



(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2020/06/18
(87) Date publication PCT/PCT Publication Date: 2020/12/24
(85) Entrée phase nationale/National Entry: 2021/12/13
(86) N° demande PCT/PCT Application No.: US 2020/038480
(87) N° publication PCT/PCT Publication No.: 2020/257487
(30) Priorité/Priority: 2019/06/19 (US62/863,786)

(51) Cl.Int./Int.Cl. *C07D 207/327* (2006.01)
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(54) Titre : INHIBITEURS DE GLYCOLATE OXYDASE POUR LE TRAITEMENT D'UNE MALADIE
(54) Title: GLYCOLATE OXIDASE INHIBITORS FOR THE TREATMENT OF DISEASE

(57) **Abrégé/Abstract:**

Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds to treat or prevent diseases or disorders associated with a defect in glyoxylate metabolism, for example a disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism. Such diseases or disorders include, for example, disorders of glyoxylate metabolism, including primary hyperoxaluria, that are associated with production of excessive amounts of oxalate.



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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

24 December 2020 (24.12.2020)



(10) International Publication Number

WO 2020/257487 A1

(51) International Patent Classification:

C07D 207/327 (2006.01)

(21) International Application Number:

PCT/US2020/038480

(22) International Filing Date:

18 June 2020 (18.06.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/863,786 19 June 2019 (19.06.2019) 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, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: GLYCOLATE OXIDASE INHIBITORS FOR THE TREATMENT OF DISEASE

(57) Abstract: Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds to treat or prevent diseases or disorders associated with a defect in glyoxylate metabolism, for example a disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism. Such diseases or disorders include, for example, disorders of glyoxylate metabolism, including primary hyperoxaluria, that are associated with production of excessive amounts of oxalate.



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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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CONTENANT LES PAGES 1 À 349

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

GLYCOLATE OXIDASE INHIBITORS FOR THE TREATMENT OF DISEASE

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/863,786, filed June 19, 2019, the content of which is incorporated herein by reference in its entirety.

FIELD

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods to treat or prevent diseases or disorders associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism. Also described herein is that such compounds are for use in said methods for treating or preventing diseases or disorders. Such diseases or disorders include, for example, disorders of glyoxylate metabolism, including primary hyperoxaluria, that are associated with production of excessive amounts of oxalate.

BACKGROUND

[0003] Primary hyperoxaluria (“PH”) is an autosomal-recessive disorder of glyoxylate metabolism. PH type I (PH1) is caused by inherited mutations in the AGXT gene encoding liver peroxisomal alanine : glyoxylate aminotransferase (AGT) which is deficient or mistargeted to mitochondria (Danpure *et al.*, *FEBS Lett.* **201**(1):20-24 (1986)). AGT detoxifies glyoxylate to glycine. When AGT activity is deficient or mistargeted, excessive glyoxylate cannot be detoxified and is oxidized by intracellular lactate dehydrogenase (“LDH”) to oxalate. Excessive amounts of oxalate lead to urolithiasis and nephrocalcinosis, and can result in renal failure, end stage renal disease and systemic oxalosis.

[0004] Glycolate oxidase (GO) is a key enzyme involved in the oxalate metabolic pathway. Glycolate from internal metabolism and from diet will be oxidized by GO to glyoxylate. This oxidation only occurs in the liver peroxisome (Holmes *et al.*, *J. Urol.* **160**(5):1617-1624 (1998 Nov.)). Under normal conditions, the glyoxylate generated by GO will be detoxified by AGT to glycine. However, in PH1 patients, where the glyoxylate to glycine pathway is blocked, the glyoxylate generated by GO is oxidized by LDH to produce excessive amounts of oxalate.

[0005] An approach to treatment of PH1 is to inhibit the GO enzyme to reduce the production of glyoxylate and ultimately reduce the production of excessive amounts of oxalate. It has been shown in HAO1 (GO)^{-/-} /AGXT^{-/-} double knockout mouse that GO deficiency can correct overproduction of urine oxalate over production in AGXT^{-/-} mouse (Martin-Higueras *et al.*, *Mol Ther.* **24**(4): 719-725 (2016)). In both humans and mice, the HAO1^{-/-} deficiency appears clinically/phenotypically normal except for the increased urine glycolate secretion (Martin-Higueras *et al.*, *Mol Ther.* **24**(4): 719-725 (2016)). Inhibition of GO with Dicer-substrate siRNA has also been shown to reduce urine oxalate secretion and reduce kidney calcium oxalate deposition in the PH1 mouse model (Dutta *et al.*, *Mol Ther.* **24**(4): 770-778 (2016 Apr.)).

[0006] The most commonly observed effect of high levels of oxalate is the formation of crystals in various tissues. Crystal oxalate formation in the kidney results in nephrolithiasis, or kidney stones. Similarly, increased urinary oxalates can also lead to nephrocalcinosis.

[0007] Accumulation of oxalate is implicated in primary hyperoxaluria type II ("PH2") and primary hyperoxaluria type III ("PH3"). Similar to PH1, mutations in a gene results in decreased production or activity of the corresponding enzymes that are produced. Such disruptions to the enzymes adversely affects the normal breakdown of glyoxylate. In healthy subjects, glyoxylate is converted to glycine, which is readily secreted. In diseased subjects, there is a build-up of glyoxylate, which gets converted to oxalate. When the buildup of oxalate exceeds the capacity of the kidney to excrete it, the oxalate starts to deposit in various organ systems in a process called systemic oxalosis. In PH2 patients, a decrease in the breakdown of glyoxylate is caused by mutations in the GRHPR gene, which normally reduces glyoxylate to glycolate. PH3 is a third type of PH, and is identified in patients with previously unclassified forms of PH. PH3 is caused by mutations in the HOGA gene (formerly known as the DHDPSTL gene). This enzyme functions in the final step of 4-hydroxyproline (Hyp) catabolic pathway. Overactivity of the enzyme leads to excess conversion of hydroxyproline to glyoxylate, which yields high levels of oxalate. The genetic mutations that cause PH are inherited as autosomal recessive traits.

[0008] Build-up of oxalate and deficiencies in processes involving urinary excretion of oxalate is further implicated in a variety of diseases and disorders, such as progressive kidney failure, recurrent kidney stones, nephrocalcinosis, urinary tract infections, chronic kidney

disease, and end stage renal disease. Reducing urinary oxalate levels and plasma oxalate levels can help in treating or ameliorating these diseases and conditions.

[0009] Hyperoxaluria is characterized by an increased urinary excretion of oxalate. Excess urinary oxalate, whether from primary or enteric hyperoxaluria, can lead to oxalate deposits in the kidney. Primary and secondary hyperoxaluria are two distinct clinical expressions of hyperoxaluria. Primary hyperoxaluria, as discussed above, is caused by genetic mutations which increase oxalate production. Secondary hyperoxaluria includes dietary hyperoxaluria, enteric hyperoxaluria and idiopathic hyperoxaluria. In addition to these types of hyperoxaluria, there are pharmacologically induced hyperoxalurias that are caused by the ingestion of compounds that can be metabolized to oxalate, such as ethylene glycol or other precursors such as hydroxyproline.

[0010] Dietary hyperoxaluria is caused by increased dietary ingestion of oxalate, precursors of oxalate or alteration in intestinal microflora. A high intake of oxalate-rich foods (eg, chocolate, nuts, spinach) and a diet rich in animal protein can result in hyperoxaluria. Low dietary calcium intake can also result in hyperoxaluria via decreased intestinal binding of oxalate and the resulting increased absorption. Ascorbic acid can be converted into oxalate, resulting in increased urinary oxalate levels. Patients with abnormal or altered cellular membrane oxalate transport mechanism have abnormally high absorption of dietary oxalate. Patients with a deficiency of oxalobacter formigenes, an intestinal oxalate degrading bacterial, will also have the increased oxalate absorption. Diets that are high in any metabolic precursor of oxalate can lead to elevated oxalate levels that could be reduced by inhibition of GO.

[0011] Enteric hyperoxaluria results from a chronic underlying gastrointestinal disorder associated with malabsorption of fat, bile acids, decreased enteric secretion of oxalate by the membrane protein anion transporter (slc26a6) due to the abnormal glycosylation of brush border, or triggered by obesity which influenced paracellular and transcellular transporting. Related diseases include steatorrhea, inflammatory bowel disease (“IBD”), biliary cirrhosis, short-bowel syndrome, celiac disease, pancreatic insufficiency, Crohn’s disease, ulcerative colitis, bariatric surgery, jejunioileal bypass, ileal dysfunction, absence of gastrointestinal tract-dwelling bacterium oxalobacter formigenes, and Roux-en-Y gastric bypass (“RYGB”). In addition, cystic fibrosis, high blood pressure, and diabetes can lead to metabolic changes which can result in

increased oxalate (*see* Nazzari, L., *et al.*, *Nephrology Dialysis Transplantation*, 31(3):375–382 (2016 Mar.)).

[0012] There is an increased risk of urolithiasis and loss of kidney function from oxalate nephropathy. With idiopathic hyperoxaluria, the causes are unknown.

[0013] Formation of oxalate crystals are associated with renal inflammation, fibrosis and progressive renal failure. Studies also show high oxalate levels can be an activator of inflammatory pathways, and in particular, with inflammasome activation and the progression of kidney disease, and NALP3-mediated inflammation (*see* Ermer, T; *et al.*, *Curr Opin Nephrol Hypertens*, 25(4):363-371 (2016 July); and Knauf, F., *et al.*, *Kidney Int.*, 84(5):895-901 (2013 Nov.)).

[0014] There is a known association of high urinary oxalate with acute kidney injury and chronic kidney disease (“CKD”). Studies show a correlation of higher urinary oxalate concentrations with a higher risk of CKD (Waikar, Sushru S., *et al.*, *JAMA Intern Med.*, 179(4):542-551 (2019)). These studies have shown that patients with chronic kidney disease that also have high normal urine oxalate levels have a more rapid disease progression rate than those similar patients with low normal urine oxalate levels. Therapeutic approaches to reduce the oxalate burden in these patients has the potential to slow the progression of disease. If any of the multiple sources of oxalate can be reduced, there could be benefits to these patients. For example, inhibition of GO or LDH (or any other metabolic step that contributes to the generation or absorption of oxalate) could reduce oxalate levels and slow the progression of disease. It has long been known that as glomerular filtration rate (GFR) becomes reduced in CKD, there is an elevation of plasma oxalate. Elevation of plasma oxalate in CKD may promote renal inflammation and more rapid progression of CKD independent of primary etiology. Higher urinary oxalate excretion among CKD patients is also associated with an elevated risk of end-stage renal disease (ESRD; also known as end-stage kidney disease, “ESKD”).

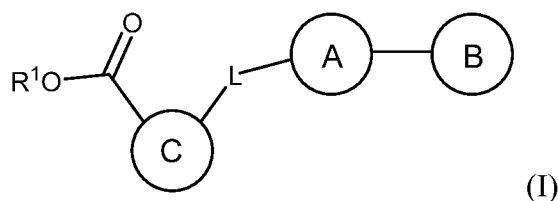
[0015] Hyperoxaluria has been implicated as a complication or undesired side effect of various diseases, such as Hirschsprung’s disease, cystic fibrosis, chronic biliary pathology, pancreatic pathology, high blood pressure, diabetes, and obesity. Hyperoxaluria can also be related to genetic or environmental vitamin B6 deficiency, genetic or environmental abnormal calcium metabolism such as, hypercalciuria and hyperparathyroidism and abnormal collagen metabolism, abnormal oxalate or oxalate precursor transporters. Reduction of oxalate levels

would also have therapeutic benefit in the management of the complications from these diseases and conditions.

[0016] Accordingly, molecules that inhibit the activity of GO may be used to treat disorders of glyoxylate metabolism, including PH1, that are associated with production of excessive amounts of oxalate. Other diseases and conditions impacted by excessive oxalate formation may benefit from treatment with a GO inhibitor, such as PH2, PH3, enteric hyperoxaluria, dietary hyperoxaluria, idiopathic hyperoxaluria, urolithiasis, nephrolithiasis, nephrocalcinosis, chronic kidney disease, end stage renal disease, or systemic oxalosis.

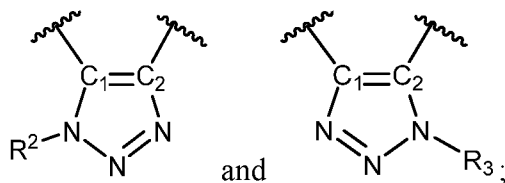
SUMMARY

[0017] In one aspect, provided herein is a compound of Formula (I):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L;

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₃₋₈ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-8 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl,

isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxy, cyano, hydroxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups;
- (ii) 2 halo groups when L is other than O;
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl;
- (iv) one halo group when L is CH_2NR^L ;
- (v) one halo group and one group selected from the group consisting of haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O, S, or $S(=O)$, wherein the phenyl is optionally substituted with halo, cyano, haloalkyl, or haloalkoxy; or
- (vi) one cyano group and one (phenyl)alkoxy group, when L is bond or O, wherein the phenyl as part of the (phenyl)alkoxy group is optionally substituted with halo or haloalkoxy;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is a bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R^1 is not hydrogen or ethyl; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O, S, or CH_2S ;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo groups; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

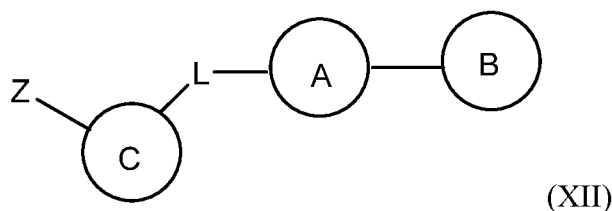
provided:

- i. when L is S or CH₂, and Ring A is phenyl other than phenyl substituted with (cycloalkyl)alkoxy, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA}, and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;

- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

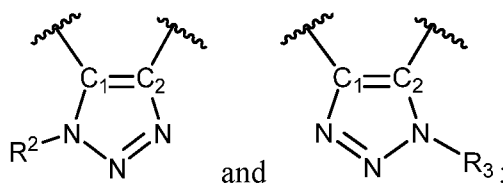
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[0018] In another aspect, provided herein is a compound of Formula (XII):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C_1 carbon to Z, and the C_2 carbon to L;

L is a CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$;

$-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$;

$-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;
each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,
hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and
cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is
optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl;
aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy;
aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy;
alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl;
dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl;
cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted
with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl
optionally substituted with one or two groups independently selected from halo, alkyl,
and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered
heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or
5-6-membered heteroaryl optionally substituted with one group selected from alkyl,
hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R² and R³ is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl;
wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy,
alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally
substituted with alkoxycarbonyl;

R⁴ is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy,
heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy,
dialkylaminocarbonyloxy, alkoxycarbonyloxy, -N(R¹⁰)C(O)R¹¹, -
N(R¹⁰)C(O)OR¹¹, -N(R¹⁰)C(O)NR¹²R¹³, -O-P(=O)(O⁻)₂, -O-P(=O)(OR⁷)(O⁻),
or -O-P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

provided:

- i. the compound represented by Formula (XII) is exclusive of:
 - a. 4-(phenylamino)-1H-1,2,3-triazole-5-carbaldehyde;
 - b. 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carbaldehyde;
 - c. ethyl hydrogen (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate;
 - d. diethyl (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate; and
 - e. 1-((4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione;
- ii. when Z is $-C(=O)H$, L is NR^L , R^L is hydrogen, and Ring A is phenyl, then Ring B is present and/or the phenyl Ring A is substituted with 1, 2, or 3 R^{A2} groups;
- iii. when Z is $-C(=O)H$, L is CH_2 , and Ring A is cyclopropyl, phenyl, indole, or thiophene, then Ring B is present;
- iv. when Z is $-C(=O)H$, L is CH_2-O , and Ring A is phenyl, then Ring B is present;
- v. when Z is $-CH_2OY$, Y is W , W is $-P(=O)(OR^7)_2$ or $-P(=O)(OR^7)(O^-)$, R^7 is ethyl, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2} ; and
- vi. when Z is $-CH_2OY$, Y is hydrogen, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2} ; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[0019] In another aspect, provided herein is a pharmaceutical composition comprising a compound disclosed herein, for example, a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), as disclosed herein, and a pharmaceutically acceptable excipient.

