1.87 (m, 2H), 1.62 (d, J=6.8 Hz, 3H), 1.60-1.42 (m, 4H). LCMS (ESI): m/z = 514.3 $[M+H]^+$.
39	 methyl 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-	Example 1, Step 1, *N*-(1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**) and methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate;	^{1}H NMR (400 MHz, DMSO-d_6) *δ (ppm)* = 8.69 (d, *J*=8.4 Hz, 1H), 8.31 (d, *J*=2.0 Hz, 2H), 8.25 (s, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.31 (s, 1H), 7.27 (dd, *J*=1.4, 7.8 Hz, 1H), 7.21-7.14 (m, 1H), 5.30-5.09 (m, 1H),

	yl)phenyl)thiophene-2-carboxylate	then Example 1, Step 2; then Example 1, Step 3; then Example 1, Step 4, CH_2Cl_2/TFA.	3.91-3.82 (m, 6H), 3.71 (s, 2H), 2.25 (s, 3H), 1.48 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 489.3 $[M+H]^+$.
42	 5-(aminomethyl)-*N*-(1-(4-methoxy-3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methylbenzamide	Example 1, Step 1, *N*-(1-(3-bromo-4-methoxy-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P11**) and thiophen-2-ylboronic acid; then Example 1, Step 2, HCl/CH_2Cl_2, 20 °C, 0.5 hour; then Example 1, Step 3; then Example 1, Step 4.	^{1}H NMR (400 MHz, CHLOROFORM-d) δ (ppm) = 7.90 (d, *J*=7.3 Hz, 2H), 7.54-7.47 (m, 2H), 7.43 (d, *J*=2.2 Hz, 1H), 7.40-7.34 (m, 2H), 7.24 (d, *J*=1.5 Hz, 1H), 7.21-7.16 (m, 1H), 7.12 (dd, *J*=3.7, 5.1 Hz, 1H), 6.15 (br d, *J*=7.7 Hz, 1H), 5.40-5.27 (m, 1H), 3.98 (s, 3H), 3.85 (s, 2H), 3.50 (s, 3H), 2.44 (s, 3H), 1.64 (d, *J*=6.8 Hz, 3H). LCMS (ESI): m/z = 461.3 $[M+H]^+$

Example 4: methyl 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1H-pyrrole-3-carboxylate



(4)

Step 1. Preparation of 1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethan-1-amine

To a solution of *N*-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**) (300.0 mg, 0.723 mmol) in MeOH (15 mL) was added HCl (3 mL, conc.). The

reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was evaporated in vacuo then partitioned between EA/sat. aq. Na_2CO_3 (50/20 mL). The organic layer was separated, and the aqueous layer was re-extracted with EA (20 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford 1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethan-1-amine (150 mg, 66.8%) as a yellow solid, which was used directly without further purification.

Step 2. Preparation of *tert*-butyl (3-((1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To the solution of 1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethan-1-amine (180.0 mg, 0.579 mmol) in DMF (5 mL) were added 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) (161 mg, 0.608 mmol), HATU (264 mg, 0.695 mmol), and DIPEA (225 mg, 1.74 mmol). The reaction was stirred at 25 °C for 12 hours. The mixture was suspended in 50 mL H_2O then extracted with EA (20 mL x 3). The organic extract was dried by Na_2SO_4, filtered, and concentrated in vacuo to produce a crude product, which was purified by silica gel chromatography (PE: EA=100:0 to 80:20) to give *tert*-butyl (3-((1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (180 mg, 55.7%) as a white solid. LCMS (ESI): m/z = 581.0 $[M+Na]^+$

Step 3. Preparation of methyl 5-(5-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1*H*-pyrrole-3-carboxylate

To a solution of *tert*-butyl (3-((1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (150.0 mg 0.269 mmol) in 1,4-dioxane (7.0 mL) were added sat. aq. Na_2CO_3 (1.0 mL), $Pd(dppf)_2Cl_2$ (19.7 mg, 0.0269 mmol), and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (67.5 mg, 0.269 mmol). The reaction mixture was stirred at 100 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. H_2O (20 mL) was added to the reaction, and the mixture was extracted with EA (20 mL x 3). The organic layer was dried by Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel chromatography (PE: EA= 1:0 to 0:1) to afford methyl 5-(5-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1*H*-pyrrole-3-carboxylate (45 mg, 28%) as a yellow solid. LCMS (ESI): m/z = 502.2 $[M+H\text{-}Boc]^+$, 624.1 $[M+Na]^+$.

Step 4. Preparation of methyl 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1*H*-pyrrole-3-carboxylate

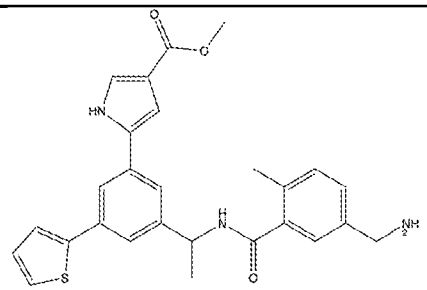
To the flask of methyl 5-(5-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido) ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1*H*-pyrrole-3-carboxylate (40 mg, 0.066 mmol) was added 4M HCl/CH_3OH (5 mL). The solution was stirred at 25 °C for 1 hour. Then the solution was concentrated to get a crude product. The crude product was dissolved in CH_3OH (2 mL) and purified by prep-HPLC to afford methyl 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1*H*-pyrrole-3-carboxylate (7.93 mg, 24%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, MeOD-d_4, 296 K) δ (ppm) = 7.81-7.77 (m, 1H), 7.76-7.71 (m, 2H), 7.68-7.64 (m, 1H), 7.60-7.56 (m, 1H), 7.53-7.49 (m, 1H), 7.49-7.45 (m, 1H), 7.42-7.37 (m, 2H), 7.36-7.31 (m, 1H), 7.28-7.24 (m, 1H), 7.01-6.99 (m, 1H), 5.36-5.30 (m, 1H), 3.86-3.85 (s, 2H), 3.84-3.82 (s, 3H), 2.37 (s, 3H), 1.65 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 502.2 $[M+H]^+$.

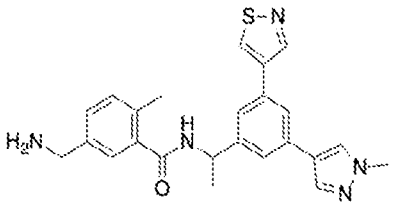
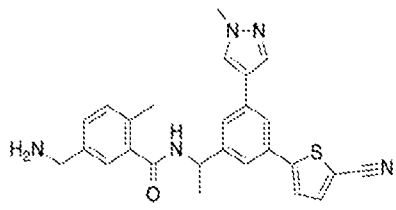
Prep-HPLC Method:

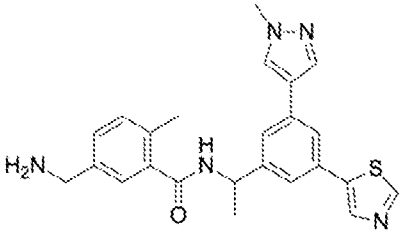
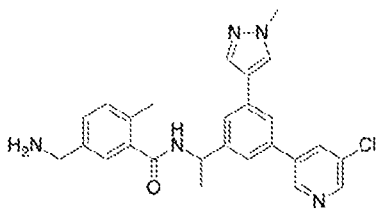
Mobile phase: A: water (0.05% ammonium hydroxide v/v); B: MeCN
Column: C18 150*30mm*5μm
Flow rate: 30 mL/min
Monitor wavelength: 220&254 nm
Gradient B% 41% to 81%, 9min; 100% B, 2 min

Further examples

The following examples were prepared in a similar manner to the 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1H-pyrrole-3-carboxylate (**Example 4**) using an appropriate sulfinamide (Step 1), an appropriate carboxylic acid (Step 2), and an appropriate boronic acid or boronic ester (Step 3).

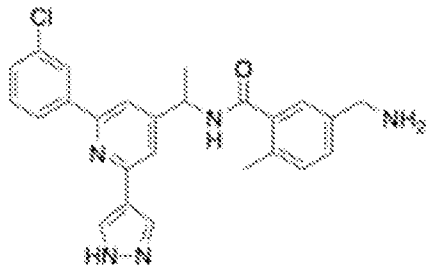
Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
22		Example 4, Step 1, N-(1-(3-bromo-5-(thiophen-2-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P7**);	^{1}H NMR (400 MHz, CD3OD, 297 K) δ (ppm) = 7.85-7.77 (m, 1H), 7.66-7.57 (m, 2H), 7.54-7.49 (m, 2H), 7.46-7.41 (m, 1H),

	methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(thiophen-2-yl)phenyl)-1H-pyrrole-3-carboxylate	then Example 4, Step 2, 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**); then Example 4, Step 3, methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate; then Example 4, Step 4	7.38-7.32 (m, 2H), 7.29-7.21 (m, 1H), 7.18-7.10 (m, 1H), 6.98 (d, J=1.5 Hz, 1H), 5.34-5.21 (m, 1H), 3.84-3.83 (m, 3H), 3.83-3.81 (m, 2H), 2.39-2.36 (m, 3H), 1.65-1.62 (m, 3H). LCMS (ESI): m/z = 474.3, $[M+H]^+$.
37	 5-(aminomethyl)-*N*-(1-(3-(isothiazol-4-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 4, Step 1, N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**); then Example 4, Step 2, 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**); then Example 4, Step 3, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole; then Example 4, Step 4	^{1}H NMR (400MHz, MeOD-d_4) δ (ppm) = 9.06 (s, 1H), 8.85 (s, 1H), 7.96 (s, 1H), 7.82 (s, 1H), 7.72 (t, *J*=1.6 Hz, 1H), 7.54-7.49 (m, 2H), 7.25-7.18 (m, 2H), 7.12 (d, *J*=7.8 Hz, 1H), 5.18 (q, *J*=7.0 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 2H), 2.23 (s, 3H), 1.51 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 432.3 $[M+H]^+$.
43	 5-(aminomethyl)-*N*-(1-(3-(5-cyanothiophen-2-yl)-5-(1-	Example 4, Step 1, N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**), using CH_2Cl_2 as solvent; then Example 4, Step 2, 5-(((tert-butoxycarbonyl)	^{1}H NMR (400MHz, MeOD-d_4) δ (ppm) = 7.98 (s, 1H), 7.82 (s, 1H), 7.71-7.64 (m, 2H), 7.57 (s, 1H), 7.51-7.46 (m, 2H), 7.26-7.20 (m, 2H), 7.13 (d, *J*=7.6 Hz, 1H), 5.17 (q, *J*=7.2 Hz,

	methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	amino)methyl)-2-methylbenzoic acid (**P3**), using CH_2Cl_2 as solvent; then Example 4, Step 3, (5-cyanothiophen-2-yl)boronic acid; then Example 4, Step 4	1H), 3.85 (s, 3H), 3.73 (s, 2H), 2.23 (s, 3H), 1.50 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 456.3 $[M+H]^+$
44	 5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl)ethyl) benzamide	Example 4, Step 1, N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**), using CH_2Cl_2 as solvent; then Example 4, Step 2, 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**), using CH_2Cl_2 as solvent; then Example 4, Step 3, 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole; then Example 4, Step 4	^{1}H NMR (400MHz, MeOD-d_4) δ (ppm) = 9.01 (s, 1H), 8.28 (s, 1H), 8.10 (s, 1H), 7.94 (s, 1H), 7.80-7.75 (m, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.38-7.30 (m, 2H), 7.25 (d, *J*=7.8 Hz, 1H), 5.29 (q, *J*=6.9 Hz, 1H), 3.97 (s, 3H), 3.83 (s, 2H), 2.36 (s, 3H), 1.62 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 432.2 $[M+H]^+$
47	 5-(aminomethyl)-N-(1-(3-(5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 4, Step 1, N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**), using CH_2Cl_2 as solvent; then Example 4, Step 2, 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**), using CH_2Cl_2 as solvent;	^{1}H NMR (400 MHz, DMSO-d_6, 350 K) δ (ppm) = 8.94 (d, J=1.8 Hz, 1H), 8.62 (d, J=2.3 Hz, 1H), 8.49-8.41 (m, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.84 (s, 1H), 7.67 (br d, J=12.2 Hz, 2H), 7.36-7.26 (m, 2H), 7.17 (d, J=7.9 Hz, 1H), 5.28 (br

		then Example 4, Step 3, (5-chloropyridin-3-yl)boronic acid; then Example 4, Step 4	t, J=7.4 Hz, 1H), 3.91 (s, 3H), 3.76 (s, 2H), 2.30 (s, 3H), 1.55 (d, J=6.9 Hz, 3H). LCMS (ESI): m/z = 460.4 $[M+H]^+$

Example 5: 5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide



(5)

Step 1. Preparation of (2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methanol

To a mixture of (2,6-dichloropyridin-4-yl)methanol (**P2**, 3000 mg, 16.85 mmol) in dioxane (60 mL) was added H_2O (6 mL), Cs_2CO_3 (11000 mg, 33.7 mmol), (3-chlorophenyl)boronic acid (2370 mg, 15.2 mmol) and, $Pd(dppf)_2Cl_2.CH_2Cl_2$ (617 mg 0.843 mmol). The mixture was stirred at 60 °C for 15 hours. LCMS showed a desired mass peak. The reaction mixture was treated with methanol and concentrated in vacuo, then extracted with EtOAc (100 mL). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a residue, which was purified by silica gel chromatography eluting with PE/EA (0-30%) to obtain (2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methanol (3.00 g, yield 70.1%) as a yellow oil. LCMS (ESI): m/z = 254.1 $[M+H]^+$.

Step 2. Preparation of 2-chloro-6-(3-chlorophenyl)isonicotinaldehyde

To a mixture of (2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methanol (3.00 g 11.81 mmol) in EtOAc (100 mL) was added MnO_2 (10.30 mg 118 mmol). The black suspension was stirred at 60 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was treated with water, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with PE/EA (0-30%) to obtain 2-chloro-6-(3-

chlorophenyl)isonicotinaldehyde (1.00 g, 33.6%) as a white solid. LCMS (ESI): m/z = 251.9 $[M+H]^+$.

Step 3. Preparation of (*E*)-*N*-((2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide

To a mixture of 2-chloro-6-(3-chlorophenyl)isonicotinaldehyde (1.00 g, 3.97 mmol) in CH_2Cl_2 (20 mL) were added K_2CO_3 (1.10 g, 7.93 mmol) and 2-methylpropane-2-sulfinamide (577 mg, 4.76 mmol). The mixture was stirred at 20 °C for 16 hours. LCMS showed that a desired mass peak was exposed. The reaction mixture was concentrated in vacuo then extracted with EtOAc (100 mL). The organic extract was washed with water (30 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by silica gel chromatography eluting with PE/EA (0-30%) to obtain (*E*)-*N*-((2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide (800 mg, 56.8%) as a yellow oil. LCMS (ESI): m/z = 376.9 $[M+Na]^+$.

Step 4. Preparation of *N*-(1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of (*E*)-*N*-((2-chloro-6-(3-chlorophenyl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide (800 mg, 2.25 mmol) in THF (20.0 mL) under N_2, was added MeMgBr (806 mg, 6.76 mmol, 3 M in THF, 2.25 mL) at 0 °C. The reaction mixture was stirred at 20 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was quenched with 6 mL sat. aq. NH_4Cl at 0 °C. The mixture was extracted with EtOAc (100 mL). The organic extract was then washed with water (30 mL), dried over Na_2SO4, filtered, concentrated in vacuo, and purified by silica gel chromatography eluting with PE/EA (0-30%) to afford *N*-(1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide (500 mg, 59.8%) as a yellow oil. LCMS (ESI): m/z = 371.2 $[M+H]^+$.

Step 5: Preparation of 1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethan-1-amine

To a stirred solution of *N*-(1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide (1.70 g, 4.58 mmol) in MeOH (20.0 mL), was added HCl (5.0 mL, conc.) at 0 °C. The reaction mixture was stirred at 20 °C for 2 hours. LCMS showed a mass peak of the desired product. The reaction mixture was concentrated in vacuo. Then MeCN was added to the residue, and the mixture was concentrated in vacuo again to in afford 1-(2-chloro-6-(3-

chlorophenyl)pyridin-4-yl)ethan-1-amine (1.60 g, 77.72%) as a white solid. LCMS (ESI): m/z = 267.2 $[M+H]^+$.

Step 6. Preparation of tert-butyl (3-((1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To a stirred solution of 1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethan-1-amine (800.0 mg, 1.78 mmol) in DMF (5.0 mL) were added HATU (1.01 g, 2.67 mmol), TEA (630 mg, 6.23 mmol) and 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**, 472 mg, 1.78 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was partitioned between EA/H_2O (100/50 mL). The organic layer was separated and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated in vacuo to afford tert-butyl (3-((1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (500 mg, 54.6%) as a yellow solid. LCMS (ESI): m/z = 536.2 $[M+Na]^+$.

Step 7. Preparation of tert-butyl (3-((1-(2-(3-chlorophenyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To a stirred solution of tert-butyl (3-((1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (250.0 mg, 0.486 mmol) in 1,4-dioxane (20.0 mL) under N_2 atmosphere was added Na_2CO_3 (155 mg, 1.46 mmol), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (135 mg, 0.486 mmol) and $Pd(dppf)_2Cl_2$ (35.6 mg, 0.0486 mmol) and H_2O (4.0 mL) at 20 °C. The reaction mixture was stirred at 100 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The crude product was purified by silica gel chromatography on a Biotage (12 g silica column, PE: EA = 1:0 to 0:1) to afford tert-butyl (3-((1-(2-(3-chlorophenyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (90 mg, 29%) as a yellow oil. LCMS (ESI): m/z = 630.4 $[M+H]^+$.

Step 8. Preparation of 5-(aminomethyl)-*N*-(1-(2-(3-chlorophenyl)-6-(1*H*-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide

To a stirred solution of tert-butyl (3-((1-(2-(3-chlorophenyl)-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (90 mg, 0.14 mmol) in

MeOH (20.0 mL) was added HCl (3.0 mL) at 0 °C. The mixture was stirred at 20 °C for 16 hours. LCMS showed a mass peak of the desired product. The reaction mixture was concentrated in vacuo, suspended in MeCN (10 mL) and concentrated in vacuo again. The crude product was purified by prep-HPLC and dried by lyophilization to give 5-(aminomethyl)-*N*-(1-(2-(3-chlorophenyl)-6-(1*H*-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (17.32 mg, 27%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.62 (d, J=7.1 Hz, 3H), 2.36 (s, 3H), 3.82 (s, 2H), 5.29 (q, J=7.1, 1H), 7.24 (d, J=7.8, 1H) 7.32-7.35 (m, 1H), 7.38 (d, J=1.7, 1H), 7.45-749 (m, 2H), 7.68 (d, J=1.0 Hz, 1H), 7.73 (d, J=1.2 Hz, 1H), 8.03 (dt, J=7.6, 1.5 Hz, 1H), 8.13 (t, J=1.8, 1H), 8.26 (s, 2H). LCMS (ESI): m/z = 446.3 $[M+H]^+$.

Prep-HPLC Method:

Mobile phase: A: water (0.5% ammonium hydroxide); B: MeCN

Column: Phenomenex C18 75*30mm*3μm

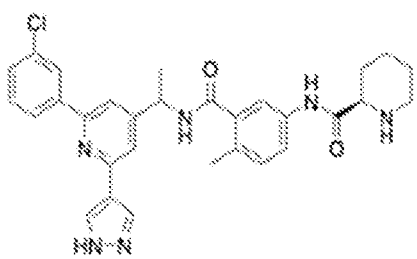
Flow rate: 60 mL/min

Monitor wavelength: 220&254 nm

Gradient B% 29% to 69%, 9min; 100% B, 2 min.

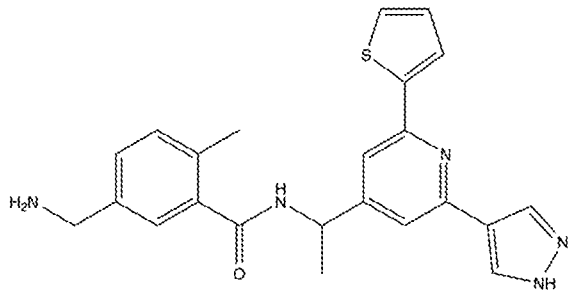
Example 6: (R)-N-(3-(((RS)-1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide

The following example was prepared in a similar manner to the 5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (in Example 5, Step 6-8), using the 1-(2-chloro-6-(3-chlorophenyl)pyridin-4-yl)ethan-1-amine, an appropriate carboxylic acid, and an appropriate boronic acid or boronic ester.

Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
6		Example 5, Step 6, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 5, Step 7 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.28-1.75 (m, 7H), 2.35 (s, 3H), 2.62-2.76 (m, 1H), 3.07-3.22 (m, 1H), 5.23-5.35 (m, 1H), 7.20-7.33 (m, 1H), 7.39-7.57 (m, 3H),

	(R)-N-(3-(((RS)-1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 5, Step 8.	7.66-7.78 (m, 1H), 7.78-7.87 (m, 1H), 8.05 (d, J=7.58 Hz, 1H), 8.16 (t, J=1.71 Hz, 1H), 8.31 (br s, 2H). LCMS (ESI): m/z = 543.4 $[M+H]^+$.

Example 12: N-(1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(aminomethyl)-2-methylbenzamid



(12)

Step 1. Preparation of (2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methanol

To a mixture of Cs_2CO_3 (5490 mg 16.9 mmol) and thiophen-2-ylboronic acid (1940 mg, 15.2 mmol) in dioxane (60.0 mL) were added H_2O (6.0 mL), (2,6-dichloropyridin-4-yl)methanol (**P2**, 3000.0 mg, 16.85 mmol), and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (617 mg, 0.843 mmol). The mixture was stirred at 75 °C for 16 hours. LCMS and TLC (PE: EA = 5:1, UV 254 nm) showed that the reaction was completed. H_2O (20 mL) was added to the mixture, and the mixture was extracted with EA (20 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to obtain (2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methanol (2100 mg, 61.3%) as a yellow oil. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.64-4.80 (m, 2H), 7.05-7.16 (m, 2H), 7.38-7.44 (m, 1H), 7.45-7.51 (m, 1H), 7.57-7.64 (m, 1H). LCMS (ESI): m/z = 226.1 $[M+H]^+$.

Step 2. Preparation of 2-chloro-6-(thiophen-2-yl)isonicotinaldehyde

To a suspension of (2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methanol (2100.0 mg, 9.305 mmol) in EtOAc (40 mL) was added MnO_2 (8090 mg, 93.0 mmol). The black suspension was stirred at 20 °C for 16 hours. LCMS showed the starting material was consumed, and a desired mass peak was observed (m/z = 225.9 $[M+H]^+$). The mixture was concentrated in vacuo, dissolved in

THF (300 mL), and then filtered. The filter cake was washed with THF (100 mL x 3). The filtrates were combined and concentrated in vacuo to give 2-chloro-6-(thiophen-2-yl)isonicotinaldehyde (1030 mg, 49.5%) as a brown solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.16-7.19 (m, 1H), 7.48-7.53 (m, 1H), 7.56-7.59 (m, 1H), 7.74-7.77 (m, 1H), 7.90-7.97 (m, 1H), 10.05-10.09 (m, 1H). LCMS (ESI): m/z = 241.9 $[M+H_2O]^+$.

Step 3. Preparation of (*E*)-*N*-((2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide

To a mixture of 2-chloro-6-(thiophen-2-yl)isonicotinaldehyde (1000.0 mg, 4.471 mmol) in CH_2Cl_2 (20.0 mL) was added 2-methylpropane-2-sulfinamide (650 mg, 5.36 mmol) and K_2CO_3 (1240 mg, 8.94 mmol). The mixture was stirred at 20 °C for 15 hours. LCMS showed that the reaction was completed. The reaction was treated with H_2O (20 mL) and then the mixture was extracted with EA (20 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography to obtain (*E*)-*N*-((2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide (1250 mg, 85.5%) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.17-1.42 (m, 9H), 7.11-7.20 (m, 1H), 7.45-7.51 (m, 1H), 7.57 (s, 1H), 7.69-7.74 (m, 1H), 7.85-7.90 (m, 1H), 8.50-8.67 (m, 1H). LCMS (ESI): m/z = 327 $[M+H]^+$.