[0020] In a further aspect, provided herein is a method of treating a disease or disorder associated with a defect in glyoxylate metabolism with a compound disclosed herein. Thus, a compound disclosed herein is for use in a method of treating a disease or disorder associated with a defect in glyoxylate metabolism, such as diseases or disorders associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism. Such a compound is, for example, a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), as disclosed herein, or a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable excipient, as disclosed herein.

[0021] In certain embodiments, the disease or disorder is a primary hyperoxaluria. In certain embodiments, the disease or disorder is primary hyperoxaluria type I. In certain embodiments, the disease or disorder is PH2. In certain embodiments, the disease or disorder is PH3. In certain embodiments, the disease or disorder is an enteric hyperoxaluria. In certain embodiments, the disease or disorder is a dietary hyperoxaluria. In certain embodiments, the disease or disorder is an idiopathic hyperoxaluria. In certain embodiments, the disease or disorder is urolithiasis. In certain embodiments, the disease or disorder is nephrolithiasis. In certain embodiments, the disease or disorder is nephrocalcinosis. In certain embodiments, the disease or disorder is chronic kidney disease. In certain embodiments, the disease or disorder is end stage renal disease. In certain embodiments, the disease or disorder is systemic oxalosis.

DETAILED DESCRIPTION**Abbreviations**

Abbreviation	Meaning
DME	Dimethoxyethane
DMF	Dimethylformamide
NBS	N-Bromosuccinimide
NIS	N-Iodosuccinimide
PMB	p-Methoxybenzyl
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
Trt	Trityl

Definitions

[0022] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art.

[0023] “About” preceding a numerical value refers to a range of values $\pm 10\%$ of the value specified.

[0024] “Acceptable” with respect to a formulation, composition or ingredient, means having no persistent detrimental effect on the general health of the subject being treated.

[0025] Whenever a group is described as being “optionally substituted,” it is meant that the referenced group can be “unsubstituted or substituted.”

[0026] “Alkoxy” means a group of the formula $-\text{OR}$, wherein R is alkyl. In certain embodiments, alkoxy includes methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, or hexyloxy.

[0027] “Alkoxyalkoxy” means a group of the formula $-\text{OR}-\text{OR}'$, wherein R is alkylene as defined herein, and R' is alkyl as defined herein.

[0028] “Alkoxy carbonyl” means a group of the formula $-\text{C}(\text{O})\text{R}$, wherein R is alkoxy, as defined herein.

[0029] “Alkoxy carbonyloxy” means a group of the formula $-\text{OC}(\text{O})\text{R}$, wherein R is alkoxy, as defined herein.

[0030] “Alkyl carbonylaminoalkoxy” means a group of the formula $-\text{OR}-\text{NH}-\text{C}(\text{O})\text{R}'$, wherein R is alkylene, as defined herein, and R' is alkyl, as defined herein.

[0031] “Alkyl” means a straight or branched saturated hydrocarbon group containing from 1-10 carbon atoms, and in certain embodiments includes 1-6 carbon atoms. In certain embodiments, alkyl includes 1-4 carbon atoms (“C₁₋₄ alkyl”). In certain embodiments alkyl includes 1-3 carbon atoms (“C₁₋₃ alkyl”). In certain embodiments, alkyl includes methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *isopentyl*, *neopentyl*, *n*-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylhexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, or *n*-decyl.

[0032] “Alkylene” means a straight or branched saturated divalent hydrocarbon group containing from 1-10 carbon atoms, and in certain embodiments includes 1-6 carbon atoms.

[0033] “Alkyl carbonylamino” means a group of the formula $-\text{NHC}(\text{O})\text{R}$, wherein R is alkyl, as defined herein.

[0034] “Amino” means an $-\text{NH}_2$ group.

[0035] “Aminoalkoxy” means a group of the formula $-\text{O}-\text{R}-\text{NH}_2$, wherein R is alkyl as defined herein. In one embodiment, (amino)alkoxy includes (amino)propyloxy.

[0036] “Alkylaminoalkoxy” means an $-\text{O}-\text{R}-\text{NHR}'$ group, wherein R and R' are independently alkyl as defined herein. In one embodiment (dialkylamino)alkoxy includes (methylamino)propyloxy.

[0037] “Aminocarbonyl” means an $-\text{C}(\text{O})\text{NH}_2$ group.

[0038] “Aminocarbonyloxy” means a group of the formula $-\text{OC}(\text{O})\text{R}$, wherein R is amino, as defined herein.

[0039] “Alkylaminocarbonyloxy” means a group of the formula $-\text{OC}(\text{O})\text{R}$, wherein R is alkylamino, as defined herein.

[0040] “Alkylamino” means a group of the formula $-\text{NHR}$, wherein R is alkyl as defined herein. In certain embodiments, alkylamino includes methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *iso*-butylamino, or *tert*-butylamino.

[0041] “Alkyl carbonyl” means a group of the formula $-\text{C}(\text{O})\text{R}$, wherein R is alkyl, as defined herein.

[0042] “Alkylcarbonyloxy” means a group of the formula --OC(O)R , wherein R is alkyl, as defined herein.

[0043] “Alkylsulfonyl” means a group of the formula $\text{--SO}_2\text{R}$, wherein R is alkyl, as defined herein.

[0044] “Aminosulfonyl” means a group of the formula $\text{--SO}_2\text{NH}_2$.

[0045] “Alkylaminosulfonyl” means a group of the formula $\text{--SO}_2\text{NHR}$, wherein R is alkyl, as defined herein.

[0046] “Dialkylaminoalkoxy” means an --O-R-NR'R'' group, wherein R, R', and R'' are independently alkyl as defined herein. In one embodiment (dialkylamino)alkoxy includes (dimethylamino)propyloxy.

[0047] “Dialkylaminosulfonyl” means a group of the formula $\text{--SO}_2\text{NRR'}$, wherein R and R' are independently alkyl, as defined herein.

[0048] “Aryl” means a monovalent six- to fourteen-membered, mono-, bi-, or tri-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic or tricyclic ring is aromatic. In certain embodiments, aryl includes phenyl, naphthyl, tetrahydronaphthyl, dihydronaphthyl, indanyl, or anthracenyl.

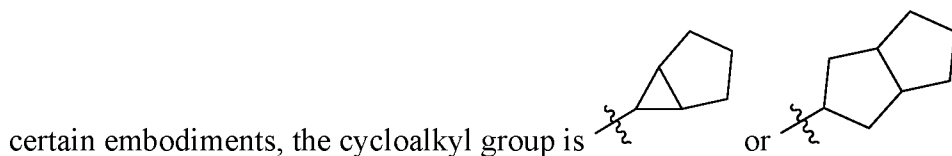
[0049] “Carbonyl” means an --C(=O) group.

[0050] “Carboxyl” means an --C(O)OH group.

[0051] “Cyano” means an --CN group.

[0052] “Cycloalkyl” means a monocyclic or bicyclic, saturated or partially unsaturated (but not aromatic), hydrocarbon ring of three to ten carbon ring atoms. Cycloalkyl groups include fused and bridged bicyclic rings. For example, when fused, the cycloalkyl group may comprise two rings that share adjacent atoms (*e.g.*, one covalent bond). When bridged, the cycloalkyl group may comprise two rings that share three or more atoms, separating the two bridgehead atoms by a bridge containing at least one atom. When a cycloalkyl group contains from x-y ring carbon atoms, it may be referred to herein as C_{x-y} cycloalkyl. In certain embodiments, cycloalkyl is C_{3-10} cycloalkyl, or is C_{5-7} cycloalkyl, or is C_{5-6} cycloalkyl, or is C_{3-6} cycloalkyl, or is C_{3-7} cycloalkyl. In certain embodiments, cycloalkyl is C_{3-8} cycloalkyl. In certain

embodiments, cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In



[0053] “(Cycloalkyl)alkyl” means an alkyl group, as defined herein, substituted with at least one cycloalkyl groups as defined herein. In certain embodiments, alkyl is substituted with 1 cycloalkyl group. In certain embodiments, alkyl is substituted with 1 or 2 cycloalkyl groups. In certain embodiments, (cycloalkyl)alkyl includes cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl.

[0054] “(Cycloalkyl)alkoxy” means a group of the formula $-OR$, wherein R is a (cycloalkyl)alkyl group as defined herein. In certain embodiments, (cycloalkyl)alkoxy includes cyclobutylmethoxy, cyclopentylmethoxy, and cyclohexylmethoxy.

[0055] “Cycloalkyloxy” means a group of the formula $-OR$, wherein R is cycloalkyl, as defined herein. In certain embodiments, cycloalkyloxy includes cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

[0056] “Cycloalkylcarbonyl” means a group of the formula $-C(O)R$, wherein R is cycloalkyl, as defined herein.

[0057] “Cycloalkylcarbonyloxy” means a group of the formula $-OC(O)R$, wherein R is cycloalkyl, as defined herein.

[0058] “Dialkylamino” means a group of the formula $-NRR'$, wherein R and R' are independently alkyl as defined herein. In certain embodiments, dialkylamino includes dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino.

[0059] “Dialkylaminocarbonyl” means a group of the formula $-C(O)R$, wherein R is dialkylamino, as defined herein.

[0060] “Dialkylaminocarbonyloxy” means a group of the formula $-OC(O)R$, wherein R is dialkylamino, as defined herein.

[0061] “Halo” means a fluoro, chloro, bromo, or iodo group.

[0062] “Haloalkoxy” means an alkoxy group, substituted with one or more halo atoms. In certain embodiments, all hydrogen atoms of the alkoxy group are replaced with halo atoms. In certain embodiments, the alkoxy is substituted with 1, 2, 3, 4, 5, or 6 halo atoms. In certain embodiments, the alkoxy is substituted with 1, 2, or 3 halo atoms. In certain other embodiments,

the alkoxy is substituted with 2 halo atoms. In certain embodiments, the alkoxy is substituted with 1 halo atom. Certain embodiments of haloalkoxy include difluoromethoxy, trifluoromethoxy, or 1,1,1-trifluoroethoxy.

[0063] “Haloalkyl” means an alkyl group substituted with one or more halo atoms. In certain embodiments, all hydrogen atoms of the alkyl group are substituted with halo atoms. In certain embodiments, the alkyl group is substituted by 1, 2, 3, 4, 5, or 6 halo atoms. In certain embodiments, the alkyl group is substituted by 1, 2, or 3 halo atoms. In certain other embodiments, the alkyl group is substituted with 2 halo atoms. In certain embodiments, the alkyl group is substituted with 1 halo atom. In certain embodiments, haloalkyl includes trifluoromethyl, fluoromethyl, perfluoroethyl, or chloromethyl. Certain other embodiments of haloalkyl include chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, or 1,1,1-trifluoroethanyl.

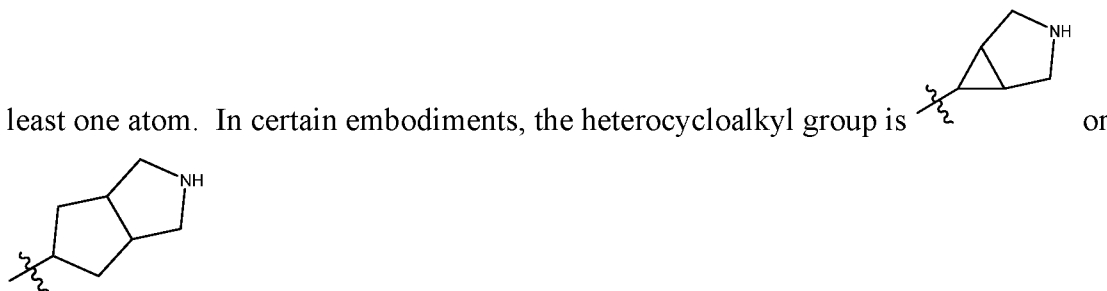
[0064] “Heteroaryl” means a monocyclic, bicyclic, or tricyclic ring of 5 to 14 ring atoms containing one or more ring heteroatoms independently selected from -O-, -S-, -N= (trivalent nitrogen), and -N(H)-, and the remaining ring atoms being carbon atoms, wherein the monocyclic ring is aromatic and wherein at least one of the rings in the bicyclic or tricyclic rings is aromatic (but does not have to be a ring which contains a heteroatom, e.g.; tetrahydroquinolinyl, dihydroisoquinolinyl, dihydrobenzodioxinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, and the like). In certain embodiments, heteroaryl is a monocyclic ring of 5 to 6 rings atoms. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting.

[0065] In certain embodiments, heteroaryl includes, but is not limited to, triazolyl, tetrazolyl, pyrrolyl, imidazolyl, thienyl, furanyl, pyrazolyl, thiazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiadiazolyl, indolyl, indolinyl, isoindolinyl, indazolyl, benzimidazolyl, benzoxazolyl, benzofuranyl, benzothienyl, benzopyranyl, benzothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, dihydroisoquinolinyl, pyrrolo[3,2-*c*]pyridinyl, pyrrolo[1,2-*b*]pyridazinyl, imidazo[1,2-*a*]pyridinyl, benzo[*d*][1,3]dioxolyl, 2,3-dihydrobenzo[*b*][1,4]dioxinyl, furo[2,3-*d*]thiazolyl, thieno[2,3-*d*]oxazolyl, thieno[3,2-*b*]furanyl, furo[2,3-*d*]pyrimidinyl, furo[3,2-*b*]pyridinyl, furo[3,2-*c*]pyridinyl, 6,7-dihydro-5*H*-cyclopenta[*b*]pyridinyl, 7,8-dihydro-6*H*-cyclopenta[*g*]quinoxalinyl, dihydrobenzodioxinyl, or 2,3-dihydrobenzo[*b*][1,4]dioxinyl.

[0066] “Heterocycloalkyl” means a saturated or partially unsaturated (but not aromatic) monocyclic ring of 3 to 9 ring atoms, or a saturated or partially unsaturated (but not aromatic) bicyclic ring of 5 to 12 ring atoms in which one or more ring atoms is a heteroatom independently selected from -O-, -S-, -N= (trivalent nitrogen), or -NH-, and the remaining ring atoms are carbon. In certain embodiments, heterocycloalkyl is a saturated or partially unsaturated monocyclic group of 4 to 7 rings atoms, or a saturated or partially unsaturated bicyclic group of 7 to 9 ring atoms. In certain embodiments, heterocycloalkyl is a saturated or partially unsaturated monocyclic group of 5 to 6 rings atoms or a saturated or partially unsaturated bicyclic group of 6 to 8 ring atoms.

[0067] In certain embodiments, the heterocycloalkyl group comprises one, two, three, or four ring heteroatoms, independently selected from -O-, -S-, -N= (trivalent nitrogen), or -NH-, and the remaining ring atoms are carbon. In certain embodiments, the heterocycloalkyl group contains only one or two nitrogen atoms, and the remaining ring atoms are carbon. When a heterocycloalkyl group contains from x to y ring atoms, it may be referred to herein as “a x-y membered heterocycloalkyl”. In certain embodiments, the heterocycloalkyl is a 4-7 membered heterocycloalkyl, or is a 5-6 membered heterocycloalkyl, or is a 7-9 membered heterocycloalkyl. In certain embodiments, the heterocycloalkyl is a 5-8 membered heterocycloalkyl.

[0068] Heterocycloalkyl groups include fused or bridged heterocycloalkyl bicyclic rings. For example, a fused heterocycloalkyl group may comprise two rings that share adjacent atoms (*e.g.*, one covalent bond). When bridged, the heterocycloalkyl group may comprise two rings that share three or more atoms, separating the two bridgehead atoms by a bridge containing at



[0069] In certain embodiments, heterocycloalkyl includes, but is not limited to, azetidiny, pyrrolidiny, 2,5-dihydro-1*H*-pyrroliny, 2,5-dihydro-1*H*-pyrroly, piperidiny, morpholiny, piperaziny, pyranly, tetrahydropyranly, tetrahydrothiopyranly, 1,3-dioxiny, 1,3-dioxanly, 1,4-dioxiny, 1,4-dioxanly, thiomorpholiny, thiamorpholiny, perhydroazepiny,

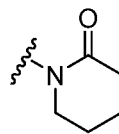
pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, octahydropyrrolo[3,4-c]pyrrolinyl, decahydroisoquinolyl, tetrahydrofuryl, 2-azaspiro[3.3]heptanyl, 4,7-diazaspiro[2.5]octanyl, 1,6-diazaspiro[3.3]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.2.1]octanyl, and 8-azabicyclo[3.2.1]octanyl.

[0070] “(Heterocycloalkyl)alkyl” means an alkyl group, as defined herein, substituted with at least one, in another example 1 or 2, heterocycloalkyl groups as defined herein. In certain embodiments, the alkyl is substituted with one heterocycloalkyl group.

[0071] “Heterocycloalkylcarbonyl” means a group of the formula $-C(O)R$, wherein R is heterocycloalkyl, as defined herein.

[0072] “Heterocycloalkylcarbonyloxy” means a group of the formula $-OC(O)R$, wherein R is heterocycloalkyl, as defined herein.

[0073] “Heterocycloalkyl-one” means a heterocycloalkyl group as defined herein and wherein one ring carbon atom of the heterocycloalkyl group forms a double bond with oxygen



atom. In certain embodiments heterocycloalkyl-one group is

[0074] “Hydroxy” means an $-OH$ group. The terms “hydroxy” and “hydroxyl” are used interchangeably and mean an $-OH$ group.

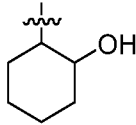
[0075] “Hydroxyalkyl” means a group of formula $-R-(OH)_z$, where R is an alkyl as defined herein and z is 1 or 2. In one embodiment, hydroxyalkyl is $-ROH$. In one embodiment, hydroxyalkyl includes $-CH_2OH$. In one embodiment, hydroxyalkyl is $-R(OH)_2$.

[0076] “Hydroxyalkoxy” means a group of formula $-O-R-(OH)_z$, where R is an alkyl as defined herein and z is 1 or 2. In one embodiment, hydroxyalkoxy is $-OR-(OH)$. In one embodiment, hydroxyalkoxy is $-OR-(OH)_2$. In one embodiment (hydroxy)alkoxy includes (hydroxy)propyloxy.

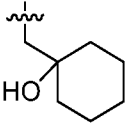
[0077] “Hydroxycarbonyl” means an $-C(O)OH$ group. As used herein, the terms “hydroxycarbonyl” and “carboxyl” are used interchangeably and refer to the same group.

[0078] “Hydroxycarbonylalkyl” means a group of the formula $-RC(O)OH$, wherein R is alkylene as defined herein.

[0079] “Hydroxycycloalkyl” means a group of the formula $-ROH$, wherein R is

cycloalkyl as defined herein. In certain embodiments, hydroxycycloalkyl is .

[0080] “(Hydroxycycloalkyl)alkyl” means a group of formula $-RR'$ wherein R is alkyl and R' is hydroxycycloalkyl as defined herein. In certain embodiments (hydroxycycloalkyl)alkyl

is .

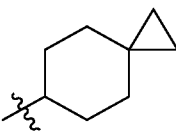
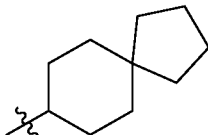
[0081] “(Phenyl)alkyl” means an alkyl group, as defined herein, substituted with at least one phenyl group. In certain embodiments, the alkyl is substituted with one phenyl group. In certain embodiments, (phenyl)alkyl is benzyl.

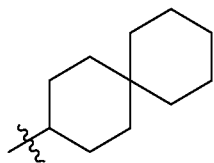
[0082] “(Phenyl)alkoxy” means a group of the formula $-OR$, wherein R is (phenyl)alkyl as defined herein.

[0083] “Phenylcarbonyloxy” means a group of the formula $-OC(O)R$, wherein R is phenyl.

[0084] “Spirocycloalkyl” means a bicyclic cycloalkyl ring of 5 to 12 carbon ring atoms having one quaternary carbon ring atom common to both rings. In certain embodiments, the spirocycloalkyl is a C₅₋₁₂ spirocycloalkyl, or is a C₈₋₁₁ spirocycloalkyl.

[0085] In certain embodiments, spirocycloalkyl groups include spiro[2.5]octane, spiro[3.4]octane, spiro[3.5]nonane, spiro[4.4]nonane, spiro[4.5]decane, or spiro[5.5]undecane.

In certain embodiments, the spirocycloalkyl group is , or is , or is



[0086] In some embodiments, compounds of the described herein exist as stereoisomers, wherein asymmetric or chiral centers are present. The term (R) and (S) used herein are configurations as defined in IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, *Pure Appl. Chem.*, (1976), **45**:13-30, hereby incorporated by reference. The

embodiments described herein specifically includes the various stereoisomers and mixtures thereof.

[0087] “Stereoisomers” include (but are not limited to) geometric isomers, enantiomers, diastereomers, and mixtures of geometric isomers, enantiomers or diastereomers. In some embodiments, individual stereoisomers of compounds are prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic column.

[0088] “Amelioration” of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[0089] The terms “effective amount” or “therapeutically effective amount,” refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or disorder being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is determined using any suitable technique, such as a dose escalation study.

[0090] “Excipient” or “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof. In one embodiment, each

component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

[0091] “Pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, or salicylic acid. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-*D*-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, or lysine, or by other methods previously determined. The pharmacologically acceptable salts are not specifically limited as far as it can be used in medicaments.

[0092] The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components, such as an excipient. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

[0093] “Subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably. In certain embodiments, the subject is a

mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is an adult human. In certain embodiments, the subject is a human child.

[0094] In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is an adult human. In certain embodiments, the subject is a human child.

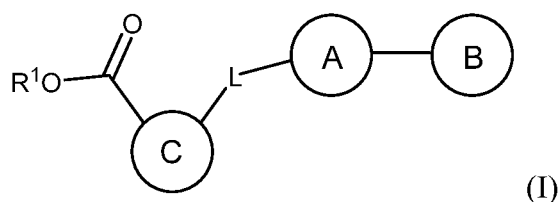
[0095] “Treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof. Often, the beneficial effects that a subject derives from a therapeutic agent do not result in a complete cure of the disease, disorder or condition.

[0096] The term “disease or disorder characterized by high oxalate content in the urine” refers to an oxylate content that is at least 10% higher than a reference level observed in a healthy patient. For example, in certain embodiments, the disease or disorder characterized by high oxalate content in the urine refers to an oxylate content that is at least 20% higher than a reference level observed in a healthy patient, such as at least 20%, at least 30%, at least 40%, at least 50%, at least 100%, or at least 200%, higher than a reference level observed in a healthy patient. In certain embodiments, the disease or disorder characterized by high oxalate content in the urine refers to an oxylate content that is about 10% higher than a reference level observed in a healthy patient, such as about 20%, about 30%, about 40%, about 50%, about 100%, about 200%, or more than 200%, higher than a reference level observed in a healthy patient. In certain embodiments, the disease or disorder characterized by high oxalate content in the urine refers to an oxylate content that is about 1.25 times higher than a reference level observed in a healthy patient, such as about 1.25 times, about 1.5 times, about 1.75 times, about 2 times, about 3 times, or more than 3 times, higher than a reference level observed in a healthy patient.

Embodiments

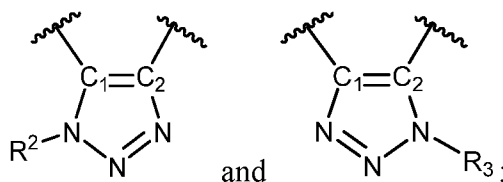
[0097] The following paragraphs present a number of embodiments of the compounds disclosed herein. In each instance the embodiment includes both the recited compound(s) as well as a single stereoisomer or mixture of stereoisomers thereof, as well as a pharmaceutically acceptable salt thereof.

[0098] In one aspect, provided herein is a compound of Formula (I):



wherein:

Ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L;

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₃₋₈ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-8 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups independently selected from halo, alkyl, alkoxy, cyano, hydroxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups;
- (ii) 2 halo groups when L is other than O;
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl;
- (iv) one halo group when L is CH₂NR^L;

- (v) one halo group and one group selected from the group consisting of haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O, S, or S(=O), wherein the phenyl is optionally substituted with halo, cyano, haloalkyl, or haloalkoxy; or
- (vi) one cyano group and one (phenyl)alkoxy group, when L is bond or O, wherein the phenyl as part of the (phenyl)alkoxy group is optionally substituted with halo or haloalkoxy;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O, S, or CH₂S;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo groups; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one;

(heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S or CH_2 , and Ring A is phenyl other than phenyl substituted with (cycloalkyl)alkoxy, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[0099] In certain embodiments, Ring B cannot be mono or di-substituted halo.

[00100] In certain embodiments, Ring B cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl.

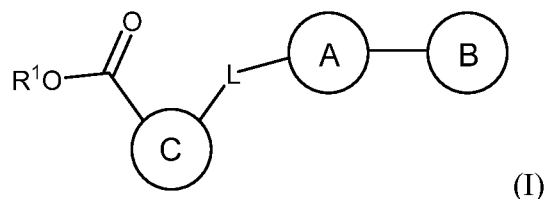
[00101] In certain embodiments, Ring A cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl, and Ring B cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl.

[00102] In certain embodiments, when L is S or CH₂, Ring B cannot be mono or di-substituted halo.

[00103] In certain embodiments, when L is S or CH₂, Ring B cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl.

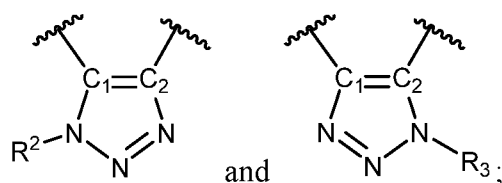
[00104] In certain embodiments, when L is S or CH₂, Ring A cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl, and Ring B cannot be unsubstituted phenyl or phenyl substituted with one or two groups independently selected from alkyl, halo, or haloalkyl.

[00105] In certain embodiments, the compound of Formula (I):



is that wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L;

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups;

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

each R^{AA} is independently alkyl; halo; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; alkylcarbonylaminoalkoxy; phenoxy optionally substituted with one or two halo; or (phenyl)alkoxy wherein the phenyl is optionally substituted with halo, cyano, haloalkyl, or haloalkoxy;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

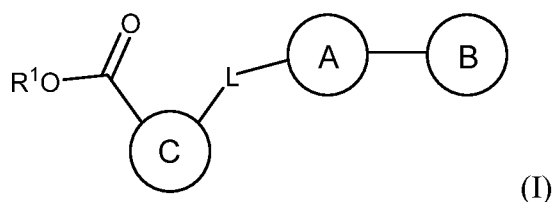
each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; and

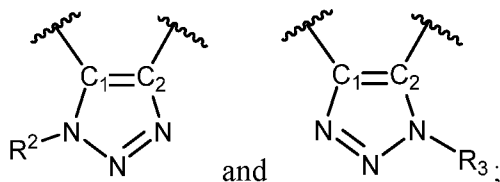
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00106] In certain embodiments, the compound of Formula (I):



is that wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to L;

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, or alkylcarbonyloxy;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, alkylcarbonylaminoalkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy,

cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00107] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups;

each R^{AA} is independently alkyl; halo; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; alkylcarbonylaminoalkoxy; phenoxy optionally substituted with one or two halo; or (phenyl)alkoxy wherein the phenyl is optionally substituted with halo, cyano, haloalkyl, or haloalkoxy;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R¹ is W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonyloxy,

cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00108] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl,
- (iv) one halo group when L is CH_2NR^L , or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then Ring A is optionally substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; alkylcarbonylaminoalkoxy; or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

provided:

- when L is S or CH_2 , and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;

- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00109] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S; R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally

substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-8 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl,
- (iv) one halo group when L is CH_2NR^L , or

- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups or
- (ii) Ring A is unsubstituted, wherein:
- 1) when Ring A is unsubstituted tetrahydroquinoliny, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxiny, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R^1 is not hydrogen or ethyl; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

provided:

- i. when L is S or CH_2 , and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00110] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S; R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl,
- (iv) one halo group when L is CH_2NR^L , or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R^1 is not hydrogen or ethyl; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-

one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl;
heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S or CH_2 , and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof. In a further embodiment, the compound of Formula (I) is that wherein: R^L is hydrogen, C_{1-4} alkyl, or benzyl; and the benzyl group is optionally substituted with one or two haloalkoxy groups; and Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-8 membered heterocycloalkyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, or

tetrahydroisoquinoliny. In a further embodiment, the compound of Formula (I) is that wherein: R^L is hydrogen, C_{1-4} alkyl, or benzyl; and the benzyl group is optionally substituted with one or two haloalkoxy groups; and Ring B, when present, is cycloalkyl, heterocycloalkyl, phenyl, tetrahydronaphthyl, quinoliny, isoquinoliny, tetrahydroquinoliny.