Step 4. Preparation of *N*-(1-(2-chloro-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of (*E*)-*N*-((2-chloro-6-(thiophen-2-yl)pyridin-4-yl)methylene)-2-methylpropane-2-sulfinamide (1250 mg, 3.824 mmol) in THF (20.0 mL) under N_2, was added MeMgBr (1370 mg, 11.5 mmol, 3M in THF, 3.83 mL) at 0 °C. The reaction mixture was stirred at 20 °C under N_2 for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was quenched with 6 mL sat. aq. NH_4Cl at 0 °C. The reaction mixture was partitioned between EA/H_2O (100/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo to give a residue, which was purified by silica gel chromatography eluting with PE/EA (0-30%) to obtain *N*-(1-(2-chloro-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide (820 mg, 62.5%) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.22-1.32 (m, 9H), 1.62-1.65 (m, 3H), 4.13 (q, *J*=7.04 Hz, 1H), 7.09-

7.14 (m, 1H), 7.14-7.17 (m, 1H), 7.39-7.45 (m, 1H), 7.53-7.56 (m, 1H), 7.63-7.67 (m, 1H). LCMS (ESI): m/z = 343.2 $[M+1]^+$.

Step 5. Preparation of 2-methyl-*N*-(1-(2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)propane-2-sulfinamide

To a solution of *N*-(1-(2-chloro-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-2-methylpropane-2-sulfinamide (420.0 mg, 1.22 mmol) in 1,4-dioxane (20.0 mL) under N_2 atmosphere was added Na_2CO_3 (389 mg 3.67 mmol), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (273 mg, 0.980 mmol) and $Pd(dppf)_2Cl_2$ (89.6 mg 0.122 mmol) and H_2O (4.0 mL) at 20 °C. The reaction mixture was stirred at 100 °C under N_2 atmosphere for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by silica gel chromatography via Biotage (12 g silica column, PE: EA= 1:2) to afford the 2-methyl-*N*-(1-(2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)propane-2-sulfinamide (290 mg, 51.6%) as a yellow oil. LCMS (ESI): m/z = 459.3 $[M+H]^+$.

Step 6. Preparation of 1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethan-1-amine

To a solution of 2-methyl-*N*-(1-(2-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)propane-2-sulfinamide (290.0 mg, 0.632 mmol) in MeOH (20.0 mL) was added HCl (3.0 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1.5 hours. LCMS showed a mass peak of the desired product. The reaction mixture was concentrated in vacuo, redissolved in MeCN, and concentrated again to give 1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethan-1-amine (200 mg, 92.1%) as a yellow solid. The product was used for the next step without further purification. LCMS (ESI): m/z = 271.0 $[M+H]^+$.

Step 7. Preparation of *tert*-butyl (3-((1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To a solution of 1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethan-1-amine (100 mg, 0.291 mmol) in DMF (5 mL) were added HATU (166 mg, 0.437 mmol), TEA (103 mg, 1.02 mmol), and 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**) (77.3 mg, 0.291 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed that the desired product was formed. The reaction mixture was partitioned between EA/H_2O (100 mL/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with EtOAc (50

ml). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated in vacuo to afford the crude *tert*-butyl (3-((1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (50 mg, 33%) as a yellow solid. LCMS (ESI): m/z = 518.1 $[M+H]^+$.

Step 8. Preparation of N-(1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(aminomethyl)-2-methylbenzamide

To a solution of *tert*-butyl (3-((1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (50 mg, 0.097 mmol) in MeOH (20.0 mL) was added HCl (3.0 mL, conc.) at 0 °C . The reaction mixture was stirred at 20 °C for 1.5 hours. LCMS showed the desired product. The reaction mixture was evaporated in vacuo. The mixture was treated with MeCN and then evaporated in vacuo. The crude product was purified by prep-HPLC and dried by lyophiliztion to afford the N-(1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(aminomethyl)-2-methylbenzamide (10.19 mg, 25%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.58-1.74 (m, 3H), 2.38 (s, 3H), 3.76-3.89 (m, 2H), 5.19-5.33 (m, 1H), 7.14-7.18 (m, 1H), 7.24-7.28 (m, 1H), 7.32-7.37 (m, 1H), 7.38-7.41 (m, 1H), 7.49-7.53 (m, 1H), 7.54-7.58 (m, 1H), 7.63-7.68 (m, 1H), 7.74 (dd, *J*=3.67, 1.10 Hz, 1H), 8.19-8.27 (m, 2H). LCMS (ESI): m/z = 418.2 $[M+H]^+$.

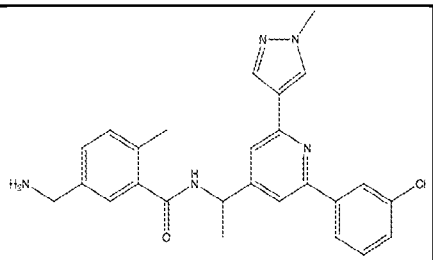
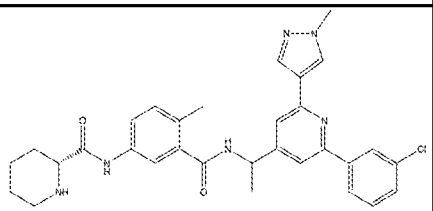
Prep-HPLC Method:

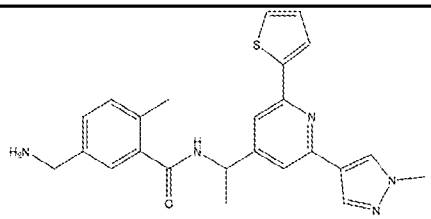
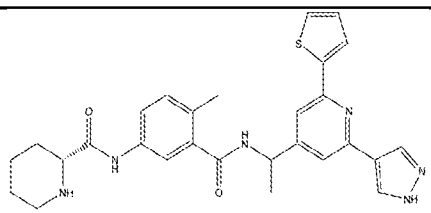
Mobile phase: A: water (0.5% ammonium hydroxide); B: MeCN
Column: Boston Prime C18 150*30mm*5μm
Flow rate: 30 mL/min
Monitor wavelength: 220&254 nm
Gradient: B%, 29% to 59%, 8min, 100% B 3 min.

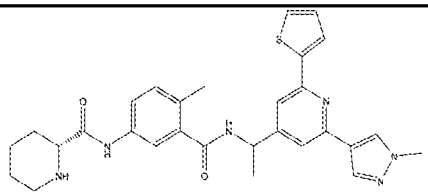
Further examples

The following examples were prepared in a similar manner to Example 12, Steps 1-8, using an appropriate boronic acid or boronic ester in step 1, an appropriate boronic acid or boronic ester in step 5, and an appropriate carboxylic acid in step 7.

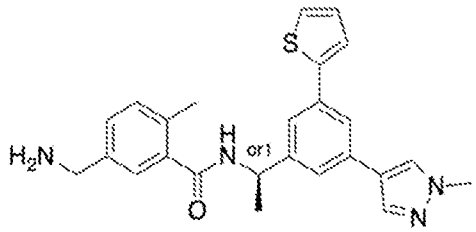
Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data

13	 5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide	Example 12, Step 1, (3-chlorophenyl)boronic acid; Then Example 12, Steps 2-4; then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole; then Example 12, Step 6-8	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.57-1.70 (m, 3H), 2.29-2.42 (m, 3H), 3.79-3.90 (m, 2H), 3.93-4.09 (m, 3H), 5.23-5.37 (m, 1H), 7.24-7.29 (m, 1H), 7.33-7.41 (m, 2H), 7.43-7.54 (m, 2H), 7.60-7.69 (m, 1H), 7.70-7.77 (m, 1H), 8.00-8.07 (m, 1H), 8.08-8.15 (m, 1H), 8.08-8.12 (m, 1H), 8.13-8.19 (m, 1H), 8.23-8.34 (m, 1H). LCMS (ESI): m/z = 460.4 [M+H]+.
14	 (R)-N-(3-(((RS)-1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	Example 12, Step 1, (3-chlorophenyl)boronic acid; Then Example 12, Step 2-4; then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole; then Example 12, Step 6; then Example 12, Step 7, (*R*)-5-(1-(*tert*-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**);	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.60-1.67 (m, 3H), 1.69-1.84 (m, 3H), 1.88-2.07 (m, 2H), 2.22-2.39 (m, 1H), 2.26-2.33 (m, 1H), 2.31-2.33 (m, 1H), 2.33-2.40 (m, 1H), 2.34-2.39 (m, 1H), 2.36 (s, 1H), 2.34-2.39 (m, 1H), 3.06-3.18 (m, 1H), 3.41-3.53 (m, 1H), 3.87-3.98 (m, 1H), 3.95 (dd, J=11.76, 2.63 Hz, 1H), 4.02 (s, 2H), 5.23-

		then Example 12, Step 8	5.39 (m, 1H), 7.21-7.34 (m, 1H), 7.46-7.63 (m, 3H), 7.72-7.87 (m, 3H), 7.97-8.07 (m, 1H), 8.08-8.17 (m, 1H), 8.17-8.28 (m, 1H), 8.32-8.43 (m, 1H), 9.02-9.12 (m, 1H). LCMS (ESI): m/z = 557.4 $[M+H]^+$.
15	 5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide	Example 12, Step 1-4; Then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Then Example 12, Steps 6-8	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.62 (d, J=7.04 Hz, 3H), 2.32-2.44 (m, 3H), 3.79-3.88 (m, 2H), 3.93-4.06 (m, 3H), 5.18-5.33 (m, 1H), 7.14-7.17 (m, 1H), 7.23-7.28 (m, 1H), 7.33-7.41 (m, 2H), 7.50-7.54 (m, 2H), 7.62-7.68 (m, 1H), 7.71-7.76 (m, 1H), 8.03-8.09 (m, 1H), 8.20-8.26 (m, 1H). LCMS (ESI): m/z = 432.3 $[M+H]^+$.
16		Example 12, Step 1-6; then Example 12, Step 7, (*R*)-5-(1-(*tert*-butoxycarbonyl)piperidine-2-carboxamido)-2-	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.44-1.68 (m, 7H), 1.89-2.01 (m, 2H), 2.31-2.40 (m, 3H), 2.62-2.77 (m, 1H), 3.07-3.20 (m, 1H),

	(*R*)-*N*-(3-(((*RS*)-1-(2-(1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide	methylbenzoic acid (**P5**); then Example 12, Step 8	3.36-3.41 (m, 1H), 5.16-5.34 (m, 1H), 7.14-7.19 (m, 1H), 7.22-7.26 (m, 1H), 7.41-7.47 (m, 1H), 7.50-7.53 (m, 1H), 7.55-7.59 (m, 1H), 7.64-7.67 (m, 1H), 7.74-7.79 (m, 1H), 7.80-7.85 (m, 1H), 8.22-8.32 (m, 2H). LCMS (ESI): m/z = 515.3, $[M+H]^+$.
17	 (*R*)-*N*-(4-methyl-3-(((*RS*)-1-(2-(1-methyl-1*H*-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide	Example 12, Step 1-4; then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole; then Example 12, Step 6; then Example 12, Step 7, (*R*)-5-(1-(*tert*-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**); then Example 12, Step 8	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 1.46-1.75 (m, 7H), 1.90-2.00 (m, 2H), 2.28-2.45 (m, 3H), 2.65-2.76 (m, 1H), 3.13 (br d, *J*=12.76 Hz, 1H), 3.33 (s, 1H), 3.90-4.09 (m, 3H), 5.17-5.28 (m, 1H), 7.14-7.17 (m, 1H), 7.21-7.26 (m, 1H), 7.42-7.47 (m, 1H), 7.50-7.54 (m, 2H), 7.64-7.67 (m, 1H), 7.75-7.77 (m, 1H), 7.79-7.83 (m, 1H), 8.07-8.11 (m, 1H), 8.24 (s, 1H). LCMS (ESI): m/z = 529.3 $[M+H]^+$.

Example 23: *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1



(23)

Step 1. Preparation of *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-1 and *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-2

1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine (prepared in Example 7) (900 mg, 3.18 mmol) was sent for chiral separation by SFC. After SFC separation, the organic solvent was evaporated, and the products were lyophilized to afford *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-1 (305 mg, 33.9% yield, the first eluted peak) and *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-2 (310 mg, 34.4% yield, the second eluted peak) as yellow oils.

SFC condition:

Column: REGIS(S,S) WHELK-O1(250mm*25mm,10μm);

Mobile phase: 0.1% $NH_3.H_2O$ ETOH; B%: 50%-50%,

Flow Raye (mL/min): 30 mL/min .

Step 2. Preparation of *rel-tert*-butyl (*R*)-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)benzyl)carbamate, ENT-1

To a solution of 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**, 93.6 mg, 0.353 mmol) in DMF (10.0 mL) was added HATU (201 mg, 0.529 mmol), TEA (107 mg, 1.06 mmol), and *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-1 (100.0 mg, 0.353 mmol) at 20°C. The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was partitioned between ethyl acetate/H_2O (50/50 mL), the organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford crude *rel-tert*-butyl (*R*)-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-

yl)phenyl)ethyl)carbamoyl)benzyl)carbamate, ENT-1 (187 mg, 99.9%) as the yellow solid, which was used in subsequent steps without further purification.. LCMS (ESI): m/z = 475.1 $[M\text{-}tBu]^+$.

Step 3. Preparation of *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1

To a solution of *rel-tert*-butyl (*R*)-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)benzyl)carbamate, ENT-1 (180 mg, 0.339 mmol) in DCM (20 mL) was added HCl (5 mL, 4 M) at 20°C. The reaction mixture was stirred at 20 °C for 1 hour. The reaction mixture was evaporated in vacuo to afford a crude. The crude was then dissolved in MeOH (8 mL) and basified with 3 mL $NH_3.H_2O$ at 0°C. The mixture was evaporated in vacuo again then dissolved in 5 mL DMF and purified by prep-HPLC to afford *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1(34 mg, 23%) as a yellow solid after solvent evaporation and lyophilization ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.06 (s, 1H), 7.90 (s, 1H), 7.73 (s, 1H), 7.58 (s, 1H), 7.55 (s, 1H), 7.49 (d, *J*=3.9 Hz, 1H), 7.42 (d, *J*=5.2 Hz, 1H), 7.36 (s, 1H), 7.35 (d, *J*=8.5 Hz, 1H), 7.25 (d, *J*=7.5 Hz, 1H), 7.14 (t, *J*=4.5 Hz, 1H), 5.28 (q, *J*=7.1 Hz, 1H), 3.97 (s, 3H), 3.85 (s, 2H), 2.36 (s, 3H), 1.62 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 431.3 $[M+H]^+$.

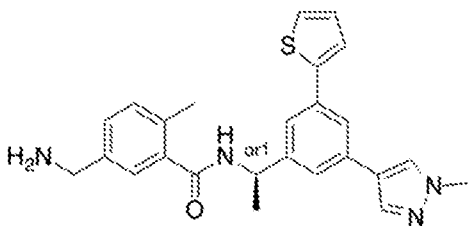
Prep-HPLC condition:

Column: C18-1 150*30mm*5μm;

Mobile phase: water (ammonium hydroxide)-ACN; B%: 26%-66%,

Flow Rate (mL/min): 30 mL/min.

Example 24: *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-2

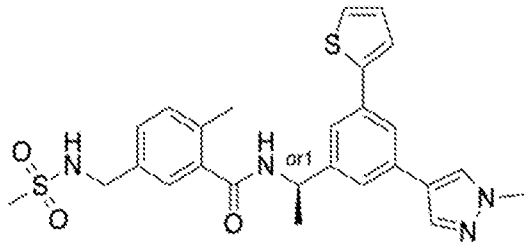


(24)

rel-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-2 (**24**) was prepared following the same procedures in Step 2 and Step 3 of **Example 23** using *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-

yl)phenyl)ethan-1-amine, ENT-2 in the place of *rel*-(*R*)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-1 (Example 23, Step 1).

Example 25: *rel*-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1



(25)

Step 1. Preparation of *rel*-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1

To a solution of *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1 (**23**) (152.0 mg, 0.353 mmol) in THF (15 mL) at 0 °C was added TEA (107 mg, 1.06 mmol) and Ms_2O (92.2 mg, 0.530 mmol). The reaction mixture was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product. The reaction mixture was then partitioned between ethyl acetate/H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, evaporated in vacuo. The residue was dissolved in 5 mL DMF and purified by prep-HPLC to afford *rel*-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1 (**25**) (38 mg, 21%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.07 (s, 1H), 7.92 (s, 1H), 7.77-7.70 (m, 1H), 7.60-7.48 (m, 3H), 7.45-7.34 (m, 3H), 7.26 (d, *J*=7.8 Hz, 1H), 7.14 (t, *J*=4.7 Hz, 1H), 5.28 (q, *J*=7.0 Hz, 1H), 4.26 (s, 2H), 3.97 (s, 3H), 2.89 (s, 3H), 2.37 (s, 3H), 1.61 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 509.2 $[M+H]^+$.

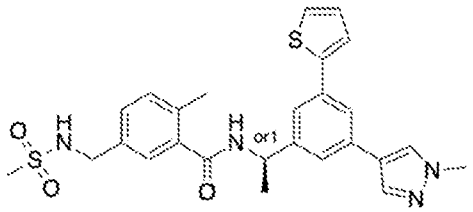
Prep-HPLC condition:

Column: Boston Prime C18 150*30mm*5μm;

Mobile phase: water (FA)-ACN; B%: 20%-60%,

Flow Rate (mL/min): 30 mL/min.

Example 26: *rel*-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-2

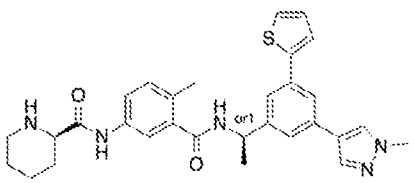


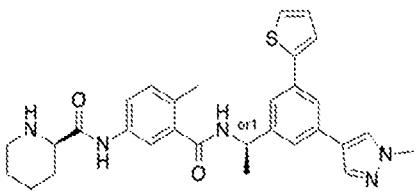
(26)

rel-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-2 (**26**) was synthesized following a similar procedure that was used to make *rel*-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1 (**25**) starting from *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-2 instead of the *rel*-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1. ^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.07 (s, 1H), 7.92 (s, 1H), 7.77-7.70 (m, 1H), 7.60-7.48 (m, 3H), 7.45-7.34 (m, 3H), 7.26 (d, *J*=7.8 Hz, 1H), 7.14 (t, *J*=4.7 Hz, 1H), 5.28 (q, *J*=7.0 Hz, 1H), 4.26 (s, 2H), 3.97 (s, 3H), 2.89 (s, 3H), 2.37 (s, 3H), 1.61 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 509.1 $[M+H]^+$.

Further examples

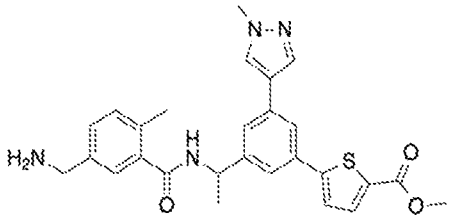
The following examples were prepared in a similar manner to the preparation of **Example 23**, Step 2-3 using the (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (P5) and a chiral amine – prepared in Example 23, Step 1.

Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
27	 (R)-N-(4-methyl-3-(((R*)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-	Example 23, Step 2, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**) and rel-(R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.56 (br s, 1H), 8.07 (s, 1H), 7.96-7.93 (m, 1H), 7.72 (d, J=4.8 Hz, 2H), 7.58-7.40 (m, 5H), 7.25 (d,

	(thiophen-2-yl)phenyl)ethyl)carbamoyl) phenyl)piperidine-2-carboxamide, ENT-1	(thiophen-2-yl)phenyl)ethan-1-amine, ENT-1 (Example 23, Step 1); Then Example 23, Step 3.	J=7.9 Hz, 1H), 7.14 (t, J=4.7 Hz, 1H), 5.27 (q, J=7.0 Hz, 1H), 3.97 (s, 3H), 3.81-3.71 (m, 1H), 3.41-3.35 (m, 1H), 3.08-2.83 (m, 2H), 2.35 (s, 3H), 2.23 (br d, J=12.0 Hz, 1H), 1.99 (br d, J=6.1 Hz, 1H), 1.92-1.82 (m, 1H), 1.79-1.63 (m, 3H), 1.61 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 528.3 $[M+ H]^+$.
28	 (R)-N-(4-methyl-3-(((R*)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2	Example 23, Step 2, (R)-5-(1-(tert-butoxycarbonyl)piperidine-2-carboxamido)-2-methylbenzoic acid (**P5**) and rel-(R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine, ENT-2 (Example 23, Step 1); then Example 23, Step 3.	^{1}H NMR (400 MHz, MeOD-d_4) δ ppm 8.08 (s, 1H), 7.93 (s, 1H), 7.72 (d, J=7.6 Hz, 2H), 7.56 (br d, J=6.1 Hz, 2H), 7.53-7.40 (m, 3H), 7.22 (d, J=8.4 Hz, 1H), 7.13 (t, J=4.6 Hz, 1H), 5.26 (q, J=6.6 Hz, 1H), 3.97 (s, 3H), 3.43-3.35 (m, 1H), 3.15 (br d, J=12.8 Hz, 1H), 2.71 (br t, J=12.0 Hz, 1H), 2.34 (s, 3H), 1.98 (br d, J=8.9 Hz,

			1H), 1.91 (br s, 1H), 1.69-1.47 (m, 7H). LCMS (ESI): m/z = 528.3 $[M+H]^+$.

Example 29: methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate



(**29**)

Step 1. Preparation of methyl 5-(3-(1-((*tert*-butylsulfinyl)amino)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate

To a solution of *N*-(1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**) (1430.0mg, 3.73 mmol) and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (1000 mg, 3.729 mmol) in 1,4-dioxane (30.0 mL) were added $Pd(dppf)_2Cl_2$ (273 mg, 0.373 mmol) and sat. aq. Na_2CO_3 (6 mL) at 20 °C. The reaction mixture was stirred at 100 °C for 15 hours then filtered. The filtrate was evaporated in vacuo and purified by silica gel chromatography via a Biotage (40 g silicon column, PE: EA= 1:0 to 0:1) to afford methyl 5-(3-(1-((*tert*-butylsulfinyl)amino)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (1400 mg, 84.2%) as a yellow oil. LCMS (ESI): m/z = 446.2 $[M+H]^+$.

Step 2. Preparation of methyl 5-(3-(1-aminoethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate

To solution of methyl 5-(3-(1-((*tert*-butylsulfinyl)amino)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (1400.0 mg, 3.142 mmol) in CH_2Cl_2 (20 mL) was slowly added 4M HCl/dixoane (10.0 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1 hour. The mixture was evaporated in vacuo then added $NH_3.H_2O$ (3 mL) to pH=8. The reaction mixture was partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (50 mL). The combined

organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford methyl 5-(3-(1-aminoethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (1050 mg, 97.9%) as an orange solid. LCMS (ESI): m/z = 325.1 $[M+H-NH_3]^+$.

Step 3. Preparation of methyl 5-(3-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate

To a solution of methyl 5-(3-(1-aminoethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (1000.0 mg, 2.929 mmol) and 5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**, 777 mg, 2.93 mmol) in DMF (20.0 mL) was added DIEA (1250 mg, 9.67 mmol), followed by HATU (1840 mg, 4.83 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 hours. The reaction mixture was partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford methyl 5-(3-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (1530 mg, 88.7%) as a yellow oil. LCMS (ESI): m/z = 533.2 $[M+H-tBu]^+$.

Step 4. Preparation of methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate

To solution of methyl 5-(3-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (100 mg, 0.170 mmol) in CH_2Cl_2 (20 mL) was slowly added HCl in 1,4-dioxane (4M, 20 mL) at 0°C. The reaction mixture was stirred at 20 °C for 1 hour. The mixture was then evaporated in vacuo and purified via prep-HPLC to afford methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (25 mg, 30%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm) = 7.96 (s, 1H), 7.80 (s, 1H), 7.68 (d, *J*=3.9 Hz, 1H), 7.67 (t, *J*=1.6 Hz, 1H), 7.52 (s, 1H), 7.50 (d, *J*=1.4 Hz, 1H), 7.42 (d, *J*=3.9 Hz, 1H), 7.25 (s, 1H), 7.22 (d, *J*=8.5 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 1H), 5.17 (q, *J*=7.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72 (s, 2H), 2.24 (s, 3H), 1.50 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 489.3 $[M+H]^+$.