[00111] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S; R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally

substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl,
- (iv) one halo group when L is CH_2NR^L , or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S or CH_2 , and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;

- v. when L is bond, Ring A is other than phenyl, Ring B is not present, and R¹ is H, then R^{AB} cannot be methyl, and
- vi. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00112] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is hydrogen, C₁₋₄ alkyl, or benzyl; and the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₅₋₆ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo and haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups; or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl; or

4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;
 each R^{AA} is independently haloalkyl; cycloalkyloxy; (cycloalkyl)alkoxy;
 alkylcarbonylaminoalkoxy; or phenoxy optionally substituted with one or two halo;
 each R^{AB} is independently halo, alkyl, haloalkyl, or haloalkoxy;
 Ring B, when present, cycloalkyl, heterocycloalkyl, phenyl, tetrahydronaphthyl,
 tetrahydroquinolinyl, quinolinyl, or isoquinolinyl; wherein each Ring B is optionally
 substituted with one or two R^B groups;
 each R^B is independently halo; cyano; alkyl; haloalkyl; haloalkoxy; alkoxyalkoxy;
 aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkoxy;
 heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; or (5-6-
 membered heterocycloalkyl-one)alkyl;
 R¹ is hydrogen, alkyl or W; wherein W is alkyl substituted with alkylcarbonyloxy,
 dialkylaminocarbonyloxy cycloalkylcarbonyloxy, or phenylcarbonyloxy;
 R² and R³ are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with
 cycloalkylcarbonyloxy or heterocycloalkylcarbonyloxy, wherein the
 heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;
 provided:

- (i) when L is S or CH₂, and Ring A is phenyl, then Ring B cannot be halo substituted phenyl;
- (ii) when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- (iii) when L is O, Ring A is phenyl substituted with 1 R^{AA}, and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- (iv) when L is O, Ring A is phenyl, Ring B is not present, and R¹ is ethyl, then R^{AA} cannot be trifluoromethoxy;
- (v) when L is bond, Ring A is other than phenyl, Ring B is not present, and R¹ is H, then R^{AB} cannot be methyl, and
- (vi) when L is NH, Ring A is pyridyl and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00113] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when L is S or CH₂, and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00114] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, O, CF₂, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H, C_{1-4} alkyl, or benzyl; and the phenyl in the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, phenyl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is cycloalkyl, heterocycloalkyl, phenyl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl, haloalkyl; haloalkoxy; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkoxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; or (5-6-membered heterocycloalkyl-one)alkyl;

R^1 is hydrogen, alkyl or W; wherein W is alkyl substituted with alkylcarbonyloxy, dialkylaminocarbonyloxy cycloalkylcarbonyloxy, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with cycloalkylcarbonyloxy or heterocycloalkylcarbonyloxy, wherein the heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00115] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is hydrogen or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, or alkylcarbonyloxy;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, alkylcarbonylaminoalkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^1 is W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00116] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is hydrogen or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiophenyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, dihydrobenzodioxiny, or tetrahydro-methanonaphthalenyl; Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring B is not present and Ring A is other than phenyl, then Ring A is optionally substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;
- iii. when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy;
- iv. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00117] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is hydrogen or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy; and

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00118] In certain embodiments, the compound of Formula (I) is that wherein:
 Ring B is present; wherein Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;
 each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl; provided when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and
 optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00119] In certain embodiments, the compound of Formula (I) is that wherein:
 Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-8 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;
 Ring B is present or not present; wherein:
 when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, haloalkoxy, (cycloalkyl)alkoxy, and cycloalkyl;
 when Ring B is not present and Ring A is other than phenyl, then
 (i) Ring A is substituted with one or two R^{AB} groups or
 (ii) Ring A is unsubstituted, wherein:
 1) when Ring A is unsubstituted tetrahydroquinoliny, then L is bond;
 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxiny, then L is O;
 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl; or
 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;
 each R^B is independently halo; cyano; alkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy;

aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00120] In certain embodiments, the compound of Formula (I) is that wherein:

ring B is not present;

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy; and

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy,

alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00121] In certain embodiments, the compound of Formula (I) is that wherein:

Ring A is phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently haloalkoxy, cycloalkyloxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, alkoxy, or haloalkoxy;

R^1 is hydrogen, alkyl, cycloalkyl, or W; where W is alkyl substituted with alkylcarbonyloxy; and

R^2 and R^3 are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with alkylcarbonyloxy; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00122] In certain embodiments, the compound of Formula (I) is that wherein:

ring B is not present;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups,

(ii) 2 halo groups when L is other than O;

- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups; or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinoliny, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxiny, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00123] In certain embodiments, the compound of Formula (I) is that wherein:

Ring A is piperidiny, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxiny, pyridyl, quinoliny, isoquinoliny, tetrahydroquinoliny, tetrahydroisoquinoliny, spiro[2.5]octane, spiro[4.5]decane, or spiro[5.5]undecane;

when Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O;
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy and (cycloalkyl)alkoxy, when L is bond, O or S;

each R^{AA} is independently haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo, alkyl, haloalkyl, or haloalkoxy;

R¹ is hydrogen, alkyl or W; wherein W is alkyl substituted with alkylcarbonyloxy;

R^2 and R^3 are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with cycloalkylcarbonyloxy or heterocycloalkylcarbonyloxy, wherein the heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00124] In certain embodiments, the compound of Formula (I) is that wherein: ring B is present;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny; wherein Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, and haloalkoxy;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or a halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00125] In certain embodiments, the compound of Formula (I) is that wherein:

L is bond, CH_2 , CF_2 , O, NR^L , S, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is hydrogen, C_{1-4} alkyl, or benzyl, wherein the phenyl, as part of the benzyl group, is optionally substituted with haloalkoxy group;

Ring A is C_{3-7} cycloalkyl, 5-6 membered heterocycloalkyl, phenyl, or naphthyl, wherein Ring A is optionally substituted with halo or haloalkoxy;

Ring B is cycloalkyl, heterocycloalkyl, phenyl, tetrahydronaphthyl, tetrahydroquinoliny, quinoliny, or, isoquinoliny; wherein each Ring B is optionally substituted with one or two R^B groups;

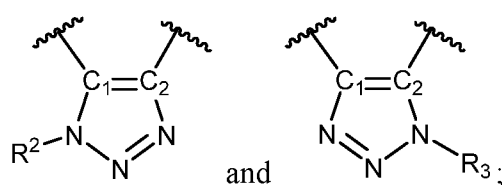
each R^B is independently halo; cyano; haloalkyl; haloalkoxy; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkoxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; or (5-6-membered heterocycloalkyl-one)alkyl; and

R^1 is hydrogen or W; wherein W is alkyl substituted with alkylcarbonyloxy, dialkylaminocarbonyloxy cycloalkylcarbonyloxy, or phenylcarbonyloxy; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00126] In certain embodiments, the compound of Formula (I) is that wherein L is bond, O, S, NR^L , CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S, and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00127] In certain embodiments, the compound of Formula (I) is that wherein L is O or S, and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00128] In certain embodiments, the compound of Formula (I) is that wherein: ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to L; and Ring B is present.

[00129] In certain embodiments, the compound of Formula (I) is that wherein: L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S; R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny; wherein Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, or haloalkoxy;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when L is S or CH₂, and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00130] In certain embodiments, the compound of Formula (I) is that wherein:

L is bond, CH₂, CF₂, O, NR^L, S, CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen, C₁₋₄ alkyl, or benzyl, wherein the phenyl in the benzyl group is optionally substituted with haloalkoxy group;

Ring A is C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, phenyl, or naphthyl, wherein Ring A is optionally substituted with halo or haloalkoxy;

Ring B is cycloalkyl, heterocycloalkyl, phenyl, tetrahydronaphthyl, tetrahydroquinoliny, quinoliny, or isoquinoliny; wherein each Ring B is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; haloalkyl; haloalkoxy; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkoxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; or (5-6-membered heterocycloalkyl-one)alkyl; and

R^L is hydrogen or W; wherein W is alkyl substituted with alkylcarbonyloxy, dialkylaminocarbonyloxy cycloalkylcarbonyloxy, or phenylcarbonyloxy;

provided that when L is S or CH₂, and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00131] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiophenyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, dihydrobenzodioxiny, or tetrahydro-methanonaphthalenyl; Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;
- iii. when L is O, Ring A is phenyl, Ring B is not present, and R¹ is ethyl, then R^{AA} cannot be trifluoromethoxy;
- iv. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00132] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H or C₁₋₄ alkyl optionally substituted with hydroxycarbonylalkyl;

Ring A is 5-6 membered heterocycloalkyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl;

wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy substituted with one or two halo;

each R^{AB} is independently halo, alkyl, alkoxy, haloalkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;

- iii. when L is O, Ring A is phenyl, Ring B is not present, and R¹ is ethyl, then R^{AA} cannot be trifluoromethoxy;
- iv. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00133] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00134] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H or C₁₋₄ alkyl optionally substituted with hydroxycarbonylalkyl;

Ring A is heterocycloalkyl, phenyl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is heterocycloalkyl, phenyl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, alkyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocycloalkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, or alkylcarbonyloxy;

R² and R³ are each hydrogen or alkyl optionally substituted with alkylcarbonyloxy;

provided that when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00135] In certain embodiments, the compound of Formula (I) is that wherein:

L is a bond, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H or C₁₋₄ alkyl;

Ring A is phenyl or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is phenyl or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

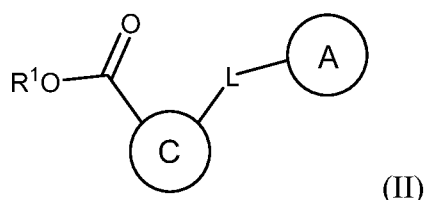
each R^B is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, or heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, or alkylcarbonyloxy;

R² and R³ are independently hydrogen or alkyl;

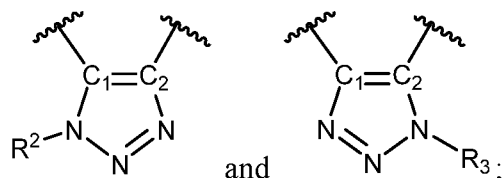
provided that when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00136] In certain embodiments, the compound of Formula (I) is according to Formula (II):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to L.

[00137] In certain embodiments, the compound of Formula (II) is that wherein: L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is H, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy; Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl; R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl; R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; provided that when L is S or CH₂, and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00138] In certain embodiments, the compound of Formula (II) is that wherein:
 L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;
 R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;
 Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O;
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups; or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl, or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, phenoxy optionally substituted with one or two halo, or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is O and Ring A is phenyl, then R^{AA} cannot be alkyl;
- ii. when L is O, Ring A is phenyl, and R^1 is ethyl, then R^{AB} cannot be trifluoromethoxy;
- ii. when L is O, Ring A is phenyl substituted with 1 R^{AA} , then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is bond, Ring A is other than phenyl, and R^1 is H, then R^{AB} cannot be methyl, and
- v. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00139] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is H, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or

alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, tetrahydronaphthyl, dihydronaphthyl, benzothiazolyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl,

tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny; provided that when L is NR^{L} or O, then Ring A cannot be tetrahydronaphthyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-\text{N}(\text{R}^{1\text{A}})\text{C}(\text{O})\text{R}^{1\text{B}}$, $-\text{N}(\text{R}^{1\text{A}})\text{C}(\text{O})\text{OR}^{1\text{B}}$, or $-\text{N}(\text{R}^{1\text{A}})\text{C}(\text{O})\text{NR}^{1\text{B}}\text{R}^{1\text{C}}$; wherein $\text{R}^{1\text{A}}$, $\text{R}^{1\text{B}}$, and $\text{R}^{1\text{C}}$ are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00140] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH_2 , O, NH, S, $\text{S}(\text{=O})$, $\text{C}(\text{=O})$, $\text{CH}_2\text{-Q}$, or Q-CH_2 ; wherein Q is O, NH, or S;

Ring A is piperidinyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxiny, pyridyl, quinoliny, isoquinoliny, tetrahydroquinoliny, tetrahydroisoquinoliny, spiro[2.5]octane, spiro[4.5]decane, or spiro[5.5]undecane;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O;
- (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl,
- (iv) one halo group when L is $\text{CH}_2\text{NR}^{\text{L}}$, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy and (cycloalkyl)alkoxy, when L is bond, O or S;

when Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups; or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinoliny, then L is bond;

- 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
- 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl, or
- 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo, alkyl, haloalkyl, or haloalkoxy;

R¹ is hydrogen, alkyl, or W; wherein W is alkyl substituted with alkylcarbonyloxy;

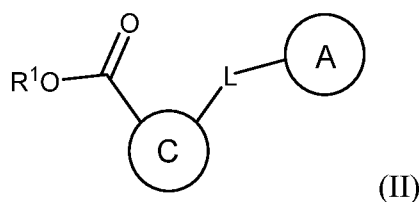
R² and R³ are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with cycloalkylcarbonyloxy or heterocycloalkylcarbonyloxy, wherein the heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

provided:

- i. when L is O, Ring A is phenyl, and R¹ is ethyl, then R^{AB} cannot be trifluoromethoxy;
- ii. when L is O, Ring A is phenyl substituted with 1 R^{AA}, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA}, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is bond, Ring A is other than phenyl, and R¹ is H, then R^{AB} cannot be methyl, and
- v. when L is NH, Ring A is pyridyl, then R^{AB} cannot be alkyl; and

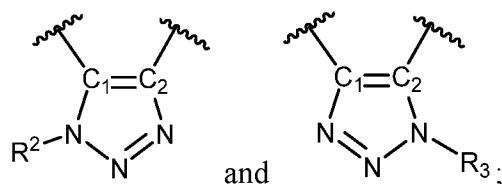
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00141] In certain embodiments, the compound of Formula (I) is according to Formula (II):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L.

[00142] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is H or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one halo or alkyl;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when L is S and Ring A is phenyl, then Ring B is not halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00143] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

R^L is hydrogen or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups; each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is O and Ring A is phenyl, then R^{AA} cannot be alkyl or trifluoromethyl;
- ii. when L is O, Ring A is phenyl, and R^1 is ethyl, then R^{AB} cannot be trifluoromethoxy;
- iii. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, then R^{AB} cannot be alkyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00144] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

R^L is H or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, tetrahydronaphthalinyl, dihydronaphthalinyl, benzothiazolyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl; provided that when L is NR^L or O, then Ring A cannot be tetrahydronaphthalinyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy;

R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00145] In certain embodiments, the compound of Formula (II) is that wherein:

L is a bond, CH₂, O, NH, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NH, or S;

Ring A is phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl;

wherein:

when Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups; each R^{AA} is independently haloalkoxy, cycloalkyloxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, alkoxy, or haloalkoxy;

R¹ is hydrogen, alkyl, cycloalkyl, or W; where W is alkyl substituted with alkylcarbonyloxy;

R² and R³ are independently hydrogen or alkyl;

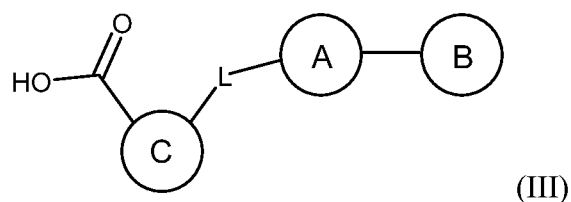
wherein the alkyl is optionally substituted with alkylcarbonyloxy;

provided:

- i. when L is O, Ring A is phenyl, and R¹ is ethyl, then R^{AB} cannot be trifluoromethoxy;
- ii. when L is NH, Ring A is pyridyl or indolinyl, then R^{AB} cannot be alkyl; and

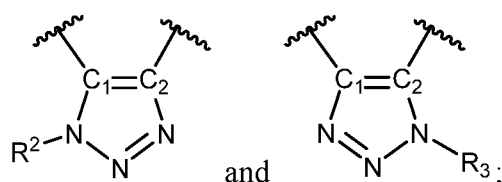
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00146] In certain embodiments, the compound of Formula (I) is according to Formula (III):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L.

[00147] In certain embodiments, the compound of Formula (III) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, , tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, and haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,

- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinoliny, then L is bond;
 - 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxiny, then L is O;
 - 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is not O; or
 - 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl halo, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl;

R² and R³ are independently hydrogen, alkyl, phenyl, or benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S or CH₂, and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;

- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- iii. when L is O, Ring A is phenyl substituted with 1 R^{AA}, and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- iv. when L is bond, Ring A is other than phenyl and Ring B is not present, then R^{AB} cannot be methyl, and
- v. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00148] In certain embodiments, the compound of Formula (III) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is hydrogen, C₁₋₄ alkyl, or benzyl; and the phenyl in the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₅₋₆ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo and haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups,
- (ii) 2 halo groups when L is other than O,
- (iii) 2 halo groups when L is O, and R² and R³ are not hydrogen or alkyl,
- (iv) one halo group when L is CH₂NR^L, or
- (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo;

when Ring B is not present and Ring A is other than phenyl, then

- (i) Ring A is substituted with one or two R^{AB} groups; or
- (ii) Ring A is unsubstituted, wherein:
 - 1) when Ring A is unsubstituted tetrahydroquinolinyl, then L is bond;

- 2) when Ring A is unsubstituted 2,3-dihydrobenzo[b][1,4]dioxinyl, then L is O;
- 3) when Ring A is unsubstituted tetrahydronaphthyl, then L is O, and R¹ is not hydrogen or ethyl; or
- 4) when Ring A is unsubstituted spirocycloalkyl, then L is O or S;

each R^{AA} is independently haloalkyl; cycloalkyloxy; (cycloalkyl)alkoxy;

alkylcarbonylaminoalkoxy; or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, haloalkyl, or haloalkoxy;

Ring B, when present, cycloalkyl, heterocycloalkyl, phenyl, tetrahydronaphthyl,

tetrahydroquinolinyl, quinolinyl, or isoquinolinyl; wherein each Ring B is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; haloalkoxy; alkoxyalkoxy;

aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkoxy;

heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; or (5-6-membered heterocycloalkyl-one)alkyl;

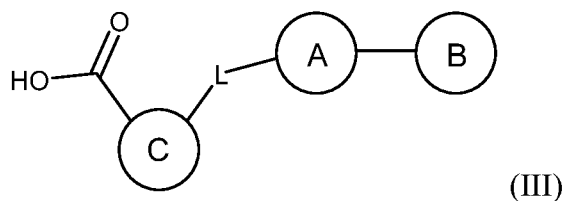
R² and R³ are independently hydrogen or alkyl; wherein the alkyl is optionally substituted with cycloalkylcarbonyloxy or heterocycloalkylcarbonyloxy, wherein the heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

provided:

- (i) when L is S or CH₂, and Ring A is phenyl, then Ring B cannot be halo substituted phenyl;
- (ii) when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl;
- (iii) when L is O, Ring A is phenyl substituted with 1 R^{AA}, and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl;
- (iv) when L is bond, Ring A is other than phenyl, Ring B is not present, then R^{AB} cannot be methyl, and
- (v) when L is NH, Ring A is pyridyl and Ring B is not present, then R^{AB} cannot be alkyl; and

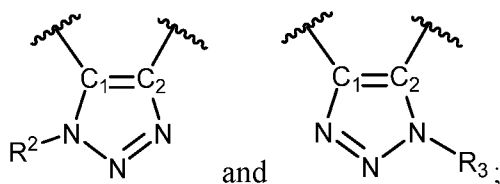
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00149] In certain embodiments, the compound of Formula (I) is according to Formula (III):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to L.

[00150] In certain embodiments, the compound of Formula (III) is that wherein:

L is a bond, CH₂, CF₂, O, NR^L, S, C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O;

when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, or benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- i. when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl;
- ii. when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;
- iii. when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl;
- iv. when L is S and Ring B is not present, then Ring A cannot be thienyl or benzothiophenyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00151] In certain embodiments provided herein of the compound according to any one Formula (I), (II) or (III), or single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt thereof, wherein L is a bond, CH_2 , CF_2 , O, NR^L , S, $S(=O)$, or $C(=O)$. In certain embodiments, L is CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S. In certain embodiments, L is CH_2 , CF_2 , O, NR^L , or S. In certain embodiments, L is CF_2 , O, NR^L , or S. In certain embodiments, L is CF_2 , O, or NR^L . In certain embodiments, L is CH_2 , O, NR^L , or S. In certain embodiments, L is O, NR^L , or S. In certain embodiments, L is CH_2 , CF_2 , or $C(=O)$. In certain embodiments, L is CH_2 , CF_2 , CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S. In certain

embodiments, L is CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S. In certain embodiments, L is bond, CF₂, O, NR^L, S, or S(=O). In certain embodiments, L is a bond, or L is CH₂, or L is CF₂. In certain embodiments, L is O. In certain embodiments, L is NR^L. In certain embodiments, L is S. In certain embodiments, L is S(=O). In certain embodiments, L is C(=O). In certain embodiments, L is CH₂-Q; wherein Q is O, NR^L, or S. In certain embodiments, L is CH₂-O, or L is CH₂-S, or L is CH₂-NR^L, or L is O-CH₂, or L is NR^L-CH₂.

[00152] In certain embodiments, R^L is H. In certain embodiments, R^L is C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is H or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is C₁₋₄ alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is substituted with one or two groups selected from halo and haloalkoxy. In certain embodiments, R^L is C₃₋₆ cycloalkyl. In certain embodiments, R^L is phenyl or benzyl; wherein the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo haloalkoxy. In certain embodiments, R^L is benzyl optionally substituted with one or two groups selected from halo and haloalkoxy.

[00153] In certain embodiments, Ring A is cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups.

[00154] In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thienyl, pyridyl, phenyl, naphthyl, tetrahydronaphthyl, dihydronaphthyl, indanyl, indolyl, indolinyl, isoindolinyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, or tetrahydro-methanonaphthalenyl.

[00155] In certain embodiments, Ring A is C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl.

[00156] In certain embodiments, Ring A is cyclopentyl, cyclohexyl, spiro[2.5]octanyl, spiro[4.5]decanyl, spiro[5.5]undecanyl, piperidinyl, piperazinyl, phenyl, naphthyl, indanyl,

tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinolinyl, isoquinolinyl, pyridyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, or 3-azabicyclo[3.1.0]hexanyl.

[00157] In certain embodiments, Ring A is cyclopentyl, cyclohexyl, bicycloheptanyl, spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolyl, imidazolyl, triazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydrobenzodioxiny, or 3-azabicyclo[3.1.0]hexanyl.

[00158] In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, phenyl, or naphthyl.

[00159] In certain embodiments, Ring A is cyclopentyl, cyclohexyl, spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl, piperidinyl, piperazinyl, phenyl, or naphthyl.

[00160] In certain embodiments, Ring A is aryl. In certain embodiments, ring A is phenyl or naphthyl. In certain embodiments, ring A is phenyl.

[00161] In certain embodiments, Ring A is spirocycloalkyl, or is C₈₋₁₁ spirocycloalkyl. In certain embodiments, ring A is spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl.

[00162] In certain embodiments, Ring A is C₃₋₇ cycloalkyl. In certain embodiments, Ring A is C₅₋₆ cycloalkyl. In certain embodiments, Ring A is cyclopentyl or cyclohexyl.

[00163] In certain embodiments, Ring A is 5-6 membered heterocycloalkyl. In certain embodiments, Ring A is piperidinyl or piperazinyl.

[00164] In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is C₃₋₇ cycloalkyl or C₈₋₁₁ spirocycloalkyl, where each is optionally substituted with 1 or 2 R^{AB} groups. In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, or 5-6 membered heterocycloalkyl, where each is optionally substituted with 1 or 2 R^{AB} groups. In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, or aryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is 5-6 membered

heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is aryl or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is phenyl or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} or R^{AB} groups. In certain embodiments, Ring A is C_{3-7} cycloalkyl or C_{8-11} spirocycloalkyl, where each is optionally substituted with 1 or 2 R^{AB} groups. In certain embodiments, Ring A is C_{3-7} cycloalkyl optionally substituted with 1 or 2 R^{AB} groups. In certain embodiments, Ring A does not include thienyl. In certain embodiments, Ring A does not include indolyl.

[00165] In certain embodiments, when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, or haloalkoxy.

[00166] In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with: (i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O.

[00167] In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with: (i) one or two R^{AA} groups, (ii) 2 halo groups when L is other than O, (iii) 2 halo groups when L is O, and R^2 and R^3 are not hydrogen or alkyl, (iv), one halo group when L is CH_2NR^L , or (v) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo.

[00168] In certain embodiments, each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, phenoxy optionally substituted with one or two groups selected from halo and alkylcarbonylaminoalkoxy. In certain embodiments, each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or alkylcarbonylaminoalkoxy. In certain embodiments, each R^{AA} is independently haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or alkylcarbonylaminoalkoxy. In certain embodiments, each R^{AA} is independently haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, alkylcarbonylaminoalkoxy, (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo, or alkylcarbonylaminoalkoxy. In certain embodiments, each R^{AA} is independently haloalkyl

or cycloalkyloxy, or is haloalkyl or (cycloalkyl)alkoxy, or is haloalkyl or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo.

[00169] In certain embodiments, each R^{AA} is independently isopropyl, trifluoromethyl, propoxy, pentyloxy, trifluoromethoxy, cyclopropylmethoxy, cyclopentylmethoxy, or cyclohexylmethoxy. In certain embodiments, each R^{AA} is independently isopropyl, trifluoromethyl, propoxy, pentyloxy, trifluoromethoxy, cyclopropylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy, or halobenzyloxy.

[00170] In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo. In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with one halo and one haloalkoxy, or with one halo and one (cycloalkyl)alkoxy, or with one halo and one (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo.

[00171] In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is unsubstituted: 1) when L is bond and Ring A is tetrahydroquinolinyl, 2) when L is O and Ring A is dihydroxybenzodioxynyl, 3) when L is O, Ring A is tetrahydronaphthalene, and R^1 is not hydrogen or ethyl, or 4) when L is O or S, and ring A is spirocycloalkyl.

[00172] In certain embodiments, each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo. In certain embodiments, each R^{AB} is independently halo, alkyl, haloalkyl, or haloalkoxy. In certain embodiments, each R^{AB} is independently chloro, bromo, fluoro, methyl, isopropyl, difluoromethyl, trifluoromethyl, trifluoromethoxy.

[00173] In certain embodiments, when Ring B is not present and Ring A is spiro[2.5]octanyl, spiro[4.5]decanyl, spiro[5.5]undecanyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, 2,3-dihydrobenzo[b][1,4]dioxynyl, pyridyl, quinolinyl, isoquinolinyl, pyridyl, tetrahydroquinolinyl, or tetrahydroisoquinolinyl; then ring A is substituted with one or two groups independently selected from the group consisting of haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, alkylcarbonylaminoalkoxy, and (phenyl)alkoxy, wherein the phenyl as part of (phenyl)alkoxy is optionally substituted with halo, or with one or two groups independently

selected from the group consisting of halo, alkyl, alkoxy, and haloalkoxy, or with difluoromethane, trifluoromethyl, cyclopropoxy, cyclopentyloxy, propylmethoxy, pentylmethoxy, hexylmethoxy, and fluorobenzyloxy, or with fluoro, chloro, bromo, methyl, isopropyl, and trifluoromethoxy.

[00174] In certain embodiments, Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups. In certain embodiments, Ring B, when present, is cycloalkyl optionally substituted with one or two R^B groups. In certain embodiments, Ring B, when present, is heterocycloalkyl optionally substituted with one or two R^B groups. In certain embodiments, Ring B, when present, is aryl optionally substituted with one or two R^B groups. In certain embodiments, Ring B, when present, is heteroaryl optionally substituted with one or two R^B groups.

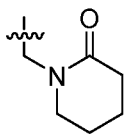
[00175] In certain embodiments, Ring B is C₄₋₆ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is C₄₋₆ cycloalkyl, 5-6 membered heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is C₄₋₆ cycloalkyl, 5-6 membered heterocycloalkyl, phenyl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, tetrahydronaphthyl, tetrahydroquinoliny, quinoliny, or isoquinoliny, tetrahydro-2H-pyrany, cyclobutyl, cyclopentyl, cyclohexyl, or pyridyl. In certain embodiments, Ring B is piperidiny, piperaziny, phenyl, tetrahydronaphthyl, tetrahydroquinoliny, quinoliny, or isoquinoliny, tetrahydro-2H-pyrany, cyclobutyl, cyclopentyl, cyclohexyl, or pyridyl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, or quinoliny. In certain embodiments, Ring B is piperidiny, piperaziny, phenyl, or heteroaryl. In certain embodiments, Ring B is cyclobutyl, cyclopentyl, cyclohexyl, piperidiny, piperaziny, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is piperidiny, piperaziny, phenyl, or quinoliny. In certain embodiments, Ring B is phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is phenyl or quinoliny. In certain embodiments, Ring B is phenyl.

[00176] In certain embodiments, Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each optionally substituted with one or two R^B groups, wherein each R^B is independently halo, cyano, alkyl, haloalkyl, haloalkoxy, alkoxyalkoxy, aminocarbonyl, alkylcarbonylaminoalkoxy, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, heterocycloalkyl

optionally substituted with alkyl, alkylcarbonyl or a halo, or (5-6-membered heterocycloalkyl-one)alkyl.

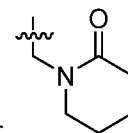
[00177] In certain embodiments, Ring B is cyclobutyl, cyclohexyl, piperidiny, tetrahydropyranyl, phenyl, quinoliny, isoquinoliny, tetrahydronaphthyl, or tetrahydroquinoliny; each substituted with one or two R^B groups, wherein each R^B is independently halo, cyano, alkyl, haloalkyl, haloalkoxy, alkoxyalkoxy, aminocarbonyl, alkylcarbonylaminoalkoxy, cycloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, (5-6-membered heterocycloalkyl-one)alkyl, or heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo.

[00178] In certain embodiments, Ring B is cyclobutyl, cyclohexyl, piperidiny, tetrahydropyranyl, phenyl, quinoliny, isoquinoliny, tetrahydronaphthyl, or tetrahydroquinoliny; each substituted with one or two R^B groups, wherein each R^B is independently aminocarbonyl, cyano, chloro, bromo, fluoro, methyl, trifluoromethyl, trifluoromethoxy, methoxyethoxy, acetamidoethoxy, cyclopropoxy, cyclopropylmethoxy, cyclobutyl, cyclohexyl, tetrahydropyranyl, pyrrolidiny, piperidiny, methylpiperidiny, difluoropiperidiny,



methylpiperaziny, acetylpiperaziny, or

[00179] In certain embodiments, Ring B is phenyl optionally substituted with one or two R^B groups, wherein each R^B is independently aminocarbonyl, cyano, chloro, bromo, fluoro, trifluoromethyl, trifluoromethoxy, methoxyethoxy, acetamidoethoxy, cyclopropoxy, cyclopropylmethoxy, cyclobutyl, cyclohexyl, tetrahydropyranyl, pyrrolidiny, piperidiny,



methylpiperidiny, difluoropiperidiny, methylpiperaziny, acetylpiperaziny, or

[00180] In certain embodiments, Ring B is cyclobutyl, cyclohexyl, piperidiny, tetrahydropyranyl, quinoliny, isoquinoliny, tetrahydronaphthyl, or tetrahydroquinoliny; each substituted with one or two R^B groups, wherein each R^B is independently chloro, bromo, fluoro, methyl, or piperidiny.

[00181] In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with one or two R^{AA} groups. In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with 2 halo groups when L is other than

O. In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with one halo group when L is $\text{CH}_2\text{NR}^{\text{L}}$. In certain embodiments, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, when L is bond, O or S, wherein the phenyl is optionally substituted with halo.

[00182] In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is unsubstituted tetrahydroquinolinyl when L is bond. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is unsubstituted dihydroxybenzodioxynyl when L is O. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is unsubstituted tetrahydronaphthalene when L is O and R^1 is not hydrogen or ethyl. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is unsubstituted spirocycloalkyl when L is O or S.

[00183] In certain embodiments, when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl.

[00184] In certain embodiments, when L is S or CH_2 , and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl.

[00185] In certain embodiments, when L is CH_2 and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl.

[00186] In certain embodiments, when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;

[00187] In certain embodiments, when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl.

[00188] In certain embodiments, when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be trifluoromethyl.

[00189] In certain embodiments, when L is O, Ring A is phenyl substituted with 1 R^{AA} , and Ring B is not present, then R^{AA} cannot be meta-substituted trifluoromethyl.

[00190] In certain embodiments, when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy.

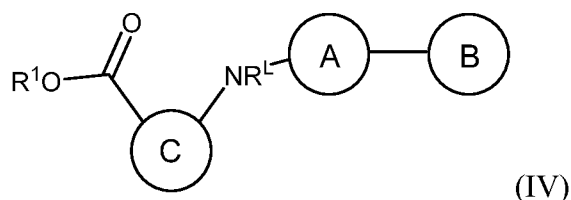
[00191] In certain embodiments, when L is NH, Ring A is pyridyl, indolyl, or indoliny, and Ring B is not present, then R^{AB} cannot be alkyl.