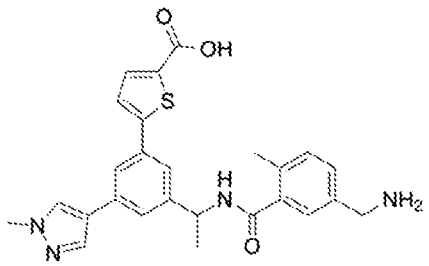
Prep-HPLC condition:

Column: Boston Prime C18 150*30mm*5μm;

Mobile phase: water (ammonium hydroxide)-ACN; B%: 35%-65%,

Flow Rate (mL/min): 30 mL/min.

Example 30: 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid



(**30**)

Step 1. Preparation of 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid

To solution of methyl 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (300.0 mg, 0.510 mmol) in MeOH (30.0 mL) was added 10% aq. NaOH (10.0 mL) at 20 °C. The reaction mixture was stirred at 70 °C for 15 hours. The mixture was evaporated to remove the MeOH then added HCl (1N) to pH = 6. The reaction mixture was partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (30 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (260 mg, 88.8%) as a yellow oil. LCMS (ESI): m/z = 597.5 $[M+Na]^+$.

Step 2. Preparation of 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid

To solution of 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (130.0 mg, 0.226 mmol) in CH_2Cl_2 (20 mL) was slowly added HCl in 1,4-dioxane (4M, 20 mL) at 0°C. The reaction mixture was stirred at 20 °C for 1 hour. The mixture was evaporated in vacuo and then purified via prep-HPLC to afford 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (52 mg, 48.6%) as a white solid after lyophilization. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.95 (d, J=8.3 Hz, 1H), 8.25 (s, 1H), 7.95 (s, 1H), 7.74 (s, 1H), 7.62 (s, 1H), 7.56-7.51 (m, 2H), 7.47-7.36 (m, 2H), 7.35-7.21 (m, 2H), 5.18 (quin, J=7.2 Hz,

1H), 4.03 (s, 2H), 3.88 (s, 3H), 2.33 (s, 3H), 1.50 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 475.4 $[M+H]^+$.

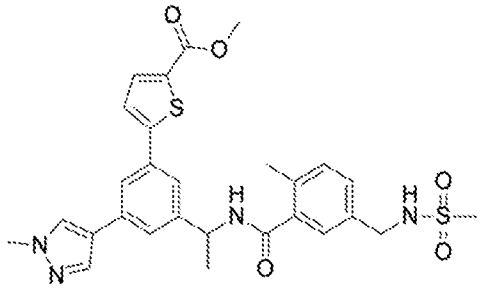
Prep-HPLC condition:

Column: Boston Prime C18 150*30mm*5μm

Mobile phase: water (ammonium hydroxide)-ACN; B%: 0%-25%,

Flow Rate (mL/min): 30 mL/min.

Example 31: methyl 5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(methylsulfonamidomethyl)benzamido)ethyl)phenyl)thiophene-2-carboxylate



(**31**)

To a solution of methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (Example 29) (90.0 mg, 0.18 mmol) in CH_2Cl_2 (15 mL) were added TEA (55.9 mg, 0.553 mmol) and methanesulfonic anhydride (48.1 mg, 0.276 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 15 hours. The reaction mixture was partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford a crude. The crude was dissolved in 5 mL DMF and purified by prep-HPLC to afford methyl 5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(methylsulfonamidomethyl)benzamido)ethyl)phenyl) thiophene-2-carboxylate (24 mg, 23%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.79 (d, J=8.1 Hz, 1H), 8.28 (s, 1H), 7.98 (s, 1H), 7.88-7.82 (m, 2H), 7.70 (d, J=3.9 Hz, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.56 (t, J=6.3 Hz, 1H), 7.35-7.29 (m, 2H), 7.28-7.20 (m, 1H), 5.20 (quin, J=7.3 Hz, 1H), 4.21-4.13 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.32-3.25 (m, 1H), 2.88 (s, 3H), 2.28 (s, 3H), 1.50 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 567.3 $[M+H]^+$.

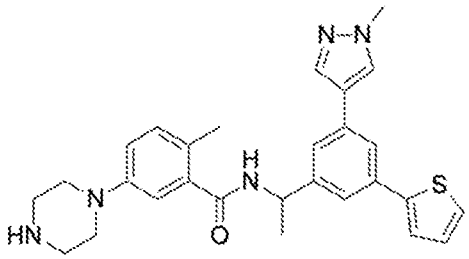
Prep-HPLC condition:

Column: C18-1 150*30mm*5μm

Mobile phase: water (ammonium hydroxide)-ACN; B%:22%-62%,

Flow Rate (mL/min): 30 mL/min.

Example 33: 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide



(**33**)

Step 1. Preparation of tert-butyl 4-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate

To a solution of 1-(3,5-dibromophenyl)ethan-1-amine (200 mg, 0.634 mmol) in DMF (20 mL) were added HATU (362 mg, 0.951 mmol), TEA (225 mg, 2.22 mmol) and 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-methylbenzoic acid (203 mg, 0.634 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 15 hours then partitioned between ethyl acetate and H_2O (15/15 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (5 mL x 2), dried with anhydrous Na_2SO_4, and evaporated in vacuo to give a residue, which was purified by silica gel chromatography (eluting with EA/PE 0-20%/100%-80%) to afford tert-butyl 4-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (180 mg, 48.8%) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 0.05-0.13 (m, 1H), 1.23-1.35 (m, 1H), 1.50 (s, 10H), 1.55-1.68 (m, 11H), 2.04-2.10 (m, 1H), 2.11-2.15 (m, 1H), 2.31-2.39 (m, 3H), 3.07-3.16 (m, 4H), 3.56-3.68 (m, 4H), 4.14 (d, J=7.09 Hz, 1H), 5.20-5.29 (m, 1H), 5.92-6.03 (m, 1H), 6.89-7.03 (m, 2H), 7.13-7.18 (m, 1H), 7.25-7.33 (m, 5H), 7.47 (d, J=1.47 Hz, 2H), 7.58-7.63 (m, 1H). LCMS (ESI): m/z = 526.1 $[M+H-tBu]^+$.

Step 2. Preparation of tert-butyl 4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate

To a solution of tert-butyl 4-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (180.0 mg, 0.310 mmol) in dioxane (5.0 mL) under N_2 were added H_2O (1.0 mL), Na_2CO_3 (98.5 mg, 0.929 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)-1H-pyrazole (58.0 mg, 0.279 mmol), and $Pd(dppf)_2Cl_2$ (6.80 mg, 0.00929 mmol) at 20 °C. The reaction mixture was stirred at 90 °C under N_2 for 3 hours then partitioned between ethyl acetate and H_2O (15/15 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (5 mL x 2), dried with anhydrous Na_2SO_4, and evaporated in vacuo to give a residue, which was purified by silica gel chromatography (eluting with EA/PE 0-60%/100%-40%) to afford tert-butyl 4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (30 mg, 17%) as a yellow oil. LCMS (ESI): m/z = 484.2 $[M+H-Boc]^+$.

Step 3. Preparation of tert-butyl 4-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxylate

To a solution of tert-butyl 4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (30.0 mg, 0.051 mmol) in dioxane (2.5 mL) under N_2 were added H_2O (0.5 mL), Na_2CO_3 (16.4 mg, 0.154 mmol), thiophen-2-ylboronic acid (9.88 mg, 0.0772 mmol) and $Pd(dppf)_2Cl_2$ (1.88 mg, 0.00257 mmol) at 20 °C. The reaction mixture was stirred at 90 °C under N_2 for 15 hours then partitioned between ethyl acetate and H_2O (15/15 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (5 mL). The combined organic layer was washed with brine (5 mL x 2), dried with anhydrous Na_2SO_4, and evaporated in vacuo to give a residue, which was purified by silica gel chromatography (eluting with EA/PE 0-60%/100%-40%) to afford tert-butyl 4-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxylate (25 mg, 84%) as a yellow oil. LCMS (ESI): m/z = 608.3 $[M+Na]^+$.

Step 4. Preparation of 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide

To a mixture of tert-butyl 4-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperazine-1-carboxylate(25 mg 0.043 mmol) in MeOH (2 mL) was added HCl/MeOH (1 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hours then concentrated to dryness and purified by prep-HPLC to afford 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide (9.18 mg, 44%) as a white solid after lyophilization. ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.20-1.37 (m, 1H),

1.60-1.73 (m, 1H), 2.28-2.46 (m, 1H), 2.94-3.22 (m, 1H), 3.86-4.11 (m, 1H), 5.31-5.46 (m, 1H), 6.02-6.18 (m, 1H), 6.85-7.02 (m, 1H), 7.07-7.09 (m, 1H), 7.08-7.16 (m, 1H), 7.08-7.16 (m, 1H), 7.10-7.18 (m, 1H), 7.26-7.30 (m, 1H), 7.31-7.34 (m, 1H), 7.35-7.39 (m, 1H), 7.39-7.44 (m, 1H), 7.45-7.53 (m, 1H), 7.59-7.65 (m, 1H), 7.66-7.74 (m, 1H), 7.78-7.87 (m, 1H). LCMS (ESI): m/z = 486.4 $[M+H]^+$.

Prep HPLC Method:

Mobile phase: A: water (0.5% ammonium hydroxide); B: ACN

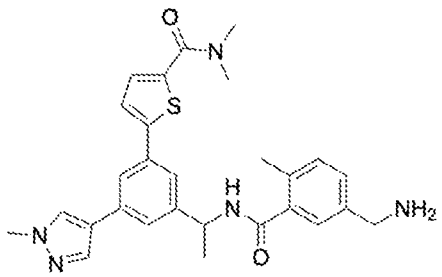
Column: Phenomenex C18 75*30mm*3µm

Flow rate: 60 mL/min

Monitor wavelength: 220&254 nm

Gradient: B%, 30% to 70%, 9min, 100% B, 2min.

Example 34: 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide



(34)

Step 1. Preparation of tert-butyl (3-((1-(3-(5-(dimethylcarbamoyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To a solution of 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (Example 30, Step 1) (130.0 mg, 0.226 mmol) and dimethylamine (184 mg, 2.26 mmol) in DMF (5.0 mL) was added DIEA (87.7 mg, 0.679 mmol), followed by HATU (129 mg, 0.339 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 hours then partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (50 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford tert-butyl (3-((1-(3-(5-(dimethylcarbamoyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (100 mg, 73.5%) as a yellow oil. LCMS (ESI): m/z = 502.2 [M+ H-Boc]+.

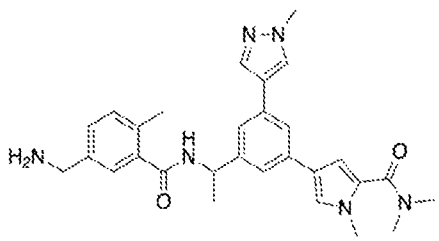
Step 2. Preparation of 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide

To solution of tert-butyl (3-((1-(3-(5-(dimethylcarbamoyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (100.0 mg, 0.166 mmol) in DCM (20 mL) was slowly added HCl in 1,4-dioxane (4M, 20 mL) at 0 °C. The reaction mixture was stirred at 20 °C for 1 hour then evaporated in vacuo to give a crude, which was purified by prep-HPLC to afford 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide (52mg, 62.3%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.81-8.70 (m, 1H), 8.27 (s, 1H), 7.96 (s, 1H), 7.79 (d, J=1.5 Hz, 1H), 7.62-7.53 (m, 4H), 7.33 (s, 1H), 7.31-7.11 (m, 3H), 5.19 (quin, J=7.2 Hz, 1H), 3.89 (s, 3H), 3.77-3.66 (m, 2H), 3.24-3.04 (m, 6H), 2.30-2.23 (m, 3H), 1.49 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 502.4 $[M+H]^+$.

Prep-HPLC condition:
Column: Boston Prime C18 150*30mm*5μm
Mobile phase: water (ammonium hydroxide v/v)-ACN; B%:20%-50%,
Flow Rate (mL/min): 30 mL/min.

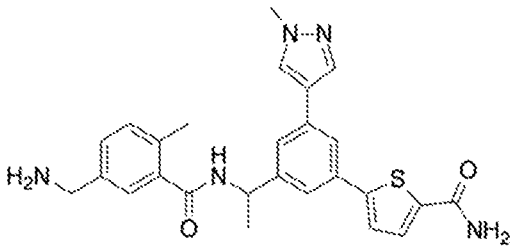
Example 41: 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-*N*,*N*,1-trimethyl-1*H*-pyrrole-2-carboxamide

The following example was prepared in a similar manner to the preparation of Example 34, using appropriate reactants.

Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
41		Example 29, Step 1, **P9** and methyl 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-2-carboxylate; then Example 29, Step 2-3; then Example, 30 Step 1, methyl 4-(3-(1-(5-(((*tert*-	^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.64 (d, *J*=8.3 Hz, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.62 (s, 1H), 7.40 (d, *J*=1.8 Hz, 2H), 7.38 (s, 1H), 7.32 (s, 1H),

	4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-*N*,*N*,1-trimethyl-1*H*-pyrrole-2-carboxamide	butoxycarbonyl)amino) methyl)-2-methyl-benzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-1-methyl-1*H*-pyrrole-2-carboxylate; Example 34, Step 1, 4-(3-(1-(5-(((*tert*-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid; Then Example 34, Step 2, *tert*-butyl (3-((1-(3-(5-(dimethylcarbamoyl)-1-methyl-1*H*-pyrrol-3-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl) carbamate	7.30-7.25 (m, 1H), 7.17 (d, *J*=7.8 Hz, 1H), 6.84 (d, *J*=1.9 Hz, 1H), 5.14 (br t, *J*=7.5 Hz, 1H), 3.87 (s, 2H), 3.79-3.62 (m, 6H), 3.09 (br s, 6H), 2.26 (s, 3H), 1.47 (br d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 499.3 $[M+H]^+$

Example 35: 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxamide



(35)

Step 1. Preparation of *tert*-butyl (3-((1-(3-(5-carbamoylthiophen-2-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate

To solution of 5-(3-(1-(5-(((*tert*-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (100.0 mg, 0.174 mmol) in DMF (5.0

mL) were added NH_4Cl (27.9 mg, 0.522 mmol), DIEA (67.5 mg, 0.522 mmol), and HATU (99.2 mg, 0.261 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 2 hours then partitioned between ethyl acetate and H_2O (50/50 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and evaporated in vacuo to afford *tert*-butyl (3-((1-(3-(5-carbamoylthiophen-2-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (80 mg, 80%) as a yellow oil. LCMS (ESI): m/z = 474.2 $[M+H\text{-}Boc]^+$.

Step 2. Preparation of 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxamide

To solution of *tert*-butyl (3-((1-(3-(5-carbamoylthiophen-2-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (80.0 mg, 0.14 mmol) in CH_2Cl_2 (20 mL) was slowly added HCl in dioxane (4M, 20 mL) at 0°C. The reaction mixture was stirred at 20 °C for 1 hour then evaporated in vacuo to give a crude, which was purified by prep-HPLC to afford 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)thiophene-2-carboxamide (15.3 mg, 23%) as a white solid after lyophilization. ^1H NMR (400 MHz, MeOD-d_4) δ (ppm) = 8.09 (s, 1H), 7.93 (s, 1H), 7.79 (t, *J*=1.5 Hz, 1H), 7.72 (d, *J*=4.0 Hz, 1H), 7.62 (s, 2H), 7.51 (d, *J*=3.9 Hz, 1H), 7.40-7.30 (m, 2H), 7.25 (d, *J*=7.8 Hz, 1H), 5.29 (q, *J*=7.1 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 2H), 2.40-2.33 (m, 3H), 1.62 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 474.2 $[M+H]^+$.

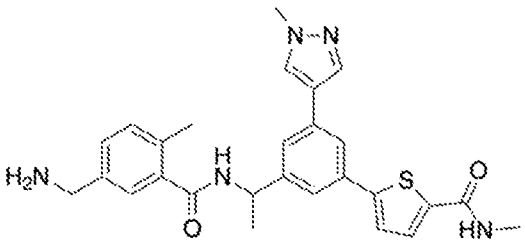
Prep-HPLC condition:

Column: C18-1 150*30mm*5μm

Mobile phase: water (NH3.H2O+NH4HCO3)-ACN; B%:24%-44%,

Flow Rate (mL/min): 30 mL/min.

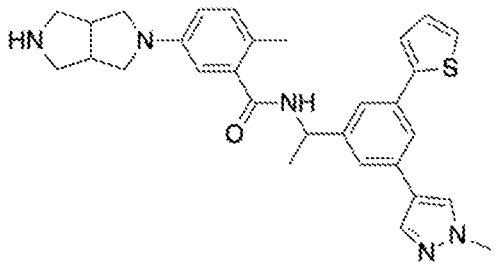
Example 36: 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-*N*-methylthiophene-2-carboxamide



(36)

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)-*N*-methylthiophene-2-carboxamide was prepared in a similar manner to the preparation of the Example 34 from 5-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid and $MeNH_2$.HCl. ^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm) = 8.08 (s, 1H), 7.93 (s, 1H), 7.78 (t, *J*=1.6 Hz, 1H), 7.66-7.59 (m, 3H), 7.50 (d, *J*=3.9 Hz, 1H), 7.37 (s, 1H), 7.34 (d, *J*=7.3 Hz, 1H), 7.25 (d, *J*=7.8 Hz, 1H), 5.29 (q, *J*=7.2 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 2H), 2.93 (s, 3H), 2.37 (s, 3H), 1.62 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 488.2 $[M+H]^+$.

Example 38: 5-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide



(38)

Step 1. Preparation of *tert*-butyl 5-(3-(methoxycarbonyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

To a solution of methyl 5-bromo-2-methylbenzoate (2.00 g, 8.73 mmol) in dioxane (100 mL) were added *tert*-butyl hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (2.78 g 13.1 mmol), Cs_2CO_3 (5.69 g, 17.5 mmol), Ru-phos (815 mg, 1.75 mmol), and $Pd(OAc)_2$ (196 mg, 0.873 mmol) at 25 °C. The mixture was bubbled with N_2 for 1 minute, then the reaction was stirred at 100 °C for 15 hours. The reaction mixture was then partitioned between ethyl acetate and H_2O (30/10 mL). The organic layer was separated, and the aqueous layer was re-extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4, and evaporated in vacuo to give a residue, which was purified by silica gel chromatography eluting with EA/PE (0-17%/100%-83%) to give *tert*-butyl 5-(3-(methoxycarbonyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (2300 mg, 73.1%) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.40-1.53 (m, 9H), 2.04-2.09 (m, 1H), 2.45-2.53 (m, 3H), 2.94-3.08 (m, 2H), 3.18-3.31 (m, 3H), 3.47-3.72 (m, 4H), 3.84-

3.93 (m, 3H), 3.85-3.96 (m, 3H), 4.08-4.19 (m, 1H), 4.09-4.17 (m, 1H), 6.57-6.70 (m, 1H), 7.06-7.15 (m, 2H), 7.27-7.33 (m, 1H). LCMS (ESI): m/z = 361.4 $[M+H]^+$.

Step 2. Preparation of 5-(5-(*tert*-butoxycarbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methylbenzoic acid

To a solution of *tert*-butyl 5-(3-(methoxycarbonyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (1 g, 2.774 mmol) in MeOH (30 mL)/H_2O (10 mL) was added NaOH (555 mg, 13.9 mmol) at 20 °C. The reaction was stirred at 20 °C for 15 hours. LCMS showed a mass peak of the desired product, but there were still starting materials left in the reaction. The reaction was kept at 50 °C for 3 more hours then concentrated in vacuo to remove most of the solvent at 20 °C. The residue was adjusted pH to 3 with HCl (1M) at 0°C. White solid was formed and collected by filtration to give 5-(5-(*tert*-butoxycarbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methylbenzoic acid (940 mg, 97.8%) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.18-1.69 (m, 9H), 1.21-1.58 (m, 9H), 2.44-2.65 (m, 3H), 2.95-3.11 (m, 2H), 3.18-3.35 (m, 3H), 3.35-3.45 (m, 1H), 3.50-3.83 (m, 5H), 4.62-4.81 (m, 2H), 6.63-6.73 (m, 1H), 7.09-7.18 (m, 1H), 7.22-7.27 (m, 1H). LCMS (ESI): m/z = 347.4 $[M+H]^+$.

Step 3. Preparation of *tert*-butyl 5-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

To the solution of 5-(5-(*tert*-butoxycarbonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methylbenzoic acid (400.0 mg, 1.15 mmol) in DMF (5 mL) were added 1-(3,5-dibromophenyl)ethan-1-amine (401 mg, 1.27 mmol), HATU (527 mg, 1.39 mmol), and DIPEA (1490 mg, 11.5 mmol). The reaction was stirred at 25 °C for 12 hours. H_2O (50 mL) was added to the reaction, and the mixture was extracted with ethyl acetate (20 mL x 3). The organic extracts were dried by Na_2SO_4, filtered, concentrated, and purified using a flash silica gel column (PE:EA=100:0 to 80:20) to give *tert*-butyl 5-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (700 mg, 99.8%) as a white solid. LCMS (ESI): m/z = 508.7 $[M+H-Boc]^+$.

Step 4. Preparation of *tert*-butyl 5-(3-((1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

To a solution of *tert*-butyl 5-(3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (150.0 mg, 0.247 mmol) in 1,4-

dioxane (3.0 mL) were added sat. aq. Na_2CO_3 (1 mL), $Pd(dppf)_2Cl_2$ (5.42 mg 0.00741 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (51.4 mg, 0.247 mmol) at 20 °C. The reaction mixture was stirred at 100 °C under N_2 for 3 hours. LCMS showed a desired mass. The reaction mixture was filtered, and the filtrate was evaporated in vacuo to give a residue, which was purified by silica gel chromatography using a Biotage (4 g silicon column, PE: EA= 1:0 to 0:1) to afford *tert*-butyl 5-(3-((1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (80 mg, 53%) as a yellow oil. LCMS (ESI): m/z = 632.3 $[M+Na]^+$.

Step 5. Preparation of *tert*-butyl 5-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate

To a solution of *tert*-butyl 5-(3-((1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (80 mg, 0.13 mmol) in 1,4-dioxane (3.0 mL) were added sat. aq. Na_2CO_3 (1 mL), $Pd(dppf)_2Cl_2$ (9.62 mg, 0.0131 mmol), and thiophen-2-ylboronic acid (25.2 mg, 0.197 mmol) at 20°C. The reaction mixture was stirred at 100°C under N_2 for 3 h then filtered. The filtrate was evaporated in vacuo to give a residue, which was purified by silica gel chromatography via a Biotage (4 g silicon column, PE: EA= 1:0 to 0:1) to afford the product *tert*-butyl 5-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (66 mg, 82 %) as a yellow oil. LCMS (ESI): m/z = 512.2 $[M+H-Boc]^+$.

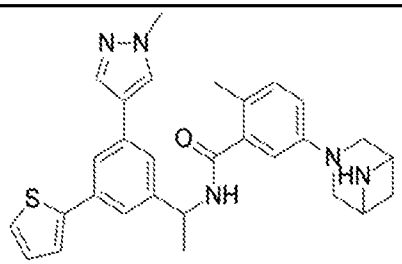
Step 6. Preparation of 5-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide

To a flask of *tert*-butyl 5-(4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (66 mg, 0.11 mmol) was added HCl/CH_3OH (4M, 5 mL) and stirred at 25 °C for 1 hour. Then the solution was concentrated in vacuo to give a solid. The solid was triturated in methyl tert-butyl ether (3 mL), filtered, redissolved in MeCN/water, and dried by lyophilization to give 5-(hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (10.14 mg, 18%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6, 296 K) δ (ppm) = 9.52-9.18 (m, 2H), 8.74 (d, *J*=8.4 Hz, 1H), 8.25 (s, 1H), 7.99-7.89 (m, 1H), 7.82-7.72 (m, 1H), 7.63-7.48 (m, 4H), 7.24-7.15 (m, 1H), 7.13-7.02 (m, 1H), 6.74-6.61

(m, 2H), 5.33-5.01 (m, 1H), 4.02-3.99 (m, 1H), 3.79-3.75 (m, 1H), 3.53-3.43 (m, 2H), 3.38-3.22 (m, 4H), 3.19-2.99 (m, 4H), 2.23-2.13 (m, 3H), 1.58-1.38 (m, 3H). LCMS (ESI): m/z = 512.2 $[M+H]^+$.