[00192] In certain embodiments, when L is bond, Ring A is other than phenyl, Ring B is not present, and R^1 is H, then R^{AB} cannot be methyl.

[00193] In certain embodiments, R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy. In certain embodiments, R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonyl, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl.

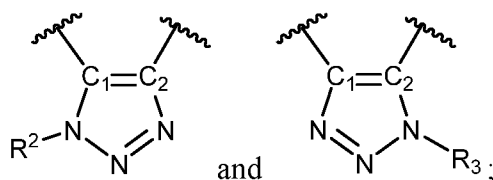
[00194] In certain embodiments, R^1 is hydrogen, alkyl, cycloalkyl, or heterocycloalkyl. In certain embodiments, R^1 is hydrogen or alkyl. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is alkyl. In certain embodiments, R^1 is hydrogen or W. In certain embodiments, R^1 is W. In certain embodiments, R^1 is W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy, or W is substituted with dialkylamino or alkylcarbonyloxy, or W is substituted with alkylcarbonyloxy, dialkylaminocarbonyloxy cycloalkylcarbonyloxy, or phenylcarbonyloxy.

[00195] In certain embodiments, the compound of Formula (I) is according to Formula (IV):



wherein:

ring C is selected from:



wherein the wavy lines () indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR^L, and the C₂ carbon to N of NR^L;

R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups;

when Ring B is not present and Ring A is 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, benzothiazolyl, quinolinyl, isoquinolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl, then Ring A is substituted with one or two R^{AB} groups;

when Ring B is not present and Ring A is pyridyl, indolyl, or indolinyl, then Ring A is substituted with one or two R^{AC} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AC} is independently halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl

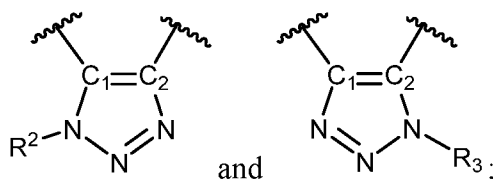
optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00196] In certain embodiments, the compound of Formula (IV) is that wherein: ring C is selected from:



wherein the wavy lines (~~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)\text{-OR}^1$, and the C_2 carbon to N of NR^L ;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C_{3-7} cycloalkyl, C_{8-11} spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, and haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AA} groups, or
- (ii) 2 halo groups;

when Ring B is not present and Ring A is 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, benzothiazolyl, quinolinyl, isoquinolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, or 2,3-dihydrobenzo[b][1,4]dioxinyl, then Ring A is substituted with one or two R^{AB} groups;

when Ring B is not present and Ring A is C₃₋₇ cycloalkyl or C₈₋₁₁ spirocycloalkyl, then Ring A is optionally substituted with one or two R^{AB} groups;

when Ring B is not present and Ring A is pyridyl, indolyl, or indolinyl, then Ring A is substituted with one or two R^{AC} groups;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

each R^{AC} is independently halo; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl;

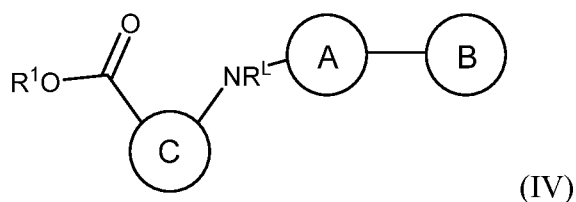
R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00197] In certain embodiments, the compound of Formula (IV) is that wherein R^L is hydrogen or C_{1-4} alkyl, and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

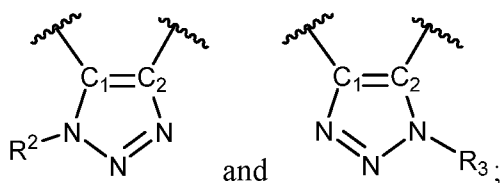
[00198] In certain embodiments, the compound of Formula (IV) is that wherein R^L is hydrogen, and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00199] In certain embodiments, the compound of Formula (I) is according to Formula (IV):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to N of NR^L ;

[00200] In certain embodiments, the compound of Formula (IV) is that wherein:

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is C₃₋₇ cycloalkyl, C₈₋₁₁ spirocycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, pyridyl, indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, 2,3-dihydrobenzo[b][1,4]dioxiny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two groups selected from halo, alkyl, alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups;

when Ring B is not present and Ring A is 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, naphthyl, indanyl, tetrahydronaphthyl, dihydronaphthyl, benzothiazolyl, quinoliny, isoquinoliny, isoindoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, or 2,3-dihydrobenzo[b][1,4]dioxiny, then Ring A is substituted with one or two R^{AB} groups;

when Ring B is not present and Ring A is C₃₋₇ cycloalkyl or C₈₋₁₁ spirocycloalkyl, then Ring A is optionally substituted with one or two R^{AB} groups;

when Ring B is not present and Ring A is pyridyl, indolyl, or indoliny, then Ring A is substituted with one or two R^{AC} groups;

each R^{AA} is independently alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or alkylcarbonylaminoalkoxy;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

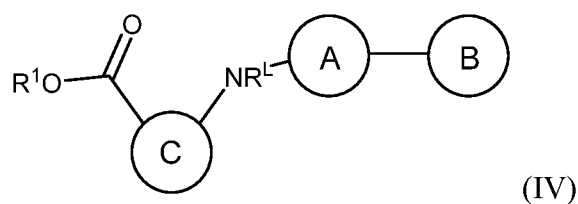
each R^{AC} is independently halo; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy;

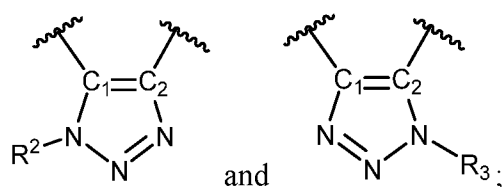
heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl; R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl; R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00201] In certain embodiments, the compound of Formula (I) is according to Formula (IV):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to N of NR^L .

[00202] In certain embodiments, the compound of Formula (IV) is that wherein:

R^L is hydrogen or C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy;

Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl,

indolyl, benzothiazolyl, quinoliny, isoquinoliny, indoliny, isoindoliny,
tetrahydroquinoliny, dihydroisoquinoliny, or tetrahydro-methanonaphthaleny;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl,
alkoxy, or haloalkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AA} groups, or (ii) 2 halo groups;

when Ring B is not present and Ring A is 5-6 membered heterocycloalkyl, pyrazolyl,
imidazolyl, triazolyl, thiazolyl, naphthyl, indanyl, tetrahydronaphthaliny,
dihydronaphthaliny, benzothiazolyl, quinoliny, isoquinoliny, isoindoliny,
tetrahydroquinoliny, or dihydroisoquinoliny, then Ring A is substituted with one or
two R^{AB} groups;

when Ring B is not present and Ring A is pyridyl, indolyl, or indoliny, then Ring A is
substituted with one or two R^{AC} groups;

each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or
phenoxy optionally substituted with one or two halo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy,
(cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AC} is independently halo, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy,
(cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is
optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl,
alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy,
(cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally
substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl,
(heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

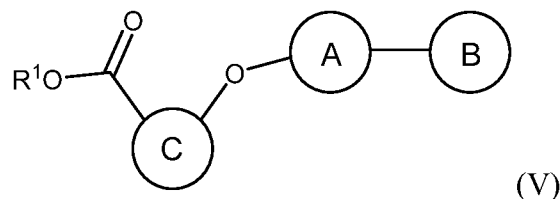
R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with
amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy,

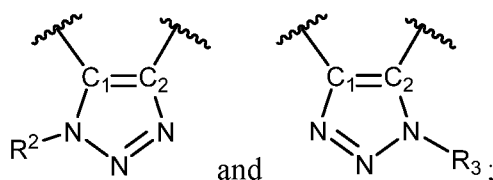
cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00203] In certain embodiments, the compound of Formula (I) is according to Formula (V):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to O;

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each is substituted with one or two R^{AB} groups; provided

when Ring B is present, then Ring A is optionally substituted with one halo or alkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AD} groups, or (ii) two groups selected from chloro or bromo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AD} is independently hydroxy, alkoxy, haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy,

(cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy, alkoxy, or phenylcarbonyloxy;

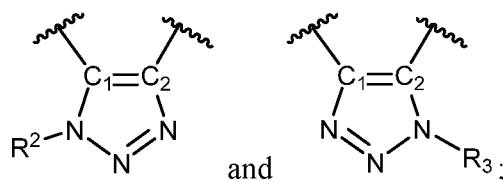
R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy, alkoxy, or alkoxy;

provided that when Ring A is phenyl, Ring B is not present, and R¹ is ethyl, then Ring A cannot be substituted with trifluoromethoxy; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00204] In certain embodiments, the compound of Formula (V) is that wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to O;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each is substituted with one or two R^{AB} groups;

Ring B is present or not present; wherein

when Ring B is present, then Ring A is optionally substituted with a group selected from halo, alkyl, alkoxy, cyano, hydroxy, and (cycloalkyl)alkoxy;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AD} groups;
- (ii) two groups selected from chloro or bromo; or

(iii) one halo group and one group selected from the group consisting of haloalkoxy, (cycloalkyl)alkoxy, and (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

(iv) one cyano group and one (phenyl)alkoxy group, wherein the phenyl as part of the (phenyl)alkoxy group is optionally substituted with halo or haloalkoxy;

or Ring A is unsubstituted C₈₋₁₁ spirocycloalkyl; unsubstituted dihydroxybenzodioxynyl; or unsubstituted tetrahydronaphthalene when R¹ is not hydrogen or ethyl;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

each R^{AD} is independently hydroxy; alkoxy; haloalkyl; cycloalkyloxy; (cycloalkyl)alkoxy; or phenoxy optionally substituted with one or two halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl; or 5-6 membered heteroaryl optionally substituted with alkyl wherein alkyl is optionally substituted with 1 or 2 groups independently selected from cycloalkyl and hydroxy; alkoxyalkyl; hydroxyalkyl; or hydroxycycloalkyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

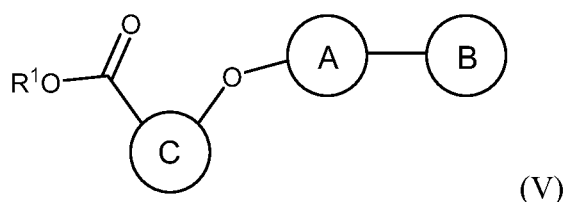
R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided:

- (i) when Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then Ring A cannot be substituted with trifluoromethoxy; and
- (ii) when Ring A is phenyl substituted with 1 R^{AD} , then R^{AD} cannot be meta-substituted trifluoromethyl;

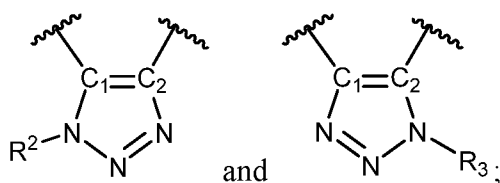
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00205] In certain embodiments, the compound of Formula (I) is according to Formula (V):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to O.

[00206] In certain embodiments, the compound of Formula (V) is that wherein: Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each is substituted with one or two R^{AB} groups; provided:

when Ring B is present, then Ring A is optionally substituted with one halo or alkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

- (i) one or two R^{AD} groups, (ii) two groups selected from chloro or bromo, or (iii) one halo group and one group selected from the group consisting of haloalkoxy,

(cycloalkyl)alkoxy, and (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

or Ring A is unsubstituted C₈₋₁₁ spirocycloalkyl; unsubstituted dihydroxybenzodioxynyl; or unsubstituted tetrahydronaphthalene when R¹ is not hydrogen or ethyl;

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

each R^{AD} is independently hydroxy, alkoxy, haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl;

R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, -N(R^{1A})C(O)R^{1B}, -N(R^{1A})C(O)OR^{1B}, or -N(R^{1A})C(O)NR^{1B}R^{1C}; wherein R^{1A}, R^{1B}, and R^{1C} are each independently hydrogen or C₁₋₆ alkyl;

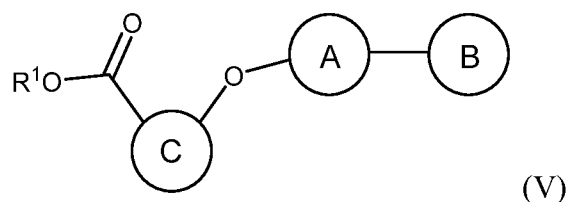
R² and R³ are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided

- (i) when Ring A is phenyl, Ring B is not present, and R¹ is ethyl, then Ring A cannot be substituted with trifluoromethoxy; and
- (ii) when Ring A is phenyl substituted with 1 R^{AD}, then R^{AD} cannot be meta-substituted trifluoromethyl; and

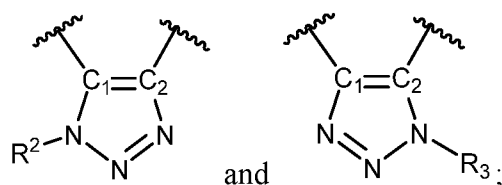
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00207] In certain embodiments, the compound of Formula (I) is according to Formula (V):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to O.

[00208] In certain embodiments, the compound of Formula (V) is that wherein:

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; each is substituted with one or two R^{AB} groups; provided:

when Ring B is present, then Ring A is optionally substituted with one halo or alkyl;

when Ring B is not present and Ring A is phenyl, then Ring A is substituted with:

(i) one or two R^{AD} groups, or (ii) two groups selected from chloro or bromo;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AD} is independently hydroxy, alkoxy, haloalkyl, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally

substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

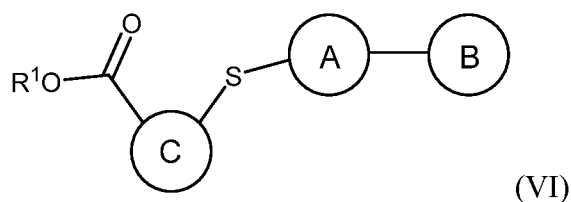
R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

provided that when Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then Ring A cannot be substituted with trifluoromethoxy; and

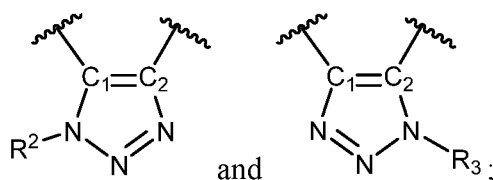
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00209] In certain embodiments, the compound of Formula (I) is according to Formula (VI):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to S;

wherein:

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl other than thienyl or benzothiophenyl; each is substituted with one or two R^{AB} groups;

provided when Ring A is phenyl and Ring B is not present, then Ring A is substituted with one or two R^{AE} ;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AE} is independently halo, alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, or (cycloalkyl)alkoxy;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

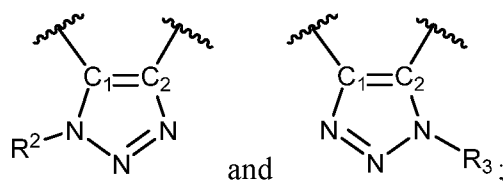
each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

provided that when Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00210] In certain embodiments, the compound of Formula (VI) is that wherein: ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to S;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl other than thienyl or benzothiophenyl; each is substituted with one or two R^{AB} groups;

provided when Ring A is phenyl and Ring B is not present, then Ring A is substituted with one or two R^{AE} ;

Ring B is present or not present; wherein:

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

each R^{AE} is independently halo; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

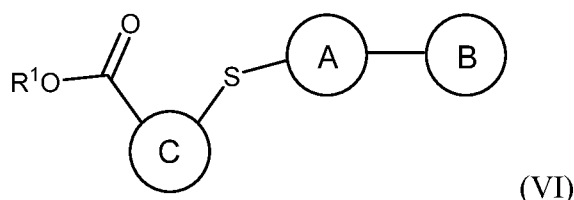
each R^B is independently halo; cyano; alkyl; alkylsulfonyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6 membered heteroaryl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, phenylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy carbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$; wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxy carbonyl;

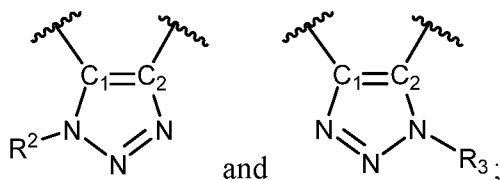
provided when Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00211] In certain embodiments, the compound of Formula (I) is according to Formula (VI):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to S.