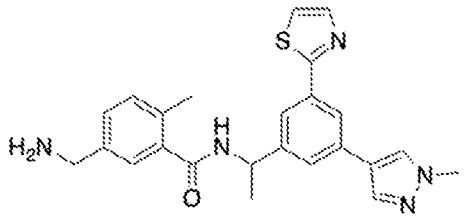
Example 40: 5-(3,6-diazabicyclo[3.1.1]heptan -3-yl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) benzamide

The following example was prepared in a similar manner to the preparation of Example 38, using appropriate reactants.

Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
40	 5-(3,6-diazabicyclo[3.1.1]heptan -3-yl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) benzamide	Example 38, Step 1, *tert*-butyl 3,6-diazabicyclo[3.1.1]heptane -6-carboxylate and methyl 5-bromo-2-methylbenzoate; Then Example 38, Step 2, *tert*-butyl 3-(3-(methoxycarbonyl)-4-methylphenyl)-3,6-diazabicyclo[3.1.1]heptane -6-carboxylate; then Example 38, Step 3, 1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine (as prepared in Example 7) and 5-(6-(*tert*-butoxycarbonyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methylbenzoic acid;	^{1}H NMR (400 MHz, MeOD-d_4) δ (ppm) = 8.04 (s, 1H), 7.88 (s, 1H), 7.71 (t, *J*=1.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.47 (dd, *J*=1.0, 3.6 Hz, 1H), 7.39 (dd, *J*=1.0, 5.1 Hz, 1H), 7.13-7.09 (m, 2H), 6.78-6.73 (m, 2H), 5.26 (d, *J*=7.0 Hz, 1H), 3.95 (s, 3H), 3.86 (br d, *J*=6.0 Hz, 2H), 3.61-3.50 (m, 4H), 2.77-2.69 (m, 1H), 2.27 (s, 3H), 1.68 (d, *J*=9.0 Hz, 1H), 1.59 (d, *J*=7.1 Hz, 3H). LCMS (ESI): m/z = 498.3 $[M+H]^+$.

		then Example 38, Step 6, tert-butyl 3-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) carbamoyl)phenyl)-3,6-diazabicyclo[3.1.1]heptane -6-carboxylate	

Example 45: 5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)benzamide



(**45**)

Step 1. Preparation of *tert*-butyl (4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)carbamoyl)benzyl)carbamate

To a solution of *tert*-butyl (3-((1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (**P18**) (100 mg, 0.19 mmol, prepared in Example 43 Step 1-2) in dioxane (5 mL) were added B_2Pin_2 (72 mg, 0.284 mmol) and KOAc (37.2 mg, 0.379 mmol). Then $Pd(dppf)_2Cl_2$ (13.9 mg, 0.019 mmol) was added to the mixture, and the reaction was stirred at 100 °C for 4 hours under N_2. TLC (EA/PE=1/1) showed that the reaction was finished. The reaction was evaporated to and used in the subsequent step directly. To the mixture above (0.19 mmol) in dioxane (3 mL) were added 2-bromothiazole (34.3 mg, 0.209 mmol), Na_2CO_3 (20.1 mg, 0.19 mmol) in H_2O (0.5 mL), and then $Pd(dppf)_2Cl_2$ (6.94 mg, 0.00948 mmol) under N_2. The mixture was stirred at 100 °C for 12 hours. LCMS showed that the starting material was consumed and a desired mass was observed (m/z = 532.0 $[M+H]^+$). The reaction mixture was then diluted with ethyl acetate (30 mL), washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue, which was purified by prep-TLC (EA, Rf=0.5) to give the product *tert*-butyl (4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)carbamoyl)benzyl)carbamate (50 mg, 49% yield) as a light yellow oil.

^{1}H NMR (400MHz, CHLOROFORM-d) δ =7.98 (s, 1H), 7.90 (d, *J*=3.2 Hz, 1H), 7.86-7.82 (m, 2H), 7.75 (s, 1H), 7.56 (s, 1H), 7.38 (d, *J*=3.2 Hz, 1H), 7.30 (br s, 1H), 7.23 (br s, 1H), 7.19 (s, 1H), 6.11 (s, 1H), 5.40 (s, 1H), 4.85 (s, 1H), 4.28 (br s, 2H), 3.98 (s, 3H), 2.42 (s, 3H), 1.67 (d, *J*=7.0 Hz, 3H), 1.44 (s, 9H). LCMS (ESI): m/z = 532.0 $[M+H]^+$.

Step 2. Preparation of 5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)benzamide

To a solution of *tert*-butyl (4-methyl-3-((1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)carbamoyl)benzyl)carbamate (50 mg, 0.094 mmol) in CH_2Cl_2 (3 mL) was added HCl/dioxane (3 mL). The mixture was stirred at 25 °C for 10 minutes. LCMS showed that the starting material was consumed and a desired mass was observed with mass value (m/z = 432.3 $[M+H]^+$). The mixture was then concentrated in vacuo to give a residue. The residue was re-dissolved in MeOH (2 mL), adjusted to pH=8 by $NH_3.H_2O$, and then concentrated in vacuo to give a crude product, which was purified by prep-HPLC to afford 5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)benzamide (7.61 mg, 19%) as a white solid. ^{1}H NMR (400MHz, MeOD-d_4) δ (ppm) = 8.10 (s, 1H), 8.06 (s, 1H), 7.95-7.90 (m, 2H), 7.88 (s, 1H), 7.75 (s, 1H), 7.66 (d, *J*=3.3 Hz, 1H), 7.40-7.32 (m, 2H), 7.24 (d, *J*=7.8 Hz, 1H), 5.32 (q, *J*=7.0 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 2H), 2.36 (s, 3H), 1.64 (d, *J*=7.0 Hz, 3H). LCMS (ESI): m/z = 432.2 $[M+H]^+$.

prep-HPLC condition:

Column: C18 150*30mm*5um;

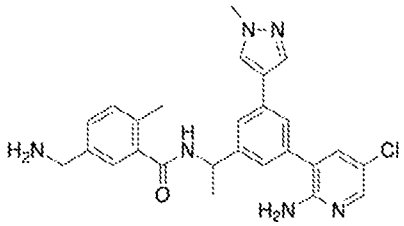
Mobile phase: water (NH_4OH + NH_4HCO_3)-MeCN, from 20% to 60%

Flow Rate (mL/min): 30 mL/min.

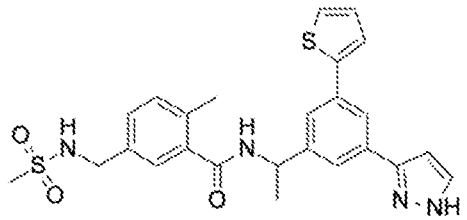
Example 46: *N*-(1-(3-(2-amino-5-chloropyridin -3-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-5-(aminomethyl) -2-methylbenzamide

The following example was prepared in a similar manner to the preparation of Example 45, using appropriate reactants.

Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data

46	 *N*-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide	Example 45, Step 1, using *tert*-butyl (3-((1-(3-bromo-5-(1-methyl-1*H*-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl) carbamate and 3-bromo-5-chloropyridin-2-amine; then Example 45, Step 2	^{1}H NMR (400 MHz, DMSO-d_6, 349 K) δ (ppm) = 8.41 (br d, J=7.6 Hz, 1H), 8.12 (s, 1H), 7.98 (d, J=2.5 Hz, 1H), 7.85 (s, 1H), 7.61 (s, 1H), 7.49 (s, 1H), 7.43 (d, J=2.5 Hz, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 7.26 (br d, J=7.9 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H), 5.63 (br s, 2H), 5.22 (br t, J=7.3 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 2H), 2.28 (s, 3H), 1.53 (d, J=7.0 Hz, 3H). LCMS (ESI): m/z = 475.4, $[M+1]^+$

Example 61: N-(1-(3-(1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide



(61)

Step 1. Preparation of N-(1-(3-bromo-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

Using a procedure analogous to the preparation of N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**), from N-(1-(3,5-dibromophenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (**P15)** (500.0 mg, 0.992 mmol) and 1-(tetrahydro-2H-

pyran-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (276.0 mg, 0.992 mmol) as reactants affords N-(1-(3-bromo-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (550.0 mg, 96.4%) as a yellow solid. LCMS (ESI): m/z = 491.2 [M+H-THP]$^+$.

Step 2. Preparation of 2-methyl-5-(methylsulfonamidomethyl)-N-(1-(3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide

Using a procedure analogous to the preparation of N-(1-(5-bromo-3'-chloro-[1,1'-biphenyl]-3-yl)ethyl)-2-methylpropane-2-sulfinamide (**P6**), from N-(1-(3-bromo-5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (550.0 mg, 0.956 mmol)) and thiophen-2-ylboronic acid (122.0 mg, 0.956 mmol) as reactants affords 2-methyl-5-(methylsulfonamidomethyl)-N-(1-(3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (116.0 mg, 21%) as a yellow oil. LCMS (ESI): m/z = 495.3 [M+H-THP]$^+$.

Step 3. Preparation of N-(1-(3-(1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

To a solution of 2-methyl-5-(methylsulfonamidomethyl)-N-(1-(3-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (116 mg, 0.200 mmol) in MeOH (20 mL) was added HCl (3 mL conc.) at 0°C. The reaction mixture was stirred at 20°C for 2 h then evaporated in vacuo to give a residue, which was suspended in MeCN and evaporated in vacuo again to give a crude product. The crude product was purified by prep-HPLC to give N-(1-(3-(1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (19.81 mg, 17.4%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.42 (d, *J* = 7.00 Hz, 3H) 2.15-2.27 (m, 3H) 2.79 (s, 3H) 4.07 (d, *J* = 6.13 Hz, 2H) 5.05-5.20 (m, 1H) 6.66-6.75 (m, 1H) 7.06-7.17 (m, 2H) 7.19-7.26 (m, 2H) 7.43-7.58 (m, 5H) 7.71-7.76 (m, 1H) 7.82-7.94 (m, 1H) 8.70-8.82 (m, 1H) 12.75-13.07 (m, 1H). LCMS (ESI): m/z = 495.3 [M+H]$^+$.

Prep. HPLC Method:

Instrument: ACSSH-CD

Mobile phase: A: water (NH_4OH+NH_4HCO3); B: MeCN

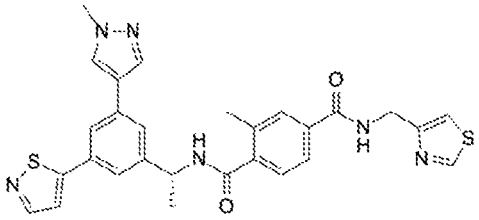
Column: C18 150*30mm*5μm

Flow rate: 30 mL/min

Monitor wavelength: 220&254 nm

Gradient: B%, 39% to 59%, 9min, 100%B Hold Time (min) 2 min.

Example 62: (R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide



(62)

Step 1. Preparation of methyl (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoate

To a mixture of 4-(methoxycarbonyl)-2-methylbenzoic acid (75.1 mg, 0.387 mmol) in DMF (1.93 mL) were added DIEA (150 mg, 1.16 mmol) and HATU (176 mg, 0.464 mmol) at 25 °C. The reaction was stirred at 25 °C for 1 h, before (R)-1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethan-1-amine (**P16)** (110.0 mg, 0.387 mmol) was added to it. The reaction was stirred at 150 °C for 16 h then quenched with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over Na_2SO_4, evaporated in vacuo to give methyl (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoate (178 mg, 100%) as a brown oil. LCMS (ESI): m/z = 461.0 $[M+H]^+$.

Step 2. Preparation of (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoic acid

To a solution of methyl (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoate (178.0 mg, 0.387 mmol) in MeOH (3.0 mL) and H_2O (1.0 mL) was added $LiOH.H_2O$ (18.5 mg, 0.773 mmol). The reaction was then heated to 40 °C for 16 h. After that, the reaction was evaporated to remove MeOH, then diluted with H_2O (5 mL), and extracted with ethyl acetate (10 mL). The ethyl acetate was discarded. The aqueous layer was acidified with 1 N HCl to pH = 3~4, then extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried with Na_2SO_4 and evaporated in vacuo to give (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoic acid (190 mg, 110%) as a yellow solid. LCMS (ESI): m/z = 447.0 $[M+H]^+$.

Step 3. Preparation of (R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide

To a mixture of (R)-4-((1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-3-methylbenzoic acid (100.0 mg, 0.224 mmol) in DMF (1.12 mL) were added DIEA (86.8 mg, 0.672 mmol) and HATU (102 mg, 0.269 mmol) at 15 °C. The reaction was stirred at 25 °C for 1 h, before thiazol-4-ylmethanamine (25.6 mg, 0.224 mmol) was added to it. The reaction mixture was then stirred at 25 °C for 16 h, then quenched with H_2O (10 mL), and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over Na_2SO_4, evalorated in vacuo to give a crude, which was purified via prep-HPLC to afford (R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide (42.26 mg, 34.8%) as a white solid. ^{1}H NMR of PLASMA-838: ^{1}H NMR (400MHz, DMSO-d6) δ = 9.09 (s, 1H), 9.06 (d, *J* = 2.0 Hz, 1H), 8.89 (d, *J* = 8.1 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H), 8.27 (s, 1H), 7.98 (d, *J* = 0.6 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.84 (t, *J* = 1.5 Hz, 1H), 7.77 (s, 2H), 7.69 (s, 1H), 7.57 (s, 1H), 7.46-7.42 (m, 2H), 5.21 (s, 1H), 4.62 (d, *J* = 5.1 Hz, 2H), 3.89 (s, 3H), 2.34 (s, 3H), 1.50 (d, *J* = 7.1 Hz, 3H). LCMS (ESI): m/z = 543.3 $[M+H]^+$.

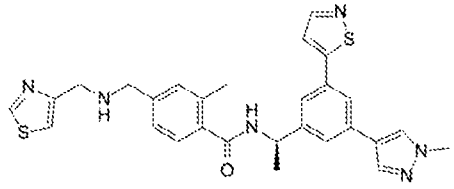
Prep-HPLC condition:

Column: Boston Prime C18 150*40mm*10μm;

Mobile phase: water (ammonium hydroxide v/v)-MeCN; B%: 19%-59%,

Flow rate (mL/min): 60 mL/min.

Example 63: (R)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-4-(((thiazol-4-ylmethyl)amino)methyl)benzamide



(63)

Step 1. Preparation of (R)-4-formyl-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide

To a mixture of 4-formyl-2-methylbenzoic acid (69.3 mg, 0.422 mmol) in DMF (2.11 mL) were added DIEA (164 mg, 1.27 mmol) and HATU (193 mg, 0.506 mmol) at 25 °C. The reaction was stirred for 1 h, before (R)-1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethan-1-

amine (**P16)** (120.0 mg, 0.422 mmol) was added to it. The reaction was stirred at 15 °C for 16 h then quenched with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over Na_2SO_4, evaporated in vacuo to give (R)-4-formyl-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (140 mg, 77.1%) as a yellow solid. LCMS (ESI): m/z = 431.0 $[M+H]^+$.

Step 2. Preparation of (R)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-4-(((thiazol-4-ylmethyl)amino)methyl)benzamide

To a solution of (R)-4-formyl-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (50.0 mg, 0.12 mmol) in THF (2.32 mL) were added thiazol-4-ylmethanamine (13.3 mg, 0.116 mmol) and Ti(O-iPr)4 (66.0 mg, 0.232 mmol) at 15 °C. The mixture was stirred at 30 °C for 16 h, before $NaBH_4$ (8.79 mg, 0.232 mmol) was added to the mixture at 15 °C. The resulting mixture was stirred at 30 °C for 1 h then quenched with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried over Na2SO4, filtered, and evaporated in vacuo to give a crude, which was purified via prep-HPLC to afford (R)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-4-(((thiazol-4-ylmethyl)amino)methyl)benzamide (11.94 mg, 19%) as a white solid. ^{1}H NMR of PLASMA-839: ^{1}H NMR (400MHz, DMSO-d6) δ = 9.04 (d, *J* = 2.0 Hz, 1H), 8.75 (d, *J* = 8.2 Hz, 1H), 8.63 (d, *J* = 1.8 Hz, 1H), 8.27 (s, 1H), 7.97 (s, 1H), 7.88-7.82 (m, 2H), 7.69 (s, 1H), 7.57 (s, 1H), 7.50-7.46 (m, 1H), 7.34-7.30 (m, 1H), 7.25-7.21 (m, 2H), 5.17 (br d, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 2H), 3.72 (s, 2H), 2.29 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 529.2 $[M+H]^+$.

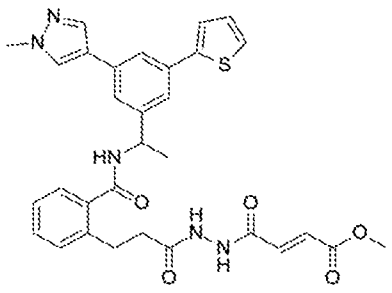
Prep-HPLC condition:

Column: Boston Prime C18 150*40mm*10μm;

Mobile phase: water (ammonium hydroxide v/v)-MeCN; B%: 21%-61%,

Flow rate (mL/min): 60 mL/min.

Example 70: methyl (E)-4-(2-(3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoyl)hydrazineyl)-4-oxobut-2-enoate



(70)

Step 1. Preparation of methyl 3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoate

To a solution of 2-(3-methoxy-3-oxopropyl)benzoic acid (300.0 mg, 1.44 mmol) and 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethan-1-amine as prepared in Example 7 (408 mg, 1.44 mmol) in DMF (10 mL) were added HATU (822 mg, 2.16 mmol) and DIEA (559 mg, 4.32 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 12 h then quenched with water (15 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, evaporated, and purified by silica gel chromatography (eluted with PE:EtOAc = 1:1) to give methyl 3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl) phenyl)propanoate (400 mg, 58.6%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 8.04-8.01 (m, 1H), 8.10-7.97 (m, 1H), 7.83 (s, 1H), 7.72 (s, 1H), 7.61 (s, 1H), 7.51 (s, 1H), 7.47-7.39 (m, 2H), 7.38-7.30 (m, 3H), 7.25 (s, 1H), 7.11 (dd, *J* = 3.7, 4.8 Hz, 1H), 6.85 (br d, *J* = 7.3 Hz, 1H), 5.38 (quin, *J* = 7.1 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 1H), 3.96 (s, 3H), 3.65-3.57 (m, 3H), 3.14-3.03 (m, 2H), 2.97 (s, 1H), 2.89 (s, 1H), 2.80-2.66 (m, 2H), 2.05 (s, 1H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 2H). LCMS (ESI): m/z = 474.3 $[M+H]^+$.

Step 2. Preparation of 2-(3-hydrazineyl-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide

To a solution of methyl 3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoate (400.0 mg, 0.845 mmol) in EtOH (8 mL) was added $NH_2NH_2.H_2O$ (90 mg, 1.4 mmol) at 25 °C. The mixture was stirred at 80 °C for 60 h then cooled to 20 °C and evaporated in vacuo to give 2-(3-hydrazineyl-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (370 mg, 92.5%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.05 (s, 1H), 7.89 (s, 1H), 7.74-7.70 (m, 1H), 7.56 (d, *J* = 9.2 Hz, 2H), 7.49-7.46 (m, 1H), 7.42-7.34 (m, 3H), 7.30-7.25 (m, 2H), 7.12 (dd, *J* = 3.5, 5.1 Hz, 1H), 5.26 (q, *J* = 7.1 Hz, 1H), 3.95 (s, 3H), 3.06-2.93 (m, 2H), 2.47-2.38 (m, 2H), 1.64-1.59 (m, 3H), 1.18 (t, *J* = 7.0 Hz, 1H). LCMS (ESI): m/z = 474.2 $[M+H]^+$.

Step 3: Preparation of methyl (E)-4-(2-(3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoyl)hydrazineyl)-4-oxobut-2-enoate

To a solution of (E)-4-methoxy-4-oxobut-2-enoic acid (41.2 mg, 0.317 mmol) in DMF (0.5 mL) were added Mukaiyama's reagent (80.9 mg, 0.317 mmol), DIEA (54.6 mg 0.422 mmol), and 2-(3-hydrazineyl-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (100 mg, 0.211 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 16 h then purified by prep-HPLC to afford methyl (E)-4-(2-(3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoyl)hydrazineyl)-4-oxobut-2-enoate (46.54 mg, 37.6%) as a yellow solid after lyophilization. ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.04 (s, 1H), 7.89 (s, 1H), 7.71 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.50-7.45 (m, 1H), 7.42-7.33 (m, 4H), 7.32-7.26 (m, 1H), 7.11 (dd, *J* = 3.7, 5.1 Hz, 1H), 7.03-6.95 (m, 1H), 6.77 (d, *J* = 15.6 Hz, 1H), 5.26 (q, *J* = 7.1 Hz, 1H), 3.94 (s, 3H), 3.79 (s, 3H), 3.12-2.99 (m, 2H), 2.65-2.54 (m, 2H), 1.61 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 586.3 $[M+H]^+$.

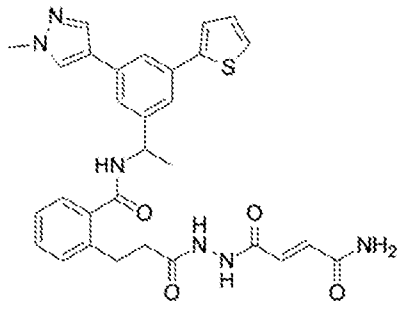
Prep-HPLC condition:

Column: C18-1 150*30mm*5μm;

Mobile phase: water(NH_4OH+NH_4HCO_3)-MeCN,

Flow rate (mL/min): 30 mL/min.

Example 71: (E)-2-(3-(2-(4-amino-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide



(71)

To a solution of (E)-4-amino-4-oxobut-2-enoic acid (36.5 mg, 0.317 mmol) in DMF (5 mL) were added butylphosphonic anhydride in ethyl acetate (50%, 218 mg, 0.422 mmol), 2-(3-hydrazineyl-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide as prepared in Example 70 step 2 (100.0 mg, 0.2112 mmol), and DIEA (54.6 mg, 0.422 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 16 h then

purified via prep-HPLC directly to afford (E)-2-(3-(2-(4-amino-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (9.97 mg, 8.27%) as a white solid after lyophilization. ^{1}H NMR (400 MHz, DMSO-d4) δ = 10.19-9.95 (m, 1H), 8.86 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 7.83 (br s, 1H), 7.72 (s, 1H), 7.60-7.49 (m, 4H), 7.40-7.25 (m, 5H), 7.16 (dd, *J* = 3.7, 5.0 Hz, 1H), 6.86 (q, *J* = 15.3 Hz, 2H), 5.18 (br t, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 2.94 (br t, *J* = 6.6 Hz, 2H), 2.52 (br s, 2H), 1.49 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 571.3 $[M+H]^+$.

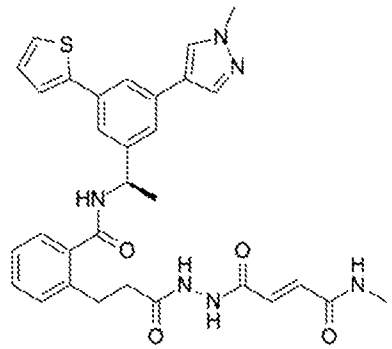
Prep-HPLC condition:

Column: C18-1 150*30mm*5μm;

Mobile phase: water(NH_4OH+NH_4HCO_3)-MeCN,

Flow Rate (mL/min): 30 mL/min

Example 72: (R,E)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-(3-(2-(4-(methylamino)-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)benzamide



(72)

To the solution of (E)-4-(methylamino)-4-oxobut-2-enoic acid (40.9 mg, 0.158 mmol) in pyridine (2.5 mL) were added EDC.HCl (30.4 mg, 0.158 mmol) and (R)-2-(3-hydrazineyl-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (50.0 mg, 0.106 mmol) at 20 °C. The reaction mixture was stirred at 30 °C for 16 h then evaporated in vacuo to give a residue, which was dissolved in DMF (2 mL) and purified by prep-HPLC to give (R,E)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-(3-(2-(4-(methylamino)-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)benzamide (7.46 mg, 12.1%) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 10.06 (br s, 1H), 8.86 (d, *J* = 8.3 Hz, 1H), 8.42-8.36 (m, 1H), 8.23 (s, 1H), 7.95 (s, 1H), 7.73 (s, 1H), 7.60-7.48 (m, 4H), 7.40-7.25 (m, 4H), 7.17 (dd, *J* = 3.7, 5.0 Hz, 1H), 6.92-6.82 (m, 2H), 5.23-5.14 (m, 1H), 3.89 (s, 3H), 3.03-2.87 (m, 2H), 2.69 (d, *J* = 4.6 Hz, 3H), 2.50-2.45 (m, 2H), 1.50 (br d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 585.3 $[M+H]^+$.

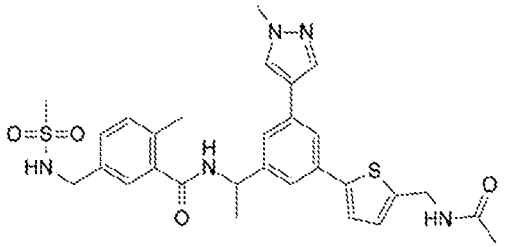
Prep-HPLC condition:

Column: Xtimate C18 150*40mm*10μm;

Mobile phase: water ($NH_4OH+NH_4HCO_3$)-MeCN; B%: 7%-47%,

Flow rate (mL/min):60 mL/min.

Example 73: N-(1-(3-(5-(acetamidomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide



(73)

Step 1. Preparation of tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)carbamate

Using a procedure analogous to Step 1 of Example 33, from 1-(3,5-dibromophenyl)ethan-1-amine and 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**); then using a procedure analogous to Step 2 of Example 33, from tert-butyl (3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole affords tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (**P18**). ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.73 (br d, *J* = 8.0 Hz, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.66-7.57 (m, 2H), 7.44-7.34 (m, 2H), 7.18 (s, 3H), 5.15-5.04 (m, 1H), 4.13-4.03 (m, 2H), 3.86 (s, 3H), 2.23 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H). LCMS (ESI): m/z = 473.0 $[M+H-tBu]^+$.

Step 2. Preparation of 5-(aminomethyl)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl) ethyl)-2-methylbenzamide

To a solution of tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate (**P18**) (1290 mg, 2.101 mmol) in DCM (20.0 mL) was added HCl/dioxane (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h then evaporated in vacuo to afford 5-(aminomethyl)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (1218 mg) as a brown solid which was used in next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.78 (d, *J* = 8.1 Hz, 1H), 8.40-

8.27 (m, 2H), 8.23 (s, 1H), 7.92 (s, 1H), 7.69-7.59 (m, 2H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.45-7.36 (m, 2H), 7.28 (d, *J* = 7.9 Hz, 1H), 5.17-5.06 (m, 1H), 4.01 (br d, *J* = 5.5 Hz, 2H), 3.86 (br s, 3H), 2.34-2.28 (m, 3H), 1.53-1.36 (m, 3H). LCMS (ESI): m/z = 429.1 $[M+H]^+$.

Step 3. Preparation of N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

To a solution of 5-(aminomethyl)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (1218 mg, 2.204 mmol) in DCM (20 mL) were added TEA (669 mg, 6.61 mmol) and Ms_2O (653 mg, 3.75 mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 3 h. After that, Ms_2O (192 mg, 1.10 mmol) was added to the mixture at 0 °C, and the reaction mixture was stirred at 20 °C for an additional 15 h. The reaction mixture was then evaporated in vacuo and purified by flash chromatography (20 g silica gel column, EA/PE from 0 to 100%) to afford N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (850 mg, 76.3%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.74 (d, *J* = 8.1 Hz, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.65 (s, 1H), 7.62-7.50 (m, 2H), 7.40 (s, 1H), 7.34-7.26 (m, 2H), 7.24-7.18 (m, 1H), 5.11 (quin, *J* = 7.4 Hz, 1H), 4.14 (d, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 2.87 (s, 3H), 2.26 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 505.1 $[M+H]^+$.

Step 4. Preparation of N-(1-(3-(5-formylthiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

To a solution of N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (850 mg, 1.51 mmol) and (5-formylthiophen-2-yl)boronic acid (235 mg, 1.51 mmol) in 1,4-dioxane (16 mL) and H_2O (4 mL) was added Na_2CO_3 (319 mg, 3.01 mmol). The mixture was bubbled with nitrogen for 3 min before $Pd(dppf)Cl_2$ (110 mg, 0.151 mmol) was added to it. The reaction mixture was then stirred at 100 °C for 15 h. After that, the reaction mixture was filtered, and the filtrate was evaporated in vacuo and then purified by flash chromatography (20 g silica gel column, EA/PE from 0 to 100%) to afford N-(1-(3-(5-formylthiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (340 mg, 42.1%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.93 (s, 1H), 8.82-8.67 (m, 1H), 8.27 (s, 1H), 8.12-8.04 (m, 1H), 8.01-7.92 (m, 1H), 7.91-7.85 (m, 1H), 7.84-7.77 (m, 1H), 7.68-7.50 (m, 3H), 7.33-7.27 (m, 2H), 7.25-7.20 (m,

1H), 5.26-5.10 (m, 1H), 4.19-4.10 (m, 2H), 3.93-3.82 (m, 3H), 2.87 (s, 3H), 2.30-2.23 (m, 3H), 1.53-1.42 (m, 3H). LCMS (ESI): m/z = 537.1 $[M+H]^+$.

Step 5. Preparation of N-(1-(3-(5-(aminomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

To a solution of N-(1-(3-(5-formylthiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (100 mg, 0.151 mmol) in MeOH (4 mL) were added hydroxylamine.HCl (31.6 mg, 0.454 mmol) and CH_3COONa (24.9 mg, 0.303 mmol) at 20 °C. The mixture was stirred at 50 °C for 16 h then evaporated to give a residue. The residue (83.6 mg) was then dissolved in AcOH (20.0 mL) and MeOH (4.0 mL) followed by the addition of Zn (48.1 mg, 0.735 mmol) at 20 °C. The mixture was stirred at 80 °C for 16 h before being quenched by water (10 mL). The mixture was then extracted by ethyl acetate (10 mL x 3). The aqueous layer was adjusted to a pH of about 8 by addition of $NH_3.H_2O$ and extracted again by ethyl acetate (15 mL x 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated in vacuo to give N-(1-(3-(5-(aminomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (30 mg, 37%) as a yellow solid. LCMS (ESI): m/z = 521.2 $[M+H-NH_3]^+$.

Step 6. Preparation of N-(1-(3-(5-(acetamidomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide

To a solution of N-(1-(3-(5-(aminomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (20.0 mg, 0.037 mmol) in DCM (5 mL) were added TEA (11.3 mg, 0.112 mmol) and Ac_2O (5.70 mg, 0.0558 mmol) at 20°C. The reaction mixture was stirred at 20 °C for 3 h before being quenched by water (10 mL). The mixture was then extracted by ethyl acetate (10 mL x 3). The combined organic layer was dried over Na_2SO_4, evaporated in vacuo to give a crude, which was purified by prep-HPLC to afford N-(1-(3-(5-(acetamidomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (19.64 mg, 91%) as a white solid after lyophilization. ^1H NMR (400 MHz, DMSO-d6) δ = 8.77 (d, *J* = 8.1 Hz, 1H), 8.49 (t, *J* = 5.8 Hz, 1H), 8.21 (s, 1H), 7.92 (s, 1H), 7.69-7.64 (m, 1H), 7.57-7.48 (m, 2H), 7.44 (s, 1H), 7.39 (d, *J* = 3.5 Hz, 1H), 7.33-7.28 (m, 2H), 7.24-7.20 (m, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 5.16 (quin, *J* = 7.2 Hz, 1H), 4.42 (d, *J* = 5.7 Hz, 2H), 4.15 (d, *J* = 6.1 Hz, 2H), 3.88 (s, 3H), 2.87 (s, 3H), 2.28 (s, 3H), 1.86 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 580.3 $[M+H]^+$.

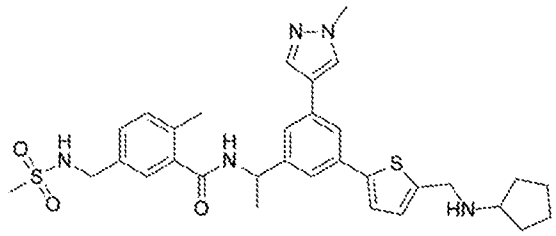
Prep-HPLC condition:

Column: Boston Prime C18 150*30mm*5μm;

Mobile phase: water (NH_4OH v/v)-$MeCN_4$; B%: 21%-51%,

Flow Rate (mL/min): 30mL/min.

Example 74: N-(1-(3-(5-((cyclopentylamino)methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide



(74)

To a solution of N-(1-(3-(5-formylthiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (100 mg, 0.151 mmol) in THF (2 mL) were added AcOH (9.10 mg, 0.151 mmol) and cyclopentanamine (12.9 mg, 0.151 mmol) at 20 °C. The reaction mixture was stirred at 50 °C for 16 h. $NaBH_3CN$ (28.6 mg, 0.454 mmol) was then added to the mixture, and the reaction was stirred at 50 °C for 5 h. After that, the reaction mixture was evaporated in vacuo to give a crude, which was purified by prep-HPLC to give N-(1-(3-(5-((cyclopentylamino)methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide (31.4 mg, 34.2%) as a white solid after lyophilization. ^1H NMR (400 MHz, DMSO-d6) δ = 9.31 (br d, *J* = 4.1 Hz, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.73 (s, 1H), 7.63-7.53 (m, 3H), 7.47 (s, 1H), 7.38 (d, *J* = 3.8 Hz, 1H), 7.35-7.27 (m, 2H), 7.25-7.19 (m, 1H), 5.17 (quin, *J* = 7.2 Hz, 1H), 4.43-4.32 (m, 2H), 4.15 (d, *J* = 5.9 Hz, 2H), 3.89 (s, 3H), 2.88 (s, 3H), 2.57-2.52 (m, 1H), 2.28 (s, 3H), 2.06-1.92 (m, 2H), 1.77-1.66 (m, 4H), 1.53 (br d, *J* = 4.1 Hz, 2H), 1.49 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 606.3 $[M+H]^+$.

Prep-HPLC condition:

Column: Boston Green ODS 150*30mm*5μm;

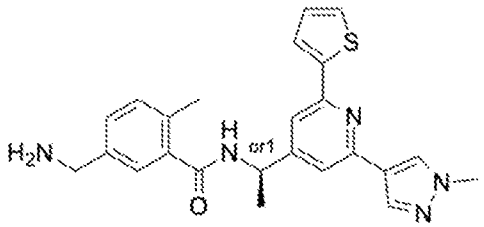
Mobile phase: water (HCl)-MeCN; B%: 18%-58%,

Flow Rate (mL/min): 30mL/min.

Example 93: rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-1

and

Example 94: rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-2



(93, 94)

5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide (Example 15) was separated by SFC to afford crude 1 (34 mg) as a colourless oil and rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-1 (20.12 mg) as a white solid. ^{1}H NMR (400 MHz, MeOD-d4, 295 K) δ (ppm) = 8.23-8.21 (s, 1H), 8.24-8.20 (s, 1H), 8.07 (s, 1H), 7.75-7.73 (m, 1H), 7.66-7.64 (m, 1H), 7.53-7.50 (m, 2H), 7.40-7.33 (m, 2H), 7.27-7.23 (m, 1H), 7.17-7.14 (m, 1H), 5.30-5.21 (m, 1H), 3.99 (s, 3H), 3.84-3.81 (s, 2H), 2.37 (s, 3H), 1.64-1.60 (m, 3H). LCMS (ESI): m/z = 432.3 $[M+H]^+$.

The crude 1 was dissolved in methanol and purified by prep-HPLC to afford rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-2 (2.92 mg) as a white solid after lyophilization. ^{1}H NMR (400 MHz, MeOD-d4, 297 K) δ (ppm) = 8.26-8.20 (s, 1H), 8.08-8.04 (s, 1H), 7.76-7.73 (m, 1H), 7.68-7.62 (m, 1H), 7.54-7.49 (m, 2H), 7.42-7.34 (m, 2H), 7.30-7.25 (m, 1H), 7.19-7.13 (m, 1H), 5.30-5.18 (m, 1H), 3.99 (s, 3H), 3.88 (s, 2H), 2.38 (s, 3H), 1.63 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 432.3 $[M+H]^+$.

Prep-SFC method:

Instrument: SFC-16

Condition: A: CO_2-EtOH (0.1% $NH_3.H_2O$); B: EtOH

Column: DAICEL CHIRALPAK AD (250mm*30mm, 10μm)

Flow rate: 30 mL/min

Monitor wavelength: 220&254 nm

Gradient: B%, 55% to 55%,

Prep-HPLC method:

Instrument: ACSSH-CP

Mobile phase: A: water (0.05% ammonium hydroxide v/v)-MeCN; B: MeCN

Column: C18 150*30mm*5μm

Flow rate: 30 mL/min

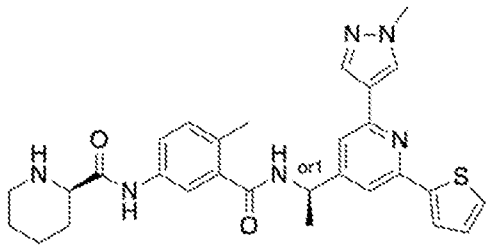
Monitor wavelength: 220&254 nm

Gradient: B%, 12% to 52%, 9min, 100%B Hold Time (min) 2min

Example 95: (R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1

and

Example 96: (R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2



(95, 96)

(2R)-N-(4-methyl-3-((1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide (43 mg, 0.084 mmol) was separated by SFC to afford (R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1 (8 mg, 18%, peak 1) as a white solid. ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.24 (s, 1H), 8.10 (s, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 1.0, 3.7 Hz, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.51 (d, *J* = 5.8 Hz, 1H), 7.45 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.16 (dd, *J* = 3.7, 5.1 Hz, 1H), 5.24 (q, *J* = 6.9 Hz, 1H), 3.99 (s, 3H), 3.42-3.35 (m, 1H), 3.19-3.11 (m, 2H), 2.75-2.67 (m, 1H), 2.35 (s, 3H), 2.03-1.90 (m, 2H), 1.69-1.48 (m, 7H). LCMS (ESI): m/z = 529.3 [M+ H] +;

and (R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2 (11.2 mg, 25%, peak 2). ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.24 (s, 1H), 8.10 (s, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 1.0, 3.7 Hz, 1H), 7.65 (s, 1H), 7.52 (s, 1H), 7.51 (d, *J* = 5.8 Hz, 1H), 7.45 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.16 (dd, *J* = 3.7, 5.1 Hz, 1H), 5.24 (q, *J* = 6.9 Hz, 1H), 3.99 (s, 3H),

3.42-3.35 (m, 1H), 3.19-3.11 (m, 2H), 2.75-2.67 (m, 1H), 2.35 (s, 3H), 2.03-1.90 (m, 2H), 1.69-1.48 (m, 7H). LCMS (ESI): m/z = 529.3 $[M+H]^+$.

SFC condition:

Column: DAICEL CHIRALPAK AD (250mm*30mm, 10μm);

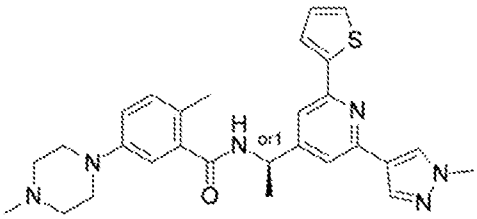
Mobile phase: CO_2-i-PrOH (0.1% NH_4OH); B%: 40%-40%,

Flow rate (mL/min): 150 mL/min.

Example 97: rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-1

and

Example 98: rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-2



(97, 98)

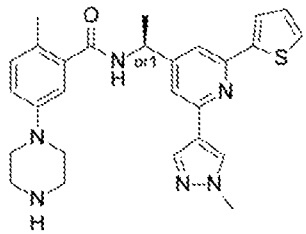
2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide (40 mg 0.080 mmol) was separated by SFC to afford two white solids rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-1 (19.3 mg, 48%); ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.22 (s, 1H) 8.06 (d, *J* = 0.61 Hz, 1H) 7.73 (dd, *J* = 3.67, 1.10 Hz, 1H) 7.65 (d, *J* = 0.98 Hz, 1H) 7.51 (td, *J* = 2.51, 1.10 Hz, 2H) 7.13-7.19 (m, 2H) 6.98-7.04 (m, 2H) 5.24 (q, *J* = 7.05 Hz, 1H) 3.99 (s, 3H) 3.19-3.25 (m, 4H) 2.60-2.67 (m, 4H) 2.37 (s, 3H) 2.29 (s, 3H) 1.61 (d, *J* = 7.09 Hz, 3H). LCMS (ESI): m/z = 501.3 [M+ H] +; and rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-2 (14.2 mg, 37%); ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.21 (s, 1H) 8.06 (s, 1H) 7.73 (dd, *J* = 3.67, 1.10 Hz, 1H) 7.64 (d, *J* = 1.10 Hz, 1H) 7.51 (td, *J* = 2.45, 1.10 Hz, 2H) 7.11-7.20 (m, 2H) 6.97-7.04 (m, 2H) 5.24 (q, *J* = 6.97 Hz, 1H) 3.99 (s, 3H) 3.18-3.25 (m, 4H) 2.59-2.69 (m, 4H) 2.38 (s, 3H) 2.29 (s, 3H) 1.61 (d, *J* = 7.09 Hz, 3H). LCMS (ESI): m/z = 501.3 $[M+H]^+$.

SFC condition:

Column: DAICEL CHIRALPAK AD(250 mm*30 mm,10 μm);

Mobile phase: CO_2-EtOH(0.1% $NH_3.H_2O$),
Flow rate (mL/min): 80 mL/min.

Example 99: rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-1
and
Example 100: rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-2

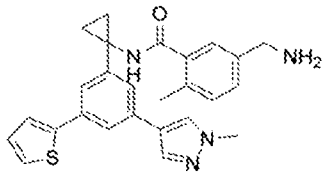
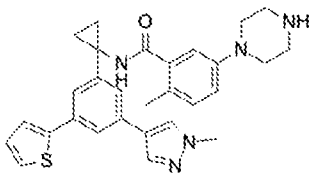


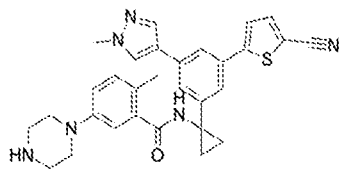
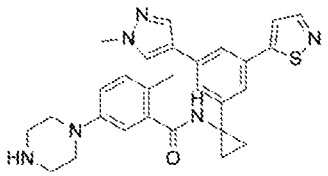
(99, 100)

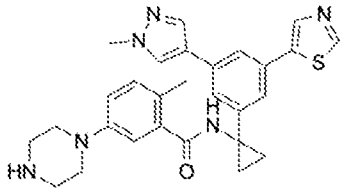
2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide (45 mg 0.092 mmol) was separated by SFC to afford two white solids rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-1 (20 mg, 44%); ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.22 (s, 1H) 8.06 (s, 1H) 7.73 (dd, *J* = 3.63, 0.88 Hz, 1H) 7.65 (s, 1H) 7.48-7.55 (m, 2H) 7.13-7.18 (m, 2H) 6.96-7.05 (m, 2H) 5.24 (q, *J* = 7.21 Hz, 1H) 3.99 (s, 3H) 3.12-3.19 (m, 4H) 2.96-3.05 (m, 4H) 2.30 (s, 3H) 1.61 (d, *J* = 7.13 Hz, 3H). LCMS (ESI): m/z = 487.4 [M+ H] +; and rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-2 (17.3 mg, 38%); ^{1}H NMR (400 MHz, MeOD-d4) δ = 8.22 (s, 1H) 8.06 (s, 1H) 7.69-7.77 (m, 1H) 7.65 (s, 1H) 7.51 (d, *J* = 2.75 Hz, 2H) 7.12-7.20 (m, 2H) 6.96-7.04 (m, 2H) 5.24 (q, *J* = 7.00 Hz, 1H) 3.99 (s, 3H) 3.09-3.19 (m, 4H) 2.96-3.04 (m, 4H) 2.30 (s, 3H) 1.61 (d, *J* = 7.13 Hz, 3H). LCMS (ESI): m/z = 487.4 $[M+H]^+$.
SFC condition:
Column: DAICEL CHIRALPAK AS(250 mm*30 mm,10 μm);
Mobile phase: CO_2-EtOH(0.1% $NH_3.H_2O$),
Flow rate (mL/min): 80 mL/min.

Further examples

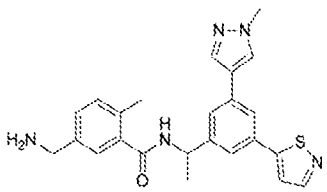
The following examples were prepared in a similar manner to Example 33, starting from an appropriate amine and using appropriate boronic acids or boronic esters.

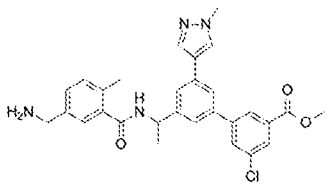
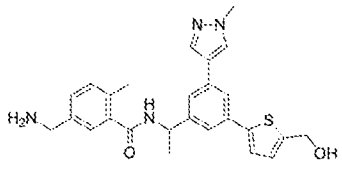
Ex. #	Structure; Compound Name	Analogous method, reactants	Characterizing Data
Ex. 48	 5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl) benzamide	Example 33, Step 1, using 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid and 1-(3,5-dibromophenyl) cyclopropan-1-amine; Example 33, Step 2, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Example 33, Step 3, using thiophen-2-ylboronic acid; Examples 33, Step 4.	^{1}H NMR (400 MHz, MeOD-d4, 296 K) δ (ppm) = 8.25 (s, 1H), 8.17-8.09 (m, 1H), 7.76-7.71 (m, 1H), 7.69-7.63 (m, 1H), 7.51-7.36 (m, 6H), 7.18-7.10 (m, 1H), 4.16-4.11 (m, 2H), 4.04 (s, 3H), 2.44 (s, 3H), 1.50-1.45 (m, 2H), 1.44-1.36 (m, 2H). LCMS (ESI): m/z = 443.3 $[M+H]^+$.
Ex. 49	 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl)-5-(piperazin-1-yl)benzamide	Example 33, Step 1, using 5-(4-(tert-butoxycarbonyl) piperazin-1-yl)-2-methylbenzoic acid and 1-(3,5-dibromophenyl) cyclopropan-1-amine; Example 33, Step 2, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Example 33, Step 3, using thiophen-2-ylboronic acid; Examples 33, Step 4.	^{1}H NMR (400 MHz, MeOD-d4, 296 K) δ (ppm) = 8.22-8.16 (m, 1H), 8.08-8.01 (m, 1H), 7.74-7.70 (m, 1H), 7.63-7.60 (m, 1H), 7.51-7.48 (m, 1H), 7.45-7.41 (m, 3H), 7.24-7.20 (m, 1H), 7.17-7.13 (m, 1H), 7.09-7.02 (m, 3H), 4.07-3.99 (m, 4H), 3.43-3.38 (m, 10H), 2.34-2.33 (m, 3H), 1.47-1.44 (m, 2H), 1.43-1.40 (m, 2H). LCMS (ESI): m/z = 498.3 $[M+H]^+$.