[00212] In certain embodiments, the compound of Formula (VI) is that wherein:

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl other than thienyl or benzothiophenyl; each is substituted with one or two R^{AB} groups;

provided when Ring A is phenyl and Ring B is not present, then Ring A is substituted with one or two R^{AE};

each R^{AB} is independently halo; alkyl; hydroxy; alkoxy; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; phenoxy optionally substituted with one or two halo; (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

each R^{AE} is independently halo; alkyl; haloalkyl; haloalkoxy; cycloalkyloxy; (cycloalkyl)alkoxy; or (phenyl)alkoxy, wherein the phenyl is optionally substituted with halo;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

each R^B is independently halo; cyano; alkyl; haloalkyl; alkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with 1 or 2 alkyl, alkylcarbonyl or halo; (5-6-membered heterocycloalkyl-one)alkyl; (heterocycloalkyl)alkyl; or heterocycloalkylcarbonyl; R¹ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; wherein W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, phenylcarbonyloxy,

aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, cycloalkylcarbonyloxy, $-N(R^{1A})C(O)R^{1B}$, $-N(R^{1A})C(O)OR^{1B}$, or $-N(R^{1A})C(O)NR^{1B}R^{1C}$;

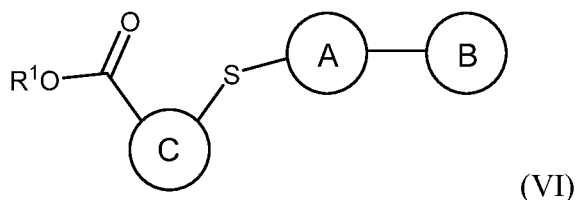
wherein R^{1A} , R^{1B} , and R^{1C} are each independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl;

wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

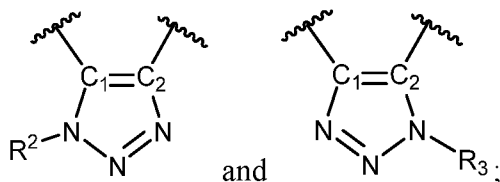
provided that when Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00213] In certain embodiments, the compound of Formula (I) is according to Formula (VI):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~~) indicate the points of attachment of the C_1 carbon to the carbonyl of $C(O)-OR^1$, and the C_2 carbon to S.

[00214] In certain embodiments, the compound of Formula (VI) is that wherein:

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl other than thienyl or benzothiophenyl; each is substituted with one or two R^{AB} groups;

provided when Ring A is phenyl and Ring B is not present, then Ring A is substituted with one or two R^{AE} ;

each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo;

each R^{AE} is independently halo, alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, or (cycloalkyl)alkoxy;

Ring B is present or not present; wherein:

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups;

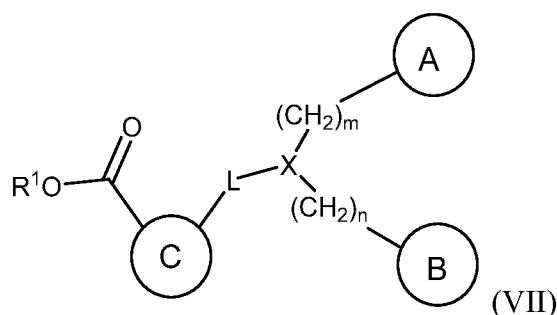
each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl;

R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxycarbonyl, or phenylcarbonyloxy;

R^2 and R^3 are independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

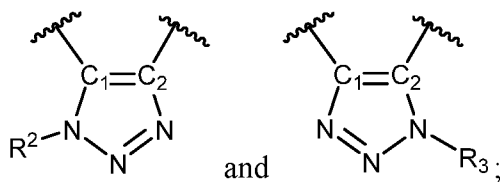
provided that when Ring A is phenyl, then Ring B cannot be halo-substituted phenyl; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00215] In another aspect, provided herein is a compound of Formula (VII):



wherein:

ring C is selected from:



wherein the wavy lines () indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to L;

R¹, R² and R³ are as defined above.

L is a bond, CH₂, CH₂CH₂, O, or CH₂O;

X is N or CH;

m is 1, 2, or 3;

n is 0, 1, 2, or 3;

Ring A and Ring B are each independently C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, aryl or heteroaryl, optionally substituted with halo, haloalkyl or phenyl; wherein phenyl is optionally substituted with halo, haloalkyl, or haloalkoxy; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00216] In certain embodiments, the compound of Formula (VII) is that wherein:

L is a bond, CH₂, CH₂CH₂, O, or CH₂O;

X is N or CH;

m is 1, 2, or 3;

n is 0, 1, 2, or 3;

Ring A and Ring B are each independently aryl, optionally substituted with halo, haloalkyl or phenyl; wherein phenyl is optionally substituted with halo, haloalkyl, or haloalkoxy; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00217] In certain embodiments, the compound of Formula (VII) is that wherein:

L is a bond, CH₂, CH₂CH₂, O, or CH₂O;

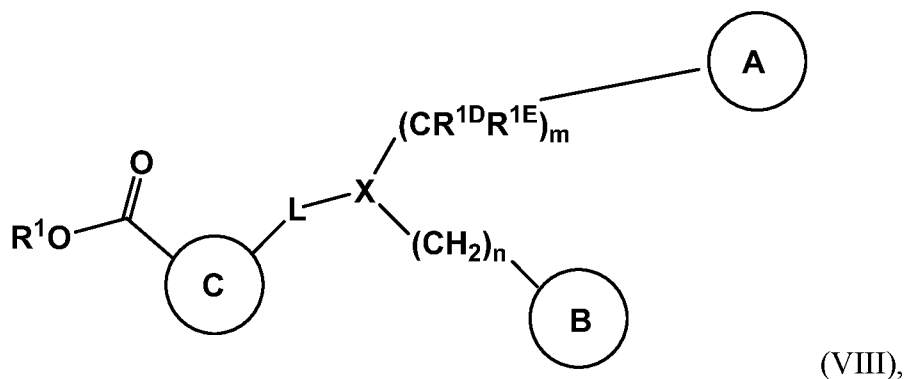
X is N or CH;

m is 1 or 2;

n is 0, 1, or 2;

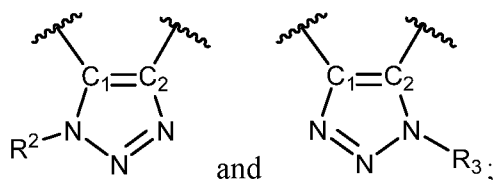
Ring A and Ring B are each independently phenyl, optionally substituted with halo, or phenyl substituted with halo or haloalkoxy; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00218] In certain embodiments, the compound of Formula (I) is according to Formula (VIII):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to the carbonyl of C(O)-OR¹, and the C₂ carbon to L;

R¹, R² and R³ are as defined above;

L is a bond, CH₂, CH₂CH₂, O, or CH₂O;

X is N or CH;

R^{1D} and R^{1E} are each independently H or hydroxy;

m is 1, 2, or 3;

n is 0, 1, 2, or 3;

Ring A and Ring B are each independently C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, aryl or heteroaryl, optionally substituted with halo, haloalkyl or phenyl; wherein phenyl is optionally substituted with halo, haloalkyl, or haloalkoxy; and optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

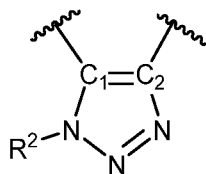
[00219] In certain embodiments of any of the above formulas, Ring A is C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, or phenyl. In certain embodiments, Ring A is C₃₋₇ cycloalkyl.

In certain embodiments, Ring A is 5-6 membered heterocycloalkyl. In certain embodiments, Ring A is phenyl.

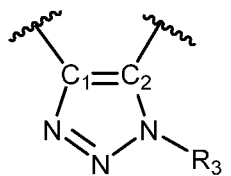
[00220] In certain embodiments of any of the above formulas, R^1 is hydrogen or W. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is W.

[00221] In certain embodiments of any of the above formulas, R^2 and R^3 are independently hydrogen. In certain embodiments, R^2 is hydrogen. In certain embodiments, R^3 is hydrogen.

[00222] In certain embodiments of any of the above formulas, Ring C is:



[00223] In certain embodiments of any of the above formulas, Ring C is:



[00224] In certain embodiments of any of the above formulas where L is present, L is a bond, CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S.

[00225] In certain embodiments, L is CH_2 , CF_2 , O, NR^L , S, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S. In certain embodiments, L is CH_2 , CF_2 , O, NR^L , or S. In certain embodiments, L is CH_2 , O, NR^L , or S. In certain embodiments, L is O, NR^L , or S. In certain embodiments, L is CH_2 , CF_2 , $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S. In certain embodiments, L is CH_2 , CF_2 , or $C(=O)$. In certain embodiments, L is CH_2 , CF_2 , CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S. In certain embodiments, L is CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S.

[00226] In certain embodiments of any of the above formulas where R^L is present, R^L is H. In certain embodiments, R^L is C_{1-4} alkyl optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is H or C_{1-4} alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is C_{1-4} alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is H or C_{1-4} alkyl substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy.

In certain embodiments, R^L is C_{1-4} alkyl substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is H or C_{1-4} alkyl substituted with hydroxycarbonyl.

[00227] In certain embodiments of any of the above formulas, Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups;

[00228] In certain embodiments of any of the above formulas, Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiophenyl, pyridyl, phenyl, naphthyl, tetrahydronaphthalinyl, dihydronaphthalinyl, indanyl, indolyl, indolinyl, isoindolinyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, dihydrobenzodioxinyl, or tetrahydro-methanonaphthalenyl.

[00229] In certain embodiments of any of the above formulas, Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00230] In certain embodiments of any of the above formulas, Ring A is heterocycloalkyl, pyrazolyl, triazolyl, thiazolyl, pyridyl, phenyl, naphthyl, tetrahydronaphthalinyl, dihydronaphthalinyl, indanyl, indolyl, isoindolinyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or dihydrobenzodioxinyl.

[00231] In certain embodiments of any of the above formulas, Ring A is heterocycloalkyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl.

[00232] In certain embodiments of any of the above formulas, Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A is heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A is aryl or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA}

groups. In certain embodiments, Ring A is heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A is phenyl or heteroaryl, where each is optionally substituted with 1 or 2 R^{AA} groups. In certain embodiments, Ring A does not include theinyl. In certain embodiments, Ring A does not include indolyl.

[00233] In certain embodiments, Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00234] In certain embodiments, Ring A is cyclohexyl, bicycloheptanyl, pyrrolidinyl, piperidinyl, pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00235] In certain embodiments, Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl. In certain embodiments, Ring A is cyclohexyl, bicycloheptanyl, pyrrolidinyl, piperidinyl, pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl.

[00236] In certain embodiments, Ring A is cyclohexyl, bicycloheptanyl, pyrrolidinyl, piperidinyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00237] In certain embodiments, Ring A is cyclohexyl, bicycloheptyl, pyrrolidinyl, piperidinyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00238] In certain embodiments, Ring A is pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl.

[00239] In certain embodiments, Ring A is pyrrolidinyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, phenyl, pyridyl, or thienyl. In certain embodiments, Ring A is pyrrolidinyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, phenyl, or pyridyl. In certain embodiments, Ring A is thiazolyl, phenyl, or pyridyl. In certain embodiments, Ring A is thiazolyl or phenyl. In certain embodiments, Ring A is phenyl.

[00240] In certain embodiments, Ring A is phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl. In certain embodiments, Ring A is phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, indolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl. In certain embodiments, Ring A is tetrahydronaphthalinyl, dihydronaphthalinyl, benzothiazolyl, quinolinyl, isoquinolinyl, or tetrahydroquinolinyl.

[00241] In certain embodiments, Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, dihydronaphthalinyl, benzothiazolyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, dihydronaphthalinyl, benzothiazolyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is pyrazolyl, imidazolyl, triazolyl,

thiazolyl, phenyl, dihydronaphthalinyl, benzothiazolyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl. In certain embodiments, Ring A is pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, benzothiazolyl, or isoquinolinyl.

[00242] In certain embodiments of any of the above formulas, when Ring B is present, then Ring A is optionally substituted with one or two halo, alkyl, alkoxy, or haloalkoxy;

[00243] In certain embodiments of any of the above formulas, when Ring B is not present and Ring A is phenyl, then Ring A is substituted with: (i) one or two R^{AA} groups, or (ii) 2 halo groups when L is other than O.

[00244] In certain embodiments, each R^{AA} is independently alkyl, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo. In certain embodiments, when Ring B is not present and Ring A is other than phenyl, then Ring A is optionally substituted with one or two R^{AB} groups.

[00245] In certain embodiments of any of the above formulas, when Ring B is not present and Ring A is other than phenyl, then Ring A is substituted with one or two R^{AB} groups.

[00246] In certain embodiments, each R^{AB} is independently halo, alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, or phenoxy optionally substituted with one or two halo.

[00247] In certain embodiments of any of the above formulas, when Ring B is not present, Ring A is pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl; wherein Ring A is substituted with one or two groups independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, and phenoxy substituted with one or two chloro groups. In certain embodiments, when Ring B is not present, Ring A is phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl; wherein Ring A is substituted with one or two groups independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, and phenoxy substituted with one or two chloro groups. In certain embodiments, when Ring B is not present, Ring A is phenyl, naphthyl, pyridyl, benzothiazolyl, quinolinyl, or isoquinolinyl; wherein Ring A is substituted with one or two groups independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy,

cycloalkyloxy, (cycloalkyl)alkoxy, and phenoxy substituted with one or two chloro groups. In certain embodiments, when Ring B is not present, Ring A is phenyl substituted with one or two groups independently selected from halo, alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyloxy, (cycloalkyl)alkoxy, and phenoxy substituted with one or two chloro groups. In certain embodiments, when Ring B is not present, Ring A is phenyl substituted with one or two groups independently selected from chloro, fluoro, trifluoromethoxy, cyclopentyloxy, and phenoxy substituted with one or two chloro groups.

[00248] In certain embodiments of any of the above formulas, Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with one or two R^B groups.

[00249] In certain embodiments, each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl.

[00250] In certain embodiments of any of the above formulas, Ring B is heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, or quinoliny. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or heteroaryl. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or quinoliny. In certain embodiments, Ring B is phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is phenyl or quinoliny. In certain embodiments, Ring B is phenyl.

[00251] In certain embodiments, Ring B is heterocycloalkyl, aryl, or heteroaryl; each substituted with one or two R^B groups, where each R^B is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocycloalkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or quinoliny; each substituted with one or two R^B groups, where each R^B is independently halo,

alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocycloalkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl.

[00252] In certain embodiments of any of the above formulas, Ring B is piperidinyl, piperazinyl, phenyl, or quinolinyl; each substituted with one or two R^B groups, where each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxo, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is phenyl or quinolinyl; each substituted with one or two R^B groups, where each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxo, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxo, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, bromo, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, or cyclopropoxy. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, trifluoromethyl, methoxy, or trifluoromethoxy.