Ex. 101	 N-(1-(3-(5-cyanothiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl) cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide	Example 33, Step 1, using 5-(4-(tert-butoxycarbonyl) piperazin-1-yl)-2-methylbenzoic acid and 1-(3,5-dibromophenyl) cyclopropan-1-amine; Example 33, Step 2, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Example 33, Step 3, using (5-cyanothiophen-2-yl)boronic acid; Examples 33, Step 4, using trimethylsilyl trifluoromethanesulfonate instead of HCl.	^{1}H NMR (400 MHz, MeOD-d4, 297 K) δ (ppm) = 8.57-8.41 (s, 2H), 8.14-8.08 (s, 1H), 7.96-7.88 (s, 1H), 7.82-7.74 (m, 2H), 7.63-7.51 (m, 3H), 7.21 (br d, *J* = 8.3 Hz, 1H), 7.09-7.01 (m, 2H), 4.00-3.95 (s, 3H), 3.44-3.34 (m, 8H), 2.32 (s, 3H), 1.52-1.35 (m, 4H). LCMS (ESI): m/z = 523.3 $[M+H]^+$.
Ex. 102	 N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide	Example 33, Step 1, using 5-(4-(tert-butoxycarbonyl) piperazin-1-yl)-2-methylbenzoic acid and 1-(3,5-dibromophenyl) cyclopropan-1-amine; Example 33, Step 2, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Example 33, Step 3, using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole; Examples 33, Step 4.	^{1}H NMR (400 MHz, MeOD-d4, 297 K) δ (ppm) = 8.52 (s, 1H), 8.15-8.07 (s, 1H), 7.94-7.88 (s, 1H), 7.79-7.67 (m, 2H), 7.56 (br d, *J* = 6.2 Hz, 2H), 7.19 (br d, *J* = 9.0 Hz, 1H), 7.09-7.02 (m, 2H), 3.96 (s, 3H), 3.47-3.27 (m, 8H), 2.32 (s, 3H), 1.50-1.38 (m, 4H). LCMS (ESI): m/z = 499.4 $[M+H]^+$.

Ex. 103	 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl) cyclopropyl)-5-(piperazin-1-yl)benzamide	Example 33, Step 1, using 5-(4-(tert-butoxycarbonyl) piperazin-1-yl)-2-methylbenzoic acid and 1-(3,5-dibromophenyl) cyclopropan-1-amine; Example 33, Step 2, using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; Example 33, Step 3, using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole; Examples 33, Step 4.	^{1}H NMR (400 MHz, MeOD-d4, 298 K) δ (ppm) = 9.04-8.96 (s, 1H), 8.28-8.21 (s, 1H), 8.10-8.06 (s, 1H), 7.94-7.87 (s, 1H), 7.76-7.69 (t, 1H), 7.57-7.47 (m, 2H), 7.19-7.13 (m, 1H), 7.05-6.95 (m, 2H), 3.96 (s, 3H), 3.19-3.14 (m, 4H), 3.05-2.97 (m, 4H), 2.31 (s, 3H), 1.47-1.41 (m, 4H). LCMS (ESI): m/z = 499.4 $[M+H]^+$.

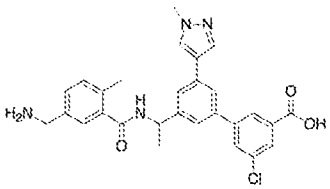
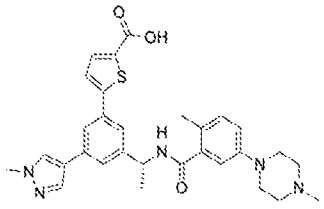
The following examples were prepared in a similar manner to the **Example 4** using an appropriate sulfinamide (Step 1), an appropriate carboxylic acid (Step 2), and an appropriate boronic acid or boronic ester (Step 3).

Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 50	 5-(aminomethyl)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 4, Step 1 using N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**); then Example 4, Step 2 using 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**);	^{1}H NMR (400 MHz, DMSO-d6) δ = 8.83-8.71 (m, 1H), 8.63 (d, *J* = 1.6 Hz, 1H), 8.27 (s, 1H), 7.98 (s, 1H), 7.88-7.81 (m, 2H), 7.70 (s, 1H), 7.58 (s, 1H), 7.35-7.21 (m, 2H), 7.21-7.15 (m, 1H), 5.19 (quin, *J* = 7.1 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 2H), 2.26 (s, 3H), 1.49 (d, *J* = 6.7 Hz, 3H) .

		then Example 4, Step 3 using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isothiazole; then Example 4, Step 4.	LCMS (ESI): m/z = 432.2 $[M+H]^+$.
Ex. 59	 methyl 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate	Example 4, Step 1 using N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**); then Example 4, Step 2 using 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**); then Example 4, Step 3 using (3-chloro-5-(methoxycarbonyl)phenyl) boronic acid; then Example 4, Step 4	^{1}H NMR (400 MHz, MeOD-d4) δ ppm 8.566 (s, 1H), 8.251 (t, *J* = 1.47 Hz, 1H), 8.118 (s, 1H), 7.992 (dt, *J* = 7.67, 1.79 Hz, 2H), 7.958 (s, 1H), 7.734-7.777 (m, 1H), 7.694 (s, 1H), 7.587 (s, 1H), 7.339-7.409 (m, 2H), 7.224-7.307 (m, 1H), 5.330 (q, *J* = 7.01 Hz, 1H), 4.552-4.710 (m, 1H), 3.976 (d, *J* = 3.67 Hz, 6H), 3.882 (s, 2H), 2.380 (s, 3H), 1.640 (d, *J* = 6.97 Hz, 3H). LCMS (ESI): m/z = 517.3 $[M+H]^+$.
Ex. 82	 5-(aminomethyl)-N-(1-(3-(5-(hydroxymethyl) thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 4, Step 1 using N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P9**); then Example 4, Step 2 using 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid (**P3**);	^{1}H NMR (400 MHz, DMSO-d6, K) Shift (ppm) = 8.16 (s, 1H), 7.90 (s, 1H), 7.65 (s, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.38 (d, *J* = 3.5 Hz, 1H), 7.31-7.17 (m, 3H), 6.97 (d, *J* = 3.5 Hz, 1H), 5.11 (br d, *J* = 6.8 Hz, 1H), 4.62 (s, 2H), 4.10 (s, 1H), 3.85 (s, 3H), 3.73 (s, 2H), 2.22 (s, 3H), 1.46 (br d, *J* = 7.0 Hz, 3H).

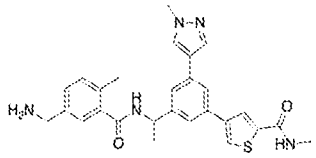
		then Example 4, Step 3 using (5-(methoxymethyl) thiophen-2-yl)boronic acid; then Example 4, Step 4 for 16 h.	LCMS (ESI): m/z = 461.3 $[M+H]^+$.

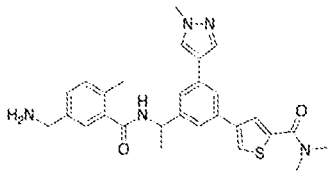
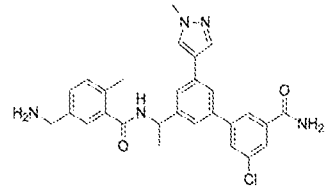
The following examples were prepared in a similar manner to the **Example 30** starting from an appropriate reactant.

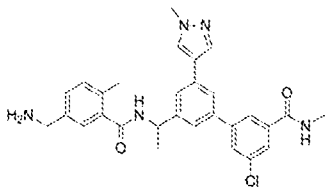
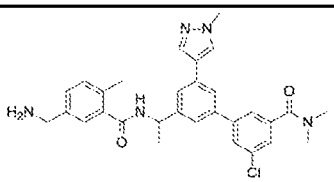
Ex. #	**Structure; Compound Name**	**Reactant**	**Characterizing Data**
Ex. 53	 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid	methyl 3'-(1-(5-(((tert-butoxycarbonyl)amino) methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate	^{1}H NMR (400 MHz, MeOD-d4) δ ppm 8.260 (s, 1H), 8.105 (s, 1H), 7.952 (s, 1H), 7.882-7.929 (m, 1H), 7.798 (t, *J* = 1.77 Hz, 1H), 7.760 (s, 1H), 7.621 (d, *J* = 7.21 Hz, 2H), 7.524 (d, *J* = 1.71 Hz, 1H), 7.399-7.452 (m, 1H), 7.320-7.381 (m, 1H), 5.299 (q, *J* = 7.21 Hz, 1H), 4.575-4.643 (m, 3H), 4.039-4.185 (m, 2H), 3.957 (s, 3H), 2.436 (s, 3H), 1.615 (d, *J* = 7.09 Hz, 3H). LCMS (ESI): m/z = 503.3 $[M+H]^+$.
Ex. 86	 (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-	methyl (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl) thiophene-2-carboxylate, using Step 1 of Example	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.728 (d, *J* = 8.19 Hz, 1H), 8.262 (s, 1H), 8.165 (s, 1H), 7.960 (d, *J* = 0.61 Hz, 1H), 7.816 (t, *J* = 1.47 Hz, 1H), 7.674 (d, *J* = 3.91 Hz, 1H), 7.577-7.633 (m,

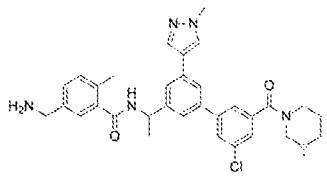
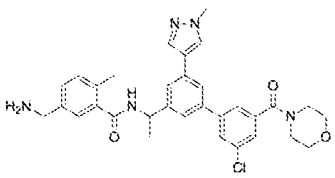
	methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylic acid	30 with LiOH instead of NaOH, then purification by prep-HPLC.	2H), 7.560 (s, 1H), 7.084 (d, *J* = 8.56 Hz, 1H), 6.872-6.961 (m, 2H), 5.156 (t, *J* = 7.52 Hz, 1H), 3.885 (s, 4H), 3.099-3.204 (m, 4H), 2.572 (t, *J* = 4.77 Hz, 4H), 2.278-2.340 (m, 3H), 2.198 (s, 3H), 1.478 (d, *J* = 6.97 Hz, 3H). LCMS (ESI): m/z = 544.3 $[M+H]^+$.

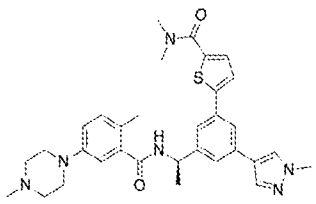
The following examples were prepared in a similar manner to the preparation of **Example 34** and the preparation of **Example 35**, using appropriate reactants.

Ex. #	**Structure; Compound Name**	**Example of analogous method, reactants**	**Characterizing Data**
Ex. 51	 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methylthiophene-2-carboxamide	Example 34, Step 1 using 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido) ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl) thiophene-2-carboxylic acid and $MeNH_2.HCl$; Then Example 34, Step 2, using tert-butyl (4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(5-(methylcarbamoyl) thiophen-3-yl)phenyl)ethyl) carbamoyl)benzyl)carbamate.	^1H NMR (400MHz, DMSO-d6) δ = 8.76-8.67 (m, 1H), 8.53 (br d, *J* = 4.5 Hz, 1H), 8.19 (d, *J* = 6.6 Hz, 2H), 8.07 (d, *J* = 1.0 Hz, 1H), 7.91 (s, 1H), 7.76 (s, 1H), 7.56 (br d, *J* = 10.1 Hz, 2H), 7.34-7.21 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 1H), 5.19 (quin, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 2H), 2.80 (d, *J* = 4.5 Hz, 3H), 2.28-2.22 (m, 3H), 1.50 (br d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 488.3 $[M+H]^+$.

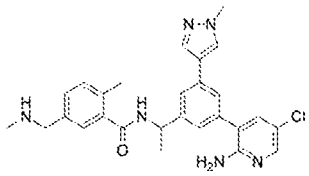
Ex. 52	 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido) ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide	Example 34, Step 1 using 4-(3-(1-(5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (**P21**) and $Me_2NH.HCl$; Then Example 34, Step 2 using tert-butyl (3-((1-(3-(5-(dimethylcarbamoyl)thiophen-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl)carbamate.	^{1}H NMR (400MHz, DMSO-d6) δ = 8.76-8.65 (m, 1H), 8.21 (s, 1H), 8.08 (d, *J* = 1.2 Hz, 1H), 7.98-7.90 (m, 2H), 7.81 (s, 1H), 7.60 (s, 1H), 7.56 (s, 1H), 7.35-7.22 (m, 2H), 7.21-7.15 (m, 1H), 5.24-5.14 (m, 1H), 3.88 (s, 3H), 3.73 (s, 2H), 3.17 (br s, 6H), 2.29-2.22 (m, 3H), 1.49 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 502.4 $[M+H]^+$.
Ex. 54	 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide	Example 34, Step 1 using 3'-(1-(5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid and NH_4Cl; Then Example 34, Step 2, using tert-butyl (3-((1-(3'-carbamoyl-5'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl) carbamoyl)-4-methylbenzyl) carbamate.	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.765 (br d, *J* = 8.44 Hz, 1H), 8.160-8.313 (m, 3H), 7.986 (d, *J* = 2.20 Hz, 2H), 7.912 (s, 1H), 7.843 (s, 1H), 7.605-7.714 (m, 3H), 7.352 (s, 1H), 7.308 (d, *J* = 7.58 Hz, 1H), 7.170-7.229 (m, 1H), 5.246 (br t, *J* = 7.46 Hz, 1H), 4.129 (br s, 1H), 3.906 (s, 3H), 3.766 (s, 2H), 2.241-2.350 (m, 3H), 1.467-1.571 (m, 3H), 1.360 (s, 1H), 1.250 (s, 1H). LCMS (ESI): m/z = 502.3 $[M+H]^+$.

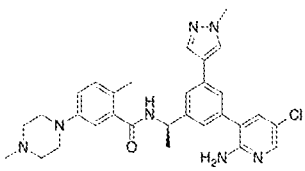
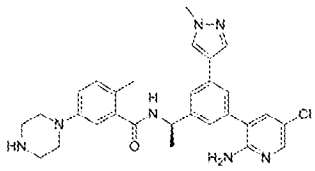
Ex. 55	 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N-methyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide	Example 34, Step 1, using 3'-(1-(5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid and $MeNH_2$.HCl; Then Example 34, Step 2, using tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(methylcarbamoyl)-[1,1'-biphenyl]-3-yl)ethyl) carbamoyl)-4-methylbenzyl) carbamate.	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.645-8.815 (m, 2H), 8.233-8.303 (m, 1H), 8.127 (s, 1H), 7.968 (br d, *J* = 7.09 Hz, 2H), 7.836 (br d, *J* = 9.90 Hz, 2H), 7.647 (br d, *J* = 17.12 Hz, 2H), 7.371 (s, 1H), 7.314 (br d, *J* = 8.07 Hz, 1H), 7.201 (br d, *J* = 7.82 Hz, 1H), 5.179-5.289 (m, 1H), 3.888 (s, 3H), 3.804 (s, 2H), 2.825 (d, *J* = 4.40 Hz, 3H), 2.226-2.299 (m, 3H), 1.507 (br d, *J* = 6.97 Hz, 3H), 1.232 (br s, 1H). LCMS (ESI): m/z = 516.3 $[M+H]^+$.
Ex. 56	 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N,N-dimethyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide	Example 34, Step 1, using 3'-(1-(5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid and Me_2NH.HCl; Then Example 34, Step 2, using tert-butyl (3-((1-(3'-chloro-5'-(dimethylcarbamoyl) -5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.726 (br d, *J* = 8.07 Hz, 1H), 8.284 (s, 1H), 7.984 (s, 1H), 7.866-7.916 (m, 1H), 7.816 (s, 1H), 7.713 (s, 1H), 7.631 (br d, *J* = 13.69 Hz, 2H), 7.461 (s, 1H), 7.248-7.357 (m, 2H), 7.178 (d, *J* = 7.58 Hz, 1H), 5.222 (s, 1H), 3.882 (s, 3H), 3.745 (s, 2H), 2.828-3.053 (m, 8H),

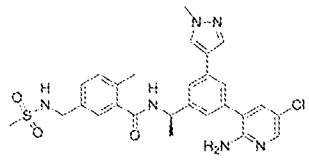
		yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate.	2.260 (s, 3H), 1.496 (br d, *J* = 6.97 Hz, 3H). LCMS (ESI): m/z = 530.4 $[M+H]^+$.
Ex. 57	 5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 34, Step 1, using 3'-(1-(5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid and piperidine; Then Example 34, Step 2, using tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate.	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.588 (br s, 2H), 7.873 (s, 1H), 7.801-7.852 (m, 2H), 7.744 (br s, 2H), 7.700 (s, 1H), 7.578-7.634 (m, 1H), 7.549 (s, 1H), 7.481-7.527 (m, 1H), 5.354-5.477 (m, 1H), 3.903-4.003 (m, 4H), 3.539-3.774 (m, 3H), 3.295-3.417 (m, 3H), 2.398-2.462 (m, 1H), 2.269 (s, 3H), 1.676 (br d, *J* = 6.72 Hz, 10H). LCMS (ESI): m/z = 570.1 $[M+H]^+$.
Ex. 58	 5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 34, Step 1, using 3'-(1-(5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid and morpholine; Then Example 34, Step 2, using tert-butyl (3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(morpholine-	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.788-7.872 (m, 3H), 7.761 (s, 1H), 7.687-7.731 (m, 2H), 7.609-7.657 (m, 1H), 7.467-7.556 (m, 3H), 7.018 (s, 1H), 3.932-3.952 (m, 3H), 3.571-3.846 (m, 9H), 3.386-3.505 (m, 3H), 2.361 (d, *J* = 1.34 Hz, 1H), 2.287 (s,

		4-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylbenzyl)carbamate.	2H), 1.669 (br d, *J* = 7.09 Hz, 5H). LCMS (ESI): m/z = 572.1 $[M+H]^+$.
Ex. 84	 (R)-N,N-dimethyl-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxamide	Example 34, Step 1, using (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl) thiophene-2-carboxylic acid and Me_2NH; then purification by prep-HPLC	^{1}H NMR (400 MHz, DMSO-d6) δ = 8.74 (br d, *J* = 8.3 Hz, 1H), 8.26 (s, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.62-7.48 (m, 4H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.95-6.82 (m, 2H), 5.15 (quin, *J* = 7.2 Hz, 1H), 3.89 (s, 3H), 3.27 (br d, *J* = 5.9 Hz, 4H), 3.13-3.00 (m, 6H), 2.47-2.38 (m, 4H), 2.20 (d, *J* = 8.9 Hz, 6H), 1.47 (br d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 571.3 $[M+H]^+$. SFC: ee = 100%

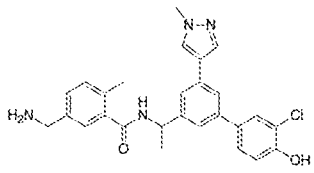
The following examples were prepared in a similar manner to the preparation of **Example 45**, using appropriate reactants.

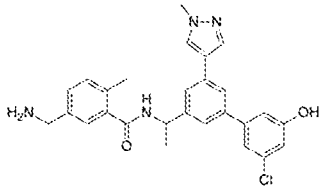
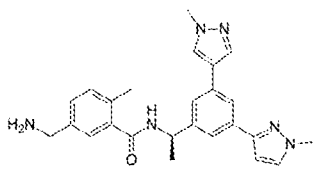
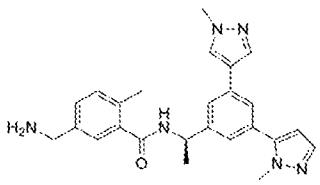
Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 60	 N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-	Example 45 Step 1 using tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)carbamoyl)-4-methylbenzyl) (methyl)carbamate and 3-	^{1}H NMR (400 MHz, MeOD-d4) δ ppm 1.63 (d, *J* = 7.09 Hz, 3H) 2.33-2.45 (m, 3H) 2.58-2.77 (m, 3H) 3.27-3.41 (m, 6H) 3.96 (s, 3H) 4.16 (s, 2H) 5.29 (q, *J* = 7.01 Hz, 1H) 7.32-7.41 (m, 2H) 7.42-7.48 (m, 2H)

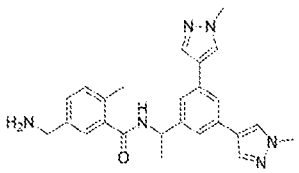
	methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-((methylamino)methyl) benzamide	bromo-5-chloropyridin-2-amine; then Example 45, Step 2	7.48-7.51 (m, 1H) 7.57 (s, 1H) 7.64-7.71 (m, 1H) 7.87-7.93 (m, 1H) 7.94-8.00 (m, 1H) 8.04-8.09 (m, 1H) 8.47-8.58 (m, 1H). LCMS (ESI): m/z = 489.3 $[M+H]^+$.
Ex. 83	 (R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide	Example 45 Step 1 using (R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide (**P23**) and 3-bromo-5-chloropyridin-2-amine; then purification by prep-HPLC	^{1}H NMR (400MHz, MeOD-d4) Shift = 8.05 (s, 1H), 7.98-7.88 (m, 2H), 7.67 (s, 1H), 7.55 (s, 1H), 7.52-7.46 (m, 1H), 7.38 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.02-6.93 (m, 2H), 5.25 (q, *J* = 7.1 Hz, 1H), 3.96 (s, 3H), 3.30-3.16 (m, 4H), 2.73-2.53 (m, 4H), 2.37 (s, 3H), 2.28 (s, 3H), 1.61 (d, *J* = 7.1 Hz, 3H). LCMS (ESI): m/z = 544.3 $[M+H]^+$.
Ex. 91	 (R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(piperazin-1-yl)benzamide	Example 45, Step 1, using tert-butyl (R)-4-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylphenyl)piperazine-1-carboxylate (**P24**) and 3-bromo-5-chloropyridin-2-amine; then Example 45, Step 2	^{1}H NMR (400 MHz, DMSO-d6) δ = 8.64 (d, *J* = 8.3 Hz, 1H), 8.19 (s, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.89 (s, 1H), 7.61 (s, 1H), 7.50 (s, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.33 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.91-6.79 (m, 2H), 5.86 (s, 2H), 5.17 (br t, *J* = 7.3 Hz, 1H), 3.87 (s, 3H), 3.03-2.93 (m, 4H), 2.85-2.75 (m, 4H), 2.18 (s, 3H), 1.49 (d, *J* = 7.0 Hz, 3H).

			LCMS (ESI): m/z = 530.4 $[M+H]^+$.
Ex. 92	 (R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamido methyl)benzamide	Example 45 Step 1 using (R)-N-(1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamido methylbenzamide and 3-bromo-5-chloropyridin-2-amine; then purification by prep-HPLC	^{1}H NMR (400MHz, MeOD-d4) Shift = 8.06 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.67 (s, 1H), 7.55 (s, 1H), 7.49 (s, 1H), 7.42-7.34 (m, 3H), 7.26 (d, *J* = 7.7 Hz, 1H), 5.30-5.24 (m, 1H), 4.26 (s, 2H), 3.96 (s, 3H), 2.90 (s, 3H), 2.37 (s, 3H), 1.61 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 553.3 $[M+H]^+$.

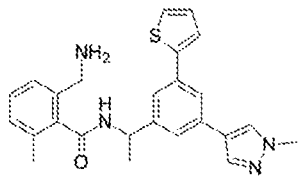
The following examples were prepared in a manner analogous to steps 3-4 of **Example 4** using appropriate reactants.

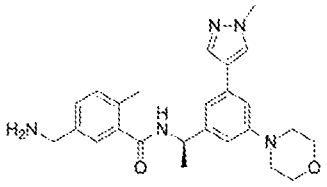
Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 77	 5-(aminomethyl)-N-(1-(3'-chloro-4'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 4, Step 3, using tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)carbamate and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole; then Example 4, Step 4.	^{1}H NMR (400MHz, DMSO-d6) δ = 10.38 (br s, 1H), 8.78 (d, *J* = 8.4 Hz, 1H), 8.26 (s, 4H), 7.96 (s, 1H), 7.72 (s, 1H), 7.69 (s, 1H), 7.58-7.47 (m, 4H), 7.41 (dd, *J* = 1.6, 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 5.22 (t, *J* = 7.5 Hz, 1H), 4.06-3.97 (m, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.51 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 475.4 $[M+H]^+$.

Ex. 78	 5-(aminomethyl)-N-(1-(3'-chloro-5'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide	Example 4, Step 3, using tert-butyl (3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)carbamate and (3-chloro-5-hydroxyphenyl)boronic acid; then Example 4, Step 4.	^{1}H NMR (400MHz, DMSO-d_6) δ = 8.49 (br d, *J* = 7.3 Hz, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.66-7.58 (m, 2H), 7.51 (s, 1H), 7.35-7.27 (m, 2H), 7.18 (s, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 6.84 (t, *J* = 1.9 Hz, 1H), 5.25 (quin, *J* = 7.3 Hz, 1H), 3.90 (s, 3H), 3.77 (s, 2H), 2.30 (s, 3H), 1.54 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 475.4 $[M+H]^+$.
Ex. 79	 (R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) benzamide	Example 4, Step 3, using tert-butyl (R)-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)carbamate and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 4, Step 4.	^{1}H NMR (400 MHz, DMSO-d6) δ = 8.70 (d, *J* = 8.3 Hz, 1H), 8.18 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.35-7.14 (m, 3H), 6.74 (d, *J* = 2.1 Hz, 1H), 5.17 (br t, *J* = 7.5 Hz, 1H), 3.90 (d, *J* = 4.1 Hz, 6H), 3.72 (s, 2H), 2.29-2.25 (m, 3H), 1.49 (d, *J* = 7.1 Hz, 3H). LCMS (ESI): m/z = 429.3 $[M+H]^+$.
Ex. 80	 (R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-methyl-1H-pyrazol-	Example 4, Step 3, using tert-butyl (R)-(3-((1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) carbamoyl)-4-methylbenzyl)carbamate and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole;	^{1}H NMR (400 MHz, DMSO-d6) δ = 8.71 (d, *J* = 8.4 Hz, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.37 (s, 1H), 7.32-7.24 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 5.20 (s, 1H), 3.88 (d, *J* = 5.4 Hz, 6H), 3.70 (s, 2H), 2.27-

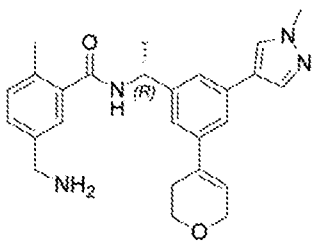
	5-yl)phenyl)ethyl) benzamide	then Example 4, Step 4.	2.22 (m, 3H), 1.49 (d, *J* = 7.1 Hz, 3H). LCMS (ESI): m/z = 429.3 $[M+H]^+$.
Ex. 81	 5-(aminomethyl)-N-(1-(3,5-bis(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 4, Step 3, using tert-butyl (3-((1-(3,5-dibromophenyl)ethyl)carbamoyl)-4-methylbenzyl) carbamate and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 4, Step 4.	^{1}H NMR (400 MHz, MeOD-d4) δ = 8.01 (s, 2H), 7.88 (s, 2H), 7.64 (s, 1H), 7.46 (d, *J* = 1.4 Hz, 2H), 7.38-7.27 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 5.33-5.19 (m, 1H), 3.94 (s, 6H), 3.84 (s, 2H), 2.34 (s, 3H), 1.59 (d, *J* = 7.1 Hz, 3H). LCMS (ESI): m/z = 429.3 $[M+H]^+$.

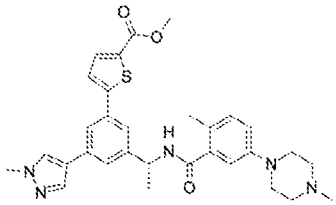
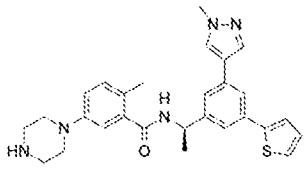
The following examples were prepared in a similar manner to Step 3-4 of Example 1 using appropriate reactants.

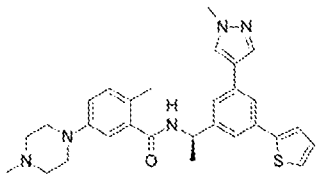
Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 64	 2-(aminomethyl)-6-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) benzamide	Example 1, Step 3, using 2-(((tert-butoxycarbonyl) amino)methyl)-6-methylbenzoic acid and 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl) phenyl)ethan-1-amine; then Example 1, Step 4, using tert-butyl (3-methyl-2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl) benzyl)carbamate.	^{1}H NMR (400 MHz, MeOD-d4) δ = 8.12-8.03 (m, 1H), 7.94-7.88 (m, 1H), 7.82-7.71 (m, 1H), 7.59-7.49 (m, 3H), 7.47-7.38 (m, 1H), 7.37-7.21 (m, 2H), 7.20-7.02 (m, 2H), 5.42-5.23 (m, 1H), 3.97 (s, 3H), 3.83-3.49 (m, 2H), 2.31 (s, 2H), 1.70-1.60 (m, 3H). LCMS (ESI): m/z = 431.0 $[M+H]^+$.

Ex. 69	 (R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl)benzamide	Example 1, Step 3, using 5-(((tert-butoxycarbonyl) amino)methyl)-2-methylbenzoic acid and (R)-1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethan-1-amine (**P22**); then Example 1, Step 4, using tert-butyl (R)-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl) carbamoyl)benzyl) carbamate.	^{1}H NMR (400 MHz, MeOD-d4, 295 K) δ (ppm) = 8.00-7.94 (s, 1H), 7.84-7.78 (s, 1H), 7.38-7.31 (m, 2H), 7.29-7.22 (m, 1H), 7.16-7.12 (s, 1H), 7.10-7.02 (s, 1H), 6.95-6.89 (s, 1H), 5.29-5.09 (m, 1H), 3.94 (s, 3H), 3.89-3.84 (m, 6H), 3.26-3.13 (m, 4H), 2.35 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 434.4 $[M+H]^+$.

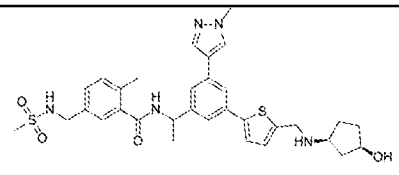
The following examples were prepared in a similar manner to the Example 1, using an appropriate halide plus boronic acid or boronic ester (in Step 1) and an appropriate carboxylic acid (in Step 3).

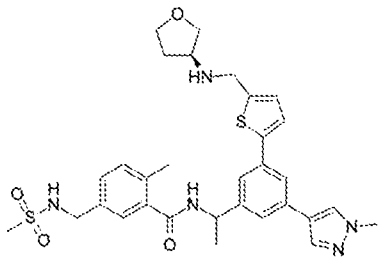
Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 68	 (R)-5-(aminomethyl)-N-(1-(3-(3,6-dihydro-2H-pyran-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide	Example 1, Step 1, using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) and 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; then Example 1 Step 2; then Example 1 Step 3 using 5-(((tert-butoxycarbonyl)	^{1}H NMR (400 MHz, MeOD-d4, 295 K) δ (ppm) = 8.01 (s, 1H), 7.90-7.81 (s, 1H), 7.53 (s, 1H), 7.52 (s, 1H), 7.39-7.31 (m, 3H), 7.26-7.21 (m, 1H), 6.27 (br s, 1H), 5.31-5.19 (m, 1H), 4.34 (q, *J* = 2.6 Hz, 2H), 3.97-3.95 (m, 5H), 3.86-3.81 (s, 2H), 2.62-2.56 (s, 2H), 2.37-2.33 (s, 3H), 1.62-1.56 (m, 3H).

		amino)methyl)-2-methylbenzoic acid; then Example 1 Step 4.	LCMS (ESI): m/z = 431.4 $[M+H]^+$.
Ex. 85	 methyl (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylate	Example 1, Step 1, using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) and (5-(methoxycarbonyl) thiophen-2-yl)boronic acid; then Example 1, Step 2; then Example 1, Step 3, using 2-methyl-5-(4-methylpiperazin-1-yl)benzoic acid; then purification by prep-HPLC.	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.747-7.812 (m, 2H), 7.677 (s, 1H), 7.617 (t, *J* = 1.53 Hz, 1H), 7.449-7.494 (m, 2H), 7.325 (d, *J* = 3.91 Hz, 1H), 7.099 (d, *J* = 8.44 Hz, 1H), 6.942 (d, *J* = 2.57 Hz, 1H), 6.882 (dd, *J* = 8.31, 2.69 Hz, 1H), 6.050 (br d, *J* = 8.07 Hz, 1H), 5.358 (t, *J* = 7.40 Hz, 1H), 3.965 (s, 3H), 3.910 (s, 3H), 3.171-3.287 (m, 4H), 2.679 (br d, *J* = 2.93 Hz, 4H), 2.425 (s, 3H), 2.336 (s, 3H), 1.640 (d, *J* = 6.97 Hz, 3H). LCMS (ESI): m/z = 558.4 $[M+H]^+$.
Ex. 87	 (R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide	Example 1, Step 1, using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) and thiophen-2-ylboronic acid; then Example 1, Step 2; then Example 1, Step 3, using 5-(4-(tert-butoxycarbonyl)piperazin-	^{1}H NMR (400MHz, DMSO-d6) δ = 8.73 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 7.73 (s, 1H), 7.59-7.56 (m, 2H), 7.52 (br d, *J* = 16.3 Hz, 2H), 7.17 (dd, *J* = 3.7, 5.1 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.92-6.86 (m, 2H), 5.14 (br t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 3.05-2.99 (m, 4H), 2.83 (br s, 4H), 2.19 (s, 3H), 1.47 (d, *J* = 6.8 Hz, 3H).

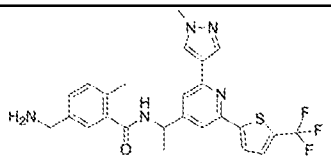
		1-yl)-2-methylbenzoic acid; then Example 1, Step 4	LCMS (ESI): m/z = 486.3 $[M+H]^+$.
Ex. 88	 (R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide	Example 1, Step 1, using (S)-N-((R)-1-(3-bromo-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylpropane-2-sulfinamide (**P19**) and thiophen-2-ylboronic acid; then Example 1, Step 2; then Example 1, Step 3, using 2-methyl-5-(4-methylpiperazin-1-yl)benzoic acid; then purification by prep-HPLC.	^{1}H NMR (400MHz, DMSO-d6) δ = 8.72 (d, *J* = 8.1 Hz, 1H), 8.23 (s, 1H), 7.93 (s, 1H), 7.73 (s, 1H), 7.59-7.56 (m, 2H), 7.51 (d, *J* = 15.6 Hz, 2H), 7.17 (dd, *J* = 3.9, 4.9 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.93-6.86 (m, 2H), 5.15 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H), 3.14-3.08 (m, 4H), 2.46-2.42 (m, 4H), 2.22 (s, 3H), 2.19 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 3H). LCMS (ESI): m/z = 500.3 $[M+H]^+$.

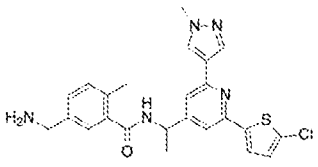
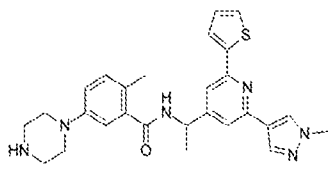
The following examples were prepared in a similar manner to the Example 74 using N-(1-(3-(5-formylthiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide and an appropriate amine.

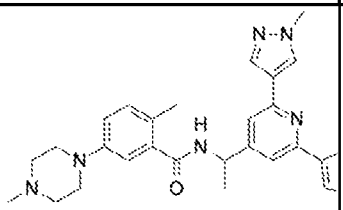
Ex. #	**Structure; Compound Name**	**Amine**	**Characterizing Data**
Ex. 75	 N-(1-(3-(5-((((1S,3R)-3-hydroxycyclopentyl)amino)methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-	(1R,3S)-3-aminocyclopentan-1-ol	^{1}H NMR (400 MHz, DMSO-d6) δ = 9.04 (br d, *J* = 2.8 Hz, 2H), 8.83-8.75 (m, 1H), 8.21 (s, 1H), 7.93 (s, 1H), 7.72 (s, 1H), 7.61-7.52 (m, 3H), 7.47 (s, 1H), 7.36-7.27 (m, 3H), 7.25-7.18 (m, 1H), 5.17 (br t, *J* = 7.4 Hz, 1H), 4.38 (br t, *J* = 5.3 Hz, 2H), 4.15 (d, *J* = 6.5 Hz, 2H), 4.13-4.09 (m, 1H), 3.89 (s, 3H),

	(methylsulfonamidomethyl) benzamide		3.49 (br s, 1H), 2.88 (s, 3H), 2.27 (s, 3H), 2.22-2.15 (m, 1H), 2.00-1.93 (m, 1H), 1.91-1.81 (m, 1H), 1.71-1.61 (m, 3H), 1.52-1.46 (m, 1H), 1.49 (d, *J* = 7.0 Hz, 2H). LCMS (ESI): m/z = 622.3 $[M+H]^+$.
Ex. 76	 2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(5-((((S)-tetrahydrofuran-3-yl)amino)methyl)thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl) benzamide	(S)-tetrahydrofuran-3-amine	^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.78 (d, *J* = 8.1 Hz, 1H), 8.22 (s, 1H), 7.92 (s, 1H), 7.68 (s, 1H), 7.55 (t, *J* = 6.4 Hz, 1H), 7.50 (s, 1H), 7.46 (s, 1H), 7.40 (d, *J* = 3.5 Hz, 1H), 7.34-7.27 (m, 2H), 7.25-7.18 (m, 1H), 6.98 (d, *J* = 3.5 Hz, 1H), 5.22-5.10 (m, 1H), 4.15 (d, *J* = 6.2 Hz, 2H), 3.93-3.89 (m, 1H), 3.88 (s, 3H), 3.88-3.75 (m, 2H), 3.74-3.61 (m, 2H), 3.47-3.35 (m, 2H), 2.87 (s, 3H), 2.28 (s, 3H), 2.01-1.88 (m, 1H), 1.75-1.63 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H). LCMS (ESI): m/z = 608.3 $[M+H]^+$.

The following examples were prepared in a similar manner to Example 12, Steps 1-8, using an appropriate boronic acid or boronic ester in step 1, an appropriate boronic acid or boronic ester in step 5, and an appropriate carboxylic acid in step 7.

Ex. #	**Structure; Compound Name**	**Analogous method, reactants**	**Characterizing Data**
Ex. 65	 5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-	Example 12, Step 1 using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole;	^{1}H NMR (400 MHz, DMSO-d6, 304 K) δ (ppm) = 8.79-8.74 (m, 1H), 8.37-8.31 (m, 1H), 8.05-8.02 (m, 1H), 7.91-7.85 (m, 2H), 7.82-7.76 (m, 1H), 7.72-7.67 (m,

	1H-pyrazol-4-yl)-6-(5-(trifluoromethyl)thiophen-2-yl)pyridin-4-yl)ethyl)benzamide	then Example 12, Step 2-4; then Example 12, Step 5 using (5-(trifluoromethyl) thiophen-2-yl)boronic acid; then Example 12, Step 6; then Example 12, Step 7 using 5-(((tert-butoxycarbonyl)amino)methyl)-2-methylbenzoic acid (**P3**); then Example 12, Step 8.	1H), 7.44-7.40 (m, 1H), 7.37-7.29 (m, 1H), 7.25-7.20 (m, 1H), 5.26-5.14 (m, 1H), 3.95 (s, 3H), 3.77 (s, 2H), 2.30 (s, 3H), 1.57-1.50 (m, 3H). LCMS (ESI): m/z = 500.3 $[M+H]^+$.
Ex. 66	 5-(aminomethyl)-N-(1-(2-(5-chlorothiophen-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide	Example 12, Step 1 using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole; then Example 12, Step 2-4; then Example 12, Step 5 using 2-(5-chlorothiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; then Example 12, Step 6; then Example 12, Step 7 using 5-(((tert-butoxycarbonyl)amino) methyl)-2-methylbenzoic acid; then Example 12 Step 8.	^{1}H NMR (400 MHz, DMSO-d6, 304 K) δ (ppm) = 8.75 (br d, *J* = 8.1 Hz, 1H), 8.37-8.22 (m, 1H), 8.04-7.92 (m, 1H), 7.75-7.71 (m, 1H), 7.68-7.64 (m, 1H), 7.62-7.59 (m, 1H), 7.44-7.39 (m, 1H), 7.35-7.30 (m, 1H), 7.24-7.18 (m, 2H), 5.22-5.10 (m, 1H), 3.94 (s, 3H), 3.79-3.74 (m, 2H), 2.32-2.26 (m, 3H), 1.56-1.49 (m,3H). LCMS (ESI): m/z = 466.2 $[M+H]^+$.
Ex. 89		Example 12, Step 1-4; then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-	^{1}H NMR (400 MHz, MeOD-d4) δ = 8.22 (s, 1H) 8.06 (s, 1H) 7.73 (dd, *J* = 3.73, 1.04 Hz, 1H) 7.65 (d, *J* = 1.10 Hz, 1H) 7.51 (dt, *J* = 3.15,

	2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide	dioxaborolan-2-yl)-1*H*-pyrazole; then Example 12, Step 6; then Example 12, Step 7, 5-(4-(tert-butoxycarbonyl) piperazin-1-yl)-2-methylbenzoic acid; then Example 12, Step 8.	1.42 Hz, 2H) 7.13-7.19 (m, 2H) 6.97-7.03 (m, 2H) 5.24 (q, *J* = 7.30 Hz, 1H) 3.99 (s, 3H) 3.15 (dd, *J* = 6.24, 3.79 Hz, 4H) 2.98-3.02 (m, 4H) 2.30 (s, 3H) 1.61 (d, *J* = 7.09 Hz, 3H). LCMS (ESI): m/z = 487.4 $[M+H]^+$.
Ex. 90	 2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide	Example 12, Step 1-4; then Example 12, Step 5, 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole; then Example 12, Step 6; then Example 12, Step 7, 2-methyl-5-(4-methylpiperazin-1-yl)benzoic acid; then purification by prep-HPLC	^{1}H NMR (400 MHz, METHANOL-d4) δ = 8.21 (s, 1H) 8.06 (d, *J* = 0.61 Hz, 1H) 7.73 (dd, *J* = 3.67, 1.10 Hz, 1H) 7.64 (d, *J* = 0.98 Hz, 1H) 7.51 (td, *J* = 2.48, 1.16 Hz, 2H) 7.13-7.18 (m, 2H) 6.97-7.03 (m, 2H) 5.24 (q, *J* = 7.01 Hz, 1H) 3.99 (s, 3H) 3.17-3.25 (m, 4H) 2.59-2.66 (m, 4H) 2.37 (s, 3H) 2.29 (s, 3H) 1.61 (d, *J* = 7.09 Hz, 3H). LCMS (ESI): m/z = 501.3 $[M+H]^+$.

Biochemical data

Compounds of the examples were tested in a Papain Like Protease (PLpro) biochemical assay in order to determine their ability to inhibit the enzyme's activity. Biochemical potencies are reported in Table 1 as the concentration of the compound required to achieve 50% inhibition of the enzyme activity in the assay (IC_{50}). The calculated inhibition constant (K_i) is also provided.

The potency of compounds against the SARS-CoV-2 Papain like protease (PLpro) was measured using a synthetic profluorogenic substrate Z-RLRGG-AMC. Compounds were serially

diluted over 11 points using 100% DMSO as a diluent, from either a top concentration of 3 mM with a half-log dilution factor or a top dose of 0.1 mM with a 2-fold dilution factor. The top dose of compound in the assay was either 30 uM or 1 uM. The assay buffer contained 50 mM HEPES, pH 7.5, 1 mM TCEP and 0.1% BSA; final assay conditions included 1% DMSO, 6.25 nM PLPro enzyme, 25 uM peptide substrate and a 60-minute enzyme reaction time.

Briefly, 250 nL of serially diluted compound was spotted into a white 384-well plate, followed by addition of SARS CoV2 PLpro enzyme (7.8 nM, 10 uL) in assay buffer. The compounds and PLpro enzyme were incubated for 30 minutes at room temperature. The reaction was then initiated by the addition of profluorogenic peptide substrate in assay buffer (5 µL, 125 µM Z-RLRGG-AMC). The reaction was allowed to progress for 60 minutes at 25 °C after which the plate was read on a Molecular Devices Spectramax M2e reader at an Ex/Em of 360 nm/460 nm. The no compound, zero percent inhibition (ZPE) control wells contained 1 % DMSO vehicle with substrate and PLpro enzyme. The hundred percent effect (HPE) wells contained an internal Pfizer control compound at a dose sufficient to accomplish complete inhibition, 1% DMSO vehicle, substrate and PLpro enzyme. Data were analyzed with ActivityBase software (ID Business Solutions, Ltd). The raw data were transformed to percent activity values using the average from the ZPE and HPE control wells. The resulting data were fit with the four-parameter logistic fit model to determine the IC_{50} value. For compounds eliciting high potencies, the percent activity values were fit to the Morrison equation to derive K_i values with the following fixed parameters: enzyme concentration, 6.25 nM; substrate Km, 962 µM; substrate concentration, 25 µM. To qualify inter-experimental performance, the internal control (R)-5-(aminomethyl)-2-methyl-N-(1-(naphthalen-1-yl)ethyl)benzamide (compound 2 from J. Med. Chem. 2009, 52, 16, 5228–5240) was tested in each run.

Table 1:

Example #	IC_{50} (µM)	K_i (µM)
1	0.009	0.006
2	0.005	0.001
3	0.027	0.021
4	0.051	0.044
5	0.066	0.061
6	0.03	0.025
7	0.018	0.014

8	0.035	0.032
9	0.02	0.016
10	0.011	0.007
11	0.009	0.005
12	0.041	0.037
13	0.059	0.056
14	0.026	0.023
15	0.052	0.047
16	0.021	0.017
17	0.02	0.016
18	0.007	0.005
19	0.01	0.007
20	0.005	0.002
22	0.028	0.024
23	0.013	0.008
24	1.163	1.079
25	2.065	2.005
26	0.025	0.020
27	0.004	<0.004
28	0.566	0.548
29	0.024	0.020
30	0.037	0.032
31	0.066	0.061
32	0.014	0.010
33	0.011	0.007
34	0.032	0.028
35	0.0130	0.015
36	0.0140	0.017
37	0.0420	0.0450
38	0.0130	0.016
39	0.0380	0.043
40	0.004	0.006

41	0.043	0.038
42	0.041	0.034
43	0.017	0.010
44	0.032	0.026
45	0.037	0.031
46	0.016	0.011
47	0.051	0.046

Table 2:

Example #	IC_{50} (μM)	K_i (μM)	Example #	IC_{50} (μM)	K_i (μM)
Ex. 48	0.02	0.017	**Ex. 76**	0.024	0.022
Ex. 49	0.005	0.003	**Ex. 77**	0.015	0.013
Ex. 50	0.03	0.025	**Ex. 78**	0.01	0.007
Ex. 51	0.036	0.032	**Ex. 79**	0.033	0.03
Ex. 52	0.035	0.031	**Ex. 80**	0.075	0.071
Ex. 53	0.161	0.15	**Ex. 81**	0.026	0.024
Ex. 54	0.015	0.013	**Ex. 82**	0.018	0.015
Ex. 55	0.017	0.015	**Ex. 83**	0.003	0.001
Ex. 56	0.014	0.011	**Ex. 84**	0.006	0.004
Ex. 57	0.013	0.008	**Ex. 85**	0.005	0.003
Ex. 58	0.015	0.01	**Ex. 86**	0.005	0.003
Ex. 59	0.025	0.02	**Ex. 87**	0.005	0.003
Ex. 60	0.012	0.009	**Ex. 88**	0.004	0.002
Ex. 61	0.053	0.048	**Ex. 89**	0.034	0.031
Ex. 62	0.003	0.002	**Ex. 90**	0.027	0.024
Ex. 63	0.003	0.002	**Ex. 91**	0.004	0.001
Ex. 64	0.107	0.103	**Ex. 92**	0.023	0.02
Ex. 65	0.061	0.057	**Ex. 93**	0.351	0.345
Ex. 66	0.039	0.036	**Ex. 94**	0.035	0.033
-	-	-	**Ex. 95**	0.008	0.006
Ex. 68	0.021	0.019	**Ex. 96**	0.889	0.934
Ex. 69	0.098	0.093	**Ex. 97**	0.035	0.032

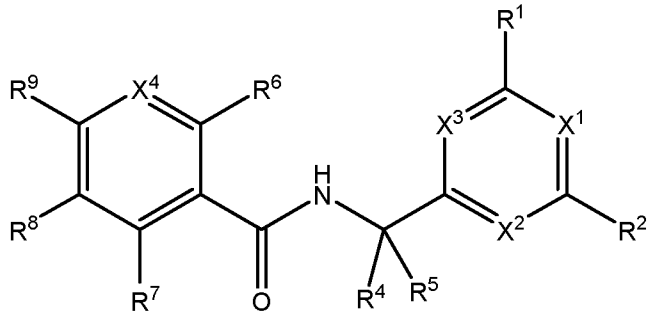
Ex. 70	0.005	0.002	**Ex. 98**	0.757	0.749
Ex. 71	0.007	0.004	**Ex. 99**	0.023	0.02
Ex. 72	0.06	0.053	**Ex. 100**	0.684	0.692
Ex. 73	0.026	0.024	**Ex. 101**	0.011	0.009
Ex. 74	0.018	0.015	**Ex. 102**	0.011	0.008
Ex. 75	0.014	0.011	**Ex. 103**	0.007	0.005

It will be apparent to those skilled in the art that various modifications and variations may be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

All references cited herein, including patents, patent applications, papers, textbooks, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated by reference in their entireties. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

CLAIMS

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

X^1, X^2, and X^3 are each independently selected from N or CR^3, with the proviso that no more than two of X^1, X^2 and X^3 are N atoms;

X^4 is N or CH;

R^1 and R^2 are each independently selected from the group consisting of C_6-C_{10} aryl, 5-10 membered heteroaryl, C_3-C_8 cycloalkyl, 3-8 membered heterocycloalkyl, C_3-C_8 cycloalkenyl and 3-8 membered heterocycloalkenyl, each optionally substituted by one, two or three R^{10};

Each R^3 is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy;

R^4 and R^5 are each independently selected from the group consisting of H and C_1-C_4 alkyl, C_1-C_4 aminoalkyl and C_1-C_4 alkoxy-C_1-C_4 alkyl, or alternatively R^4 and R^5 together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl optionally substituted by one R^{10} or a 4-8 membered heterocycloalkyl optionally substituted by one R^{10};

R^6 is selected from the group consisting of H, halogen, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, $-OR^{12}$, $-SR^{12}$, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-oxiran-C(=O)-O-C_1-C_6 alkyl, C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-oxiran-C(=O)-OH and C_1-C_3 alkyl-C(=O)-N(R^e)-N(R^f)-C(=O)-CH=CH-C(=O)-N(R^{11})R^{12};

R^e and R^f are each independently selected from the group consisting of H and C_1-C_4 alkyl;

R^7 and R^8 are each independently selected from the group consisting of H, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, 4-10 membered heterocycloalkyl, -C_1-C_6 alkyl-$NR^{14}R^{15}$, -NHR^{16}, -$N(R^{13})$-C(=O)-R^{16} and -C(=O)-$NR^{14}R^{15}$, wherein any said 4-10 membered heterocycloalkyl is optionally substituted with one, two or three R^{10};

R^9 is selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkyl-C(=O)-OH, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-$N(R^{11})R^{12}$, -C(=O)-$N(R^{11})$-(CR^gR^h)-R^{12}, -(CR^gR^h)-$N(R^{11})$-(CR^gR^h)-R^{12}, -(CR^gR^h)-O-(CR^gR^h)-R^{12}, -(CR^gR^h)-S-(CR^gR^h)-R^{12}, -(CR^gR^h)-S(=O)-(CR^gR^h)-R^{12}, -(CR^gR^h)-SO_2-(CR^gR^h)-R^{12},-SO_2-$N(R^{11})$-(CR^gR^h)-R^{12} , -(CR^gR^h)-C(=O)-$N(R^{11})R^{12}$, -(CR^gR^h)-SO_2-$N(R^{11})R^{12}$, -C_1-C_3 alkyl-C(=O)-$N(R^{11})$-C_1-C_3 alkyl-R^{12}, -$N(R^{11})R^{12}$, -$N(R^{11})$-C_1-C_3 alkyl-R^{12}, -O-C_1-C_3 alkyl-R^{12}, -$N(R^{11})$-C(=O)-$N(R^{13})$-R^{12}, -C_1-C_3 alkyl-$N(R^{11})R^{12}$, -(CR^gR^h)-$N(R^{11})$-(CR^gR^h)-R^{12}, -C_1-C_3 alkyl-$N(R^{11})$-C(=O)-R^{12}, -(CR^gR^h)-$N(R^{11})$-C(=O)-R^{12} and -C_1-C_3 alkyl-$N(R^{11})$-C(=O)-C_1-C_3 alkyl-R^{12};

Each of R^g and R^h is independently selected from the group consisting of H, cyano, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkyl, -C_1-C_6 alkoxy-C_1-C_6 alkyl, or alternatively, R^g and R^h together with the carbon atom to which they are attached form a C_3-C_6 cycloalkyl or a 4-8 membered Heterocycloalkyl, each optionally substituted by one R^{10};with the proviso that at least one of R^7, R^8 and R^9 is H and that R^6, R^7, R^8 and R^9 are not all H at the same time;

Each R^{10} is independently selected at each occurrence from the group consisting of cyano, nitro, oxo, 1-(1-cyanocyclopropyl)methyl, halogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -C_1-C_6 alkyl-R^{12}, C_1-C_6 alkoxy, -C_1-C_6 alkoxy-C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, 3-8 membered heterocycloalkyl, -COOH, -C(=O)-O-C_1-C_6 alkyl, -C(=O)-$N(R^{11})R^{12}$, -$N(R^{11})R^{12}$, -C_1-C_3 alkyl-$N(R^{11})R^{12}$, -$N(R^{11})C(=O)R^{12}$, -C_1-C_3 alkyl-$N(R^{11})C(=O)R^{12}$, -$S(O)R^{12}$, -$S(O)_2R^{12}$, -$S(O)_2N(R^{11})R^{12}$, -$N(R^{13})S(O)_2N(R^{11})R^{12}$, -$N(R^{13})S(O)_2R^{12}$, -$OR^{12}$,-$C_1$-$C_3$ alkyl-OR^{12} and -SR^{12};

Each R^{11} is independently selected from H, -SO_2CH_3, -C(=O)CH_3 and C_1-C_6 alkyl;

Each R^{12} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl, C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl, wherein said C_3-C_8 cycloalkyl, 4-8 membered heterocycloalkyl, phenyl and 5-6 membered heteroaryl are each optionally substituted by one or two R^{17};

Or alternatively R^{11} and R^{12} together form a 4-8 membered heterocycloalkyl;

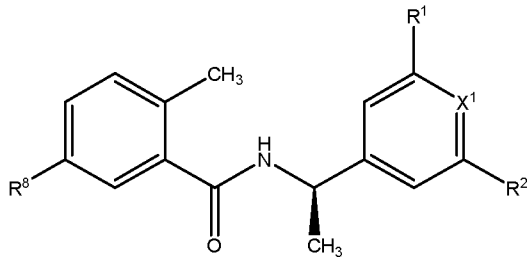
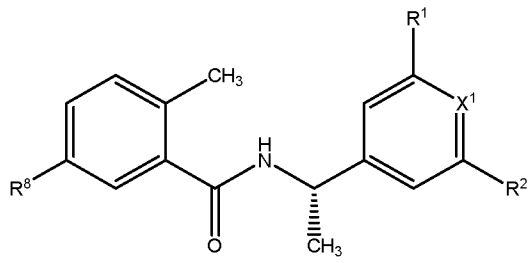
Each R^{13} is independently selected from H and C_1-C_6 alkyl;

Each R^{14} and R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_1-C_6 aminoalkyl, -SO_2-C_1-C_6 alkyl and C_1-C_6 alkoxy-C_1-C_6 alkyl;

Each R^{16} is a 3-8 membered heterocycloalkyl optionally substituted with one, two or three R^{10}; and

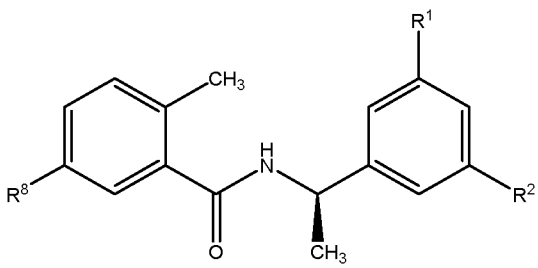
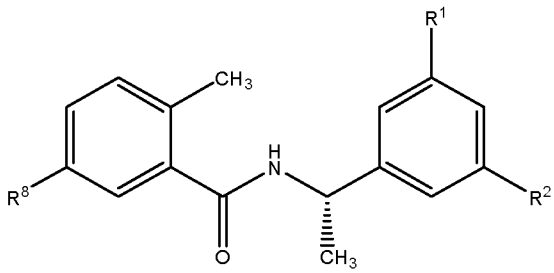
Each R^{17} is independently selected from the group consisting of H, halogen, hydroxy, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 aminoalkyl, C_1-C_6 fluoroalkyl and C_1-C_6 alkoxy.

2. A compound of claim 1 which is of formula:

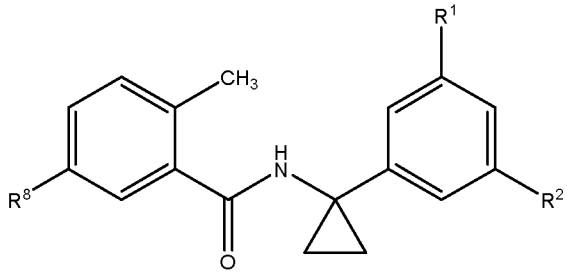
or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^3 or N and R^3 is H or methoxy.

3. A compound of claim 2 which is of formula:

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 having Formula (Ic):



(Ic)

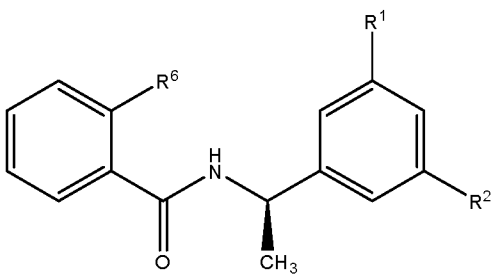
or a pharmaceutically acceptable salt thereof.

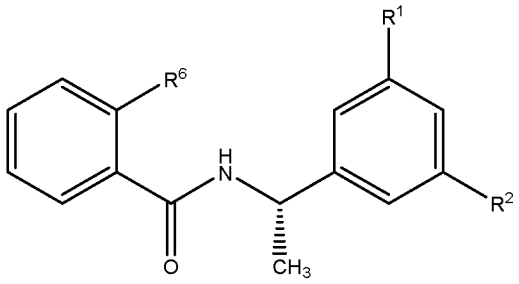
5. A compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of 4-10 membered heterocycloalkyl optionally substituted with one substituent selected from C_1-C_6 alkyl, C_1-C_6 alkyl-$NR^{14}R^{15}$, -NHR^{16} and -$N(R^{13})$-C(=O)-R^{16}.

6. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^{13} is H; each R^{14} and R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl and -SO_2-C_1-C_6 alkyl; and R^{16} is a 4-6 membered heterocycloalkyl.

7. A compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^8 is selected from the group consisting of -CH_2-NH_2, -CH_2-NH-methyl, -CH_2-NH-SO_2-methyl, -NH-C(=O)-piperidinyl, -NH-azetidinyl, piperazin-1-yl, 4-methyl-piperazin-1-yl, hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl and 3,6-diazabicyclo[3.1.1]heptan-3-yl.

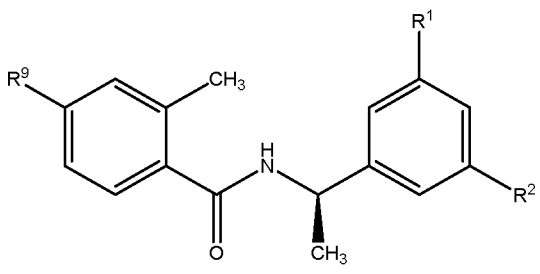
8. A compound of claim 1 which is of formula:

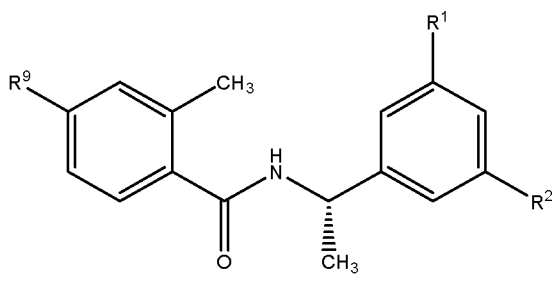


or


or a pharmaceutically acceptable salt thereof, wherein R^6 is -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-O-CH_3, -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-NH(CH_3) or -CH_2-CH_2-C(=O)-NH-NH-C(=O)-CH=CH-C(=O)-NH_2.

9. A compound of claim 1 which is of formula:



or


or a pharmaceutically acceptable salt thereof.

10. A compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^9 is -C(=O)-NH-CH_2-R^{12} and R^{12} is a 5- or 6-membered heteroaryl.

11. A compound of claim 10 or a pharmaceutically acceptable salt thereof, wherein said 5- or 6-membered heteroaryl is a thiazolyl.

12. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from the group consisting of C_6-C_{10} aryl and 5-10 membered heteroaryl, each optionally substituted by one or two R^{10} group.

13. A compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from the group consisting of phenyl, pyridinyl, a 6-membered heterocycloalkenyl and 5-membered heteroaryl, each optionally substituted by one or two R^{10} group.

14. A compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected from phenyl, pyridinyl, 3,6-dihydro-2H-pyranyl, pyrazolyl, pyrrolyl, thiazolyl, isothiazolyl, morpholinyl and thiophenyl, each optionally substituted by one or two R^{10} group.

15. A compound of any one of claims 12 to 14, or a pharmaceutically acceptable salt thereof, wherein each said R^{10} is selected from the group consisting of methyl, cyano, amino, chloro, -COOH, -C(=O)-O-methyl, -C(=O)-NH_2, -C(=O)-NH-methyl, -C(=O)-$N(CH_3)_2$, -C(=O)-pyperidin-1-yl, -C(=O)-morpholin-4-yl, hydroxy, -CH_2-NH-(3-hydroxy-cyclopentyl), -CH_2-NH-(cyclopentyl), -CH_2-NH-(tetrahydrofuranyl), -CH_2-OH, -$S(O)_2$-CH_3, -CH_2-NH-C(=O)-CH_3, -$S(O)_2$-$N(CH_3)_2$, -CF_3 and -OCH_3.

16. A compound of claim 1, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**1**);

(2R)-N-(3-((1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**2**);

5-(azetidin-3-ylamino)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**3**);

methyl 5-(5-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-3'-chloro-[1,1'-biphenyl]-3-yl)-1H-pyrrole-3-carboxylate (**4**);

5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (**5**);

(2R)-N-(3-((1-(2-(3-chlorophenyl)-6-(1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**6**);

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-((methylamino)methyl)benzamide (**7**);

5-(azetidin-3-ylamino)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**8**);

N-(1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**9**);

(2R)-N-(3-((1-(3-(1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**10**);

(2R)-N-(3-((1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**11**);

N-(1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**12**);

5-(aminomethyl)-N-(1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide (**13**);

(2R)-N-(3-((1-(2-(3-chlorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**14**);

5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide (**15**);

(2R)-N-(3-((1-(2-(1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**16**);

(2R)-N-(4-methyl-3-((1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide (**17**);

5-(aminomethyl)-N-(1-(3'-chloro-5-(1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide (**18**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**19**);

(2R)-N-(4-methyl-3-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide (**20**);

methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(thiophen-2-yl)phenyl)-1H-pyrrole-3-carboxylate (**22**);

rel-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-1 (**23**);

rel-(*R*)-5-(aminomethyl)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide, ENT-2 (**24**);

rel-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-1 (**25**);

rel-(*R*)-2-methyl-*N*-(1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl)benzamide, ENT-2 (**26**);

(*R*)-*N*-(4-methyl-3-(((*R**)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1 (**27**);

(*R*)-*N*-(4-methyl-3-(((*R**)-1-(3-(1-methyl-1*H*-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2 (**28**);

methyl 5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (**29**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylic acid (**30**);

methyl 5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(methylsulfonamidomethyl)benzamido)ethyl)phenyl)thiophene-2-carboxylate (**31**);

(2R)-N-(3-((1-(3-(1H-pyrazol-5-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)-4-methylphenyl)piperidine-2-carboxamide (**32**);

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide (**33**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide (**34**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxamide (**35**);

5-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methylthiophene-2-carboxamide (**36**);

5-(aminomethyl)-N-(1-(3-(isothiazol-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**37**);

5-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**38**);

methyl 4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)thiophene-2-carboxylate (**39**);

5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide (**40**);

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N,1-trimethyl-1H-pyrrole-2-carboxamide (**41**);

5-(aminomethyl)-N-(1-(4-methoxy-3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methylbenzamide (**42**);

5-(aminomethyl)-N-(1-(3-(5-cyanothiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**43**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl)ethyl)benzamide (**44**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-2-yl)phenyl)ethyl)benzamide (**45**);

N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-5-(aminomethyl)-2-methylbenzamide (**46**); and

5-(aminomethyl)-N-(1-(3-(5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide (**47**);

5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl) benzamide **(48)**;

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)cyclopropyl)-5-(piperazin-1-yl)benzamide **(49)**;

5-(aminomethyl)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(50)**;

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N-methylthiophene-2-carboxamide **(51)**;

4-(3-(1-(5-(aminomethyl)-2-methylbenzamido) ethyl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-N,N-dimethylthiophene-2-carboxamide **(52)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylic acid **(53)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(54)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N-methyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(55)**;

3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-N,N-dimethyl-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxamide **(56)**;

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(57)**;

5-(aminomethyl)-N-(1-(3'-chloro-5-(1-methyl-1H-pyrazol-4-yl)-5'-(morpholine-4-carbonyl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(58)**;

methyl 3'-(1-(5-(aminomethyl)-2-methylbenzamido)ethyl)-5-chloro-5'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-carboxylate **(59)**;

N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-((methylamino)methyl) benzamide **(60)**;

N-(1-(3-(1H-pyrazol-3-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(61)**;

(R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide **(62)**;

(R)-N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-4-(((thiazol-4-ylmethyl)amino)methyl)benzamide **(63)** ;

2-(aminomethyl)-6-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl) benzamide **(64)**;

5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(5-(trifluoromethyl)thiophen-2-yl)pyridin-4-yl)ethyl)benzamide **(65)**;

5-(aminomethyl)-N-(1-(2-(5-chlorothiophen-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)ethyl)-2-methylbenzamide **(66)**;

(R)-5-(aminomethyl)-N-(1-(3-(3,6-dihydro-2H-pyran-4-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(68)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-morpholinophenyl)ethyl)benzamide **(69)**;

methyl (E)-4-(2-(3-(2-((1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)carbamoyl)phenyl)propanoyl)hydrazineyl)-4-oxobut-2-enoate **(70)**;

(E)-2-(3-(2-(4-amino-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)benzamide **(71)** ;

(R,E)-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-2-(3-(2-(4-(methylamino)-4-oxobut-2-enoyl)hydrazineyl)-3-oxopropyl)benzamide **(72)**;

N-(1-(3-(5-(acetamidomethyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(73)**;

N-(1-(3-(5-((cyclopentylamino)methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl)benzamide **(74)**;

N-(1-(3-(5-((((1S,3R)-3-hydroxycyclopentyl)amino) methyl)thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamidomethyl) benzamide **(75)**;

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(5-((((S)-tetrahydrofuran-3-yl)amino)methyl)thiophen-2-yl)phenyl)ethyl)-5-(methylsulfonamidomethyl) benzamide **(76)**;

5-(aminomethyl)-N-(1-(3'-chloro-4'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(77)**;

5-(aminomethyl)-N-(1-(3'-chloro-5'-hydroxy-5-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-3-yl)ethyl)-2-methylbenzamide **(78)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl) benzamide **(79)**;

(R)-5-(aminomethyl)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-methyl-1H-pyrazol-5-yl)phenyl)ethyl) benzamide **(80)**;

5-(aminomethyl)-N-(1-(3,5-bis(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(81)**;

5-(aminomethyl)-N-(1-(3-(5-(hydroxymethyl) thiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methylbenzamide **(82)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide **(83)** ;

(R)-N,N-dimethyl-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxamide **(84)**;

methyl (R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylate **(85)**;

(R)-5-(3-(1-methyl-1H-pyrazol-4-yl)-5-(1-(2-methyl-5-(4-methylpiperazin-1-yl)benzamido)ethyl)phenyl)thiophene-2-carboxylic acid **(86)**;

(R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(piperazin-1-yl)benzamide **(87)**;

(R)-2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiophen-2-yl)phenyl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide **(88)**;

2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide **(89)**;

2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide **(90)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(piperazin-1-yl)benzamide **(91)**;

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(methylsulfonamido methyl)benzamide **(92)**;

rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-1 **(93)**;

rel-(R)-5-(aminomethyl)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)benzamide, ENT-2 **(94)**;

(R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-1 **(95)**;

(R)-N-(4-methyl-3-(((R*)-1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)carbamoyl)phenyl)piperidine-2-carboxamide, ENT-2 **(96)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-1 **(97)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(4-methylpiperazin-1-yl)benzamide, ENT-2 **(98)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-1 **(99)**;

rel-(R)-2-methyl-N-(1-(2-(1-methyl-1H-pyrazol-4-yl)-6-(thiophen-2-yl)pyridin-4-yl)ethyl)-5-(piperazin-1-yl)benzamide, ENT-2 **(100)**;

N-(1-(3-(5-cyanothiophen-2-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl) cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide **(101)**;

N-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)cyclopropyl)-2-methyl-5-(piperazin-1-yl)benzamide **(102)**; and

2-methyl-N-(1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(thiazol-5-yl)phenyl) cyclopropyl)-5-(piperazin-1-yl)benzamide **(103)**.

17. A compound of claim 1, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of:

(R)-N1-(1-(3-(isothiazol-5-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-N4-(thiazol-4-ylmethyl)terephthalamide (**62**);

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(4-methylpiperazin-1-yl)benzamide (**83**), and

(R)-N-(1-(3-(2-amino-5-chloropyridin-3-yl)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)ethyl)-2-methyl-5-(piperazin-1-yl)benzamide (**91**).

18. A pharmaceutical composition comprising a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

19. A method for treating a viral infection, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof.

20. A method for treating a viral infection of claim 19, wherein the compound of any one of claims 1 to 34, or a pharmaceutically acceptable salt thereof, is administered as a single agent.

21. A method for treating a viral infection of claim 19, further comprising administering a therapeutically effective amount of an additional therapeutic agent selected from the list consisting of viral RNA polymerase inhibitors, Mpro inhibitors, nucleoside inhibitors, host factor inhibitors, other PLpro inhibitors and metabolism boosting agents.

22. A method for treating a viral infection of any one of claims 19 to 21, wherein said viral infection is a coronavirus infection.

23. A compound of any one of claims 1 to 17, for use as a medicament.

24. A compound of any one of claims 1 to 17, for use in the treatment of a viral infection.

25. Use of a compound of any one of claims 1 to 17 for the manufacture of a medicament for the treatment of a viral infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/062180

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D231/12 C07D401/04 C07D401/10 C07D401/12 C07D403/10
C07D403/12 C07D409/10 C07D409/14 C07D417/10 C07D417/14
C07D471/08 C07D487/04 A61P31/12 A61K31/4164

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 115 093 400 A (BEIJING PHARSCIN INNOBIO CO LTD) 23 September 2022 (2022-09-23) the whole document	1-25
X	WO 2022/189810 A1 (INFEX THERAPEUTICS LTD [GB]) 15 September 2022 (2022-09-15) cited in the application claim 1; compounds 229,230,233,234,242,243	1-3,5-25

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2024	01/03/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grassi, Damian

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2023/062180

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SHEN ZHENGNAN ET AL: "Design of SARS-CoV-2 PLpro Inhibitors for COVID-19 Antiviral Therapy Leveraging Binding Cooperativity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 65, no. 4, 19 October 2021 (2021-10-19), pages 2940-2955, XP093058249, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.1c01307 figure 1 -----	1-25
X,P	WO 2023/028286 A1 (UT BATTELLE LLC [US]; SANDERS BRIAN [US] ET AL.) 2 March 2023 (2023-03-02) the whole document -----	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2023/062180

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		BR 112023018437 A2	10-10-2023
		CA 3208103 A1	15-09-2022
		EP 4305022 A1	17-01-2024
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		KR 20230158007 A	17-11-2023
		WO 2022189810 A1	15-09-2022
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		WO 2023028286 A1	02-03-2023