[00253] In certain embodiments, when L is S and Ring A is phenyl, then Ring B cannot be halo-substituted phenyl.

[00254] In certain embodiments, when L is O, Ring A is phenyl, and Ring B is not present, then R^{AA} cannot be alkyl or trifluoromethyl;

[00255] In certain embodiments, when L is O, Ring A is phenyl, Ring B is not present, and R^1 is ethyl, then R^{AA} cannot be trifluoromethoxy.

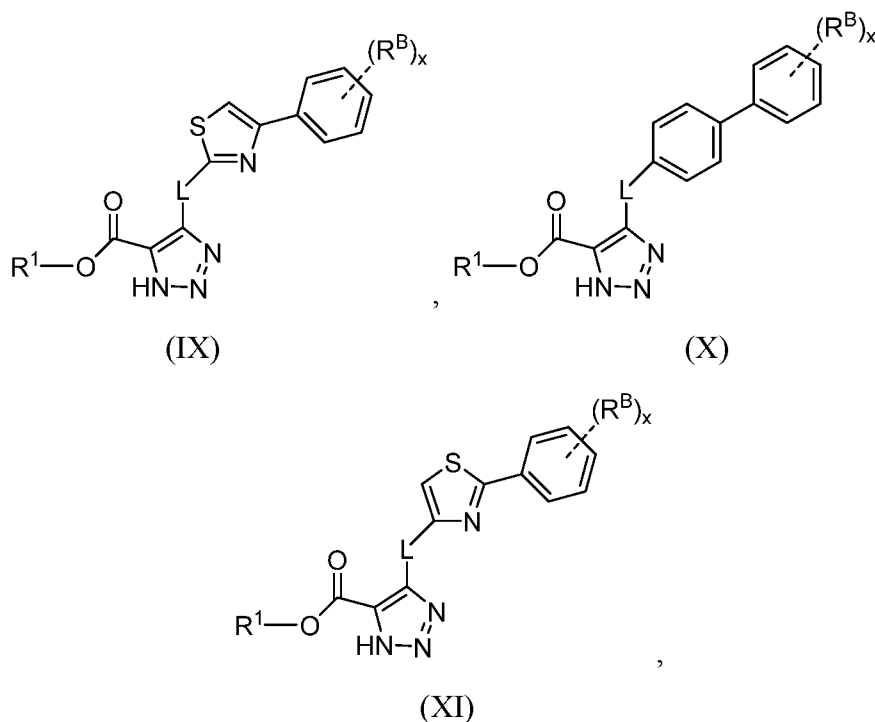
[00256] In certain embodiments, when L is NH, Ring A is pyridyl, indolyl, or indolinyl, and Ring B is not present, then R^{AB} cannot be alkyl.

[00257] In certain embodiments, R^1 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, or W; where W is alkyl substituted with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy.

[00258] In certain embodiments, R^1 is hydrogen, alkyl, cycloalkyl, or heterocycloalkyl. In certain embodiments, R^1 is hydrogen or alkyl. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is alkyl. In certain embodiments, R^1 is W; where W is alkyl substituted

with amino, alkylamino, dialkylamino, alkylcarbonyloxy, alkoxy carbonyl, or phenylcarbonyloxy. In certain embodiments, R^1 is W; where W is alkyl substituted with dialkylamino or alkylcarbonyloxy.

[00259] In some embodiments provided herein is a compound or pharmaceutically acceptable salt thereof where the compound has Formula (IX), (X) or (XI):



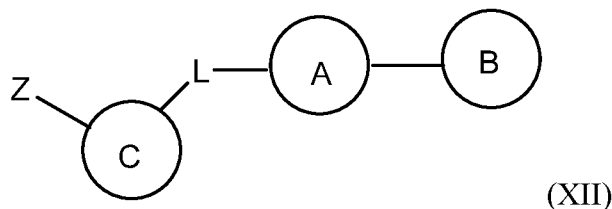
wherein

R^1 and R^B are as defined in any of the above formulas;

L is S, O, NH or NR^L;

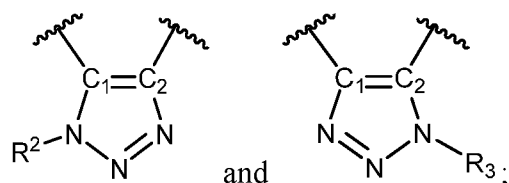
R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxy carbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy; and subscript x is 0, 1, 2 or 3.

[00260] In another aspect, provided herein is a compound of Formula (XII):



wherein:

ring C is selected from:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to Z, and the C₂ carbon to L;

L is a bond, CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;
Z is -C(=O)H or -CH₂OY;

Y is hydrogen or W;

W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵; -S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); -SO₂NR⁵R⁶; -P(=O)(OR⁷)₂; -P(=O)(O⁻)₂; -P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO⁻;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;
each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl;

dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

provided:

- i. the compound represented by Formula (XII) is exclusive of:
 - a. 4-(phenylamino)-1H-1,2,3-triazole-5-carbaldehyde;
 - b. 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carbaldehyde;
 - c. ethyl hydrogen (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate;

- d. diethyl (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate; and
- e. 1-((4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione;
- ii. when Z is -C(=O)H, L is NR^L, R^L is hydrogen, and Ring A is phenyl, then Ring B is present and/or the phenyl Ring A is substituted with 1, 2, or 3 R^{A2} groups;
- iii. when Z is -C(=O)H, L is CH₂, and Ring A is cyclopropyl, phenyl, indole, or thiophene, then Ring B is present;
- iv. when Z is -C(=O)H, L is CH₂-O, and Ring A is phenyl, then Ring B is present;
- v. when Z is -CH₂OY, Y is W, W is -P(=O)(OR⁷)₂ or -P(=O)(OR⁷)(O⁻), R⁷ is ethyl, L is CH₂, and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2}; and
- vi. when Z is -CH₂OY, Y is hydrogen, L is CH₂, and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2}; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00261] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

Z is -C(=O)H or -CH₂OY;

Y is hydrogen or W;

W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵;

-S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); -SO₂NR⁵R⁶; -P(=O)(OR⁷)₂; -P(=O)(O⁻)₂;

-P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO⁻;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups; Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

provided:

- i. the compound represented by Formula (XII) is exclusive of:
 - a. 4-(phenylamino)-1H-1,2,3-triazole-5-carbaldehyde;
 - b. 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carbaldehyde;
 - c. ethyl hydrogen (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate;
 - d. diethyl (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate; and
 - e. 1-((4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione;
- ii. when Z is $-C(=O)H$, L is NR^L , R^L is hydrogen, and Ring A is phenyl, then Ring B is present and/or the phenyl Ring A is substituted with 1, 2, or 3 R^{A2} groups;
- iii. when Z is $-C(=O)H$, L is CH_2 , and Ring A is cyclopropyl, phenyl, indole, or thiophene, then Ring B is present;
- iv. when Z is $-C(=O)H$, L is CH_2-O , and Ring A is phenyl, then Ring B is present;
- v. when Z is $-CH_2OY$, Y is W, W is $-P(=O)(OR^7)_2$ or $-P(=O)(OR^7)(O^-)$, R^7 is ethyl, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2} ; and
- vi. when Z is $-CH_2OY$, Y is hydrogen, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2} ; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00262] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CF_2 , O, S, $S(=O)$, $C(=O)$, CH_2-NR^L , CH_2-S , or $Q-CH_2$; wherein Q is O, NR^L , or S;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$; $-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$; $-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups; each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy,

alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00263] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CH_2 , CF_2 , O , NR^L , S , $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O , NR^L , or S ;

Z is $-CH_2OY$;

Y is hydrogen or W ;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$; $-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$; $-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups; Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00264] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

Z is $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$;

$-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$;

$-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,

hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl;

aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy;

aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy;

alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl;

dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl;

cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted

with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

provided:

- i. the compound represented by Formula (XII) is exclusive of:
 - a. ethyl hydrogen (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate;
 - b. diethyl (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate; and
 - c. 1-((4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione;

- ii. when Z is $-\text{CH}_2\text{OY}$, Y is W, W is $-\text{P}(=\text{O})(\text{OR}^7)_2$ or $-\text{P}(=\text{O})(\text{OR}^7)(\text{O}^-)$, R^7 is ethyl, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 $\text{R}^{\text{A}2}$; and
- iii. when Z is $-\text{CH}_2\text{OY}$, Y is hydrogen, L is CH_2 , and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 $\text{R}^{\text{A}2}$; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00265] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CF_2 , O, NR^{L} , S, $\text{S}(=\text{O})$, $\text{C}(=\text{O})$, $\text{CH}_2\text{-Q}$, or Q-CH_2 ; wherein Q is O, NR^{L} , or S;

Z is $-\text{CH}_2\text{OY}$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-\text{C}(=\text{O})\text{R}^5$; $-\text{C}(=\text{O})\text{OR}^5$; $-\text{C}(=\text{O})\text{NR}^5\text{R}^6$; $-\text{C}(=\text{O})\text{SR}^5$;

$-\text{S}(\text{O})\text{R}^5$; $-\text{S}(\text{O})_2\text{R}^5$; $-\text{S}(\text{O})(\text{OR}^5)$; $-\text{S}(\text{O})_2(\text{OR}^5)$; $-\text{SO}_2\text{NR}^5\text{R}^6$; $-\text{P}(=\text{O})(\text{OR}^7)_2$; $-\text{P}(=\text{O})(\text{O}^-)_2$;

$-\text{P}(=\text{O})(\text{OR}^7)(\text{O}^-)$; or $-\text{P}(=\text{O})(\text{X})$ wherein X is $-\text{O}(\text{C}(\text{R}^8)_2)_m\text{O}-$;

R^{L} is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 $\text{R}^{\text{A}1}$ groups;

each $\text{R}^{\text{A}1}$ is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,

hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 $\text{R}^{\text{A}2}$ groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^{B} groups;

each $\text{R}^{\text{A}2}$ and R^{B} is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl;

aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy;

aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy;

alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00266] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CF_2 , O, S, $S(=O)$, $C(=O)$, CH_2-NR^L , CH_2-S , or $Q-CH_2$; wherein Q is O, NR^L , or S;

Z is $-C(=O)H$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups; each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00267] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CF₂, O, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;

Z is -C(=O)H or -CH₂OY;

Y is hydrogen or W;

W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵;

-S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); -SO₂NR⁵R⁶; -P(=O)(OR⁷)₂; -P(=O)(O⁻)₂;

-P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,

hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl;

aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy;

aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy;

alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl;

dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl;

cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted

with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl

optionally substituted with one or two groups independently selected from halo, alkyl,

and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered

heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or

5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

provided:

- i. the compound represented by Formula (XII) is exclusive of 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carbaldehyde; and
- ii. when Z is $-C(=O)H$, L is CH_2-O , and Ring A is phenyl, then Ring B is present;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00268] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CF_2 , O, S, $S(=O)$, or $C(=O)$;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$;

$-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$;

$-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups; each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy,

dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00269] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a O or S;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$; $-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$; $-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C_{8-11} spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,

hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R² and R³ is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R⁴ is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, -N(R¹⁰)C(O)R¹¹, -N(R¹⁰)C(O)OR¹¹, -N(R¹⁰)C(O)NR¹²R¹³, -O-P(=O)(O⁻)₂, -O-P(=O)(OR⁷)(O⁻), or -O-P(=O)(X) wherein X is -O(C(R⁸)₂)_mO⁻;

each R⁸ is independently hydrogen, halo, -CN, -OR⁹, -C(=O)R⁹, -C(=O)OR⁹, -C(=O)N(R⁹)₂, -N(R⁹)₂, -SR⁹, -S(O)R⁹, -S(O)₂R⁹, -OC(=O)R⁹, -OC(=O)OR⁹, -OC(=O)N(R⁹)₂, -N(R⁹)C(=O)R¹⁴, -N(R⁹)C(=O)OR¹⁴, -SO₂N(R⁹)₂, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R⁵, R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00270] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a O;

Z is -C(=O)H or -CH₂OY;

Y is hydrogen or W;

W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵;

-S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); -SO₂NR⁵R⁶; -P(=O)(OR⁷)₂; -P(=O)(O⁻)₂;

-P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO⁻;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy,

hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl;

aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy;

aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy;

alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl;

dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl;

cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl

optionally substituted with one or two groups independently selected from halo, alkyl,

and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered

heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl; each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00271] In certain embodiments, the compound of Formula (XII) is that wherein:

L is a CH_2 , CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-Q , or $Q-CH_2$; wherein Q is O, NR^L , or S;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen or W;

W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$;

$-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; $-SO_2NR^5R^6$; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$; $-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

R^L is hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl, or benzyl; wherein the C_{1-4} alkyl is optionally substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or

alkylcarbonyloxy; and the phenyl group alone or as a part of the benzyl group is optionally substituted with one or two groups selected from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

Ring B is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R² and R³ is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R⁴ is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, -N(R¹⁰)C(O)R¹¹, -N(R¹⁰)C(O)OR¹¹, -N(R¹⁰)C(O)NR¹²R¹³, -O-P(=O)(O⁻)₂, -O-P(=O)(OR⁷)(O⁻), or -O-P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-;

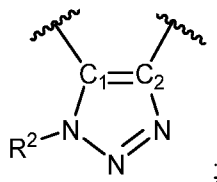
each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;

each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and

m is 1, 2, or 3; and

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00272] In certain embodiments, the compound of Formula (XII) is that wherein: ring C is:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C_1 carbon to Z , and the C_2 carbon to L ;

L is O or S ;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen;

Ring A is C_{5-7} cycloalkyl, 7-9 membered heterocycloalkyl, aryl, or heteroaryl; wherein Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

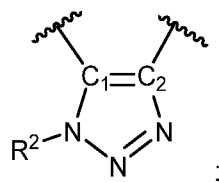
Ring B is C_{5-7} cycloalkyl, 7-9 membered heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; C_{1-4} alkyl; C_{1-4} hydroxyalkyl; C_{1-4} haloalkyl; C_{1-4} alkoxy; C_{1-4} aminoalkoxy; C_{1-4} hydroxyalkoxy; C_{1-4} haloalkoxy; C_{1-4} alkylcarbonyl; C_{1-4} alkoxyalkoxy; C_{1-4} aminocarbonyl; C_{3-6} cycloalkyl; 7-9 membered heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; and

R^2 is independently hydrogen;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00273] In certain embodiments, the compound of Formula (XII) is that wherein:
ring C is:



wherein the wavy lines (~~~~) indicate the points of attachment of the C_1 carbon to Z, and the C_2 carbon to L;

L is O or S;

Z is $-C(=O)H$ or $-CH_2OY$;

Y is hydrogen;

Ring A is C_{5-7} cycloalkyl, piperidinyl, or phenyl; wherein Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

Ring B is C_{5-7} cycloalkyl, 7-9 membered heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

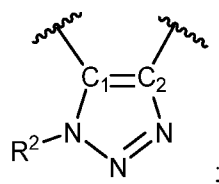
each R^{A2} and R^B is independently halo; cyano; C_{1-4} alkyl; C_{1-4} hydroxyalkyl; C_{1-4} haloalkyl;

C_{1-4} alkoxy; C_{1-4} hydroxyalkoxy; C_{1-4} haloalkoxy; C_{3-6} cycloalkyl; 7-9 membered heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; and

R^2 is independently hydrogen;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00274] In certain embodiments, the compound of Formula (XII) is that wherein:
ring C is:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to Z, and the C₂ carbon to L;

L is O or S;

Z is -C(=O)H or -CH₂OY;

Y is hydrogen;

Ring A is C₅₋₇ cycloalkyl, piperidinyl, or phenyl;

Ring B is C₅₋₇ cycloalkyl, piperidinyl, phenyl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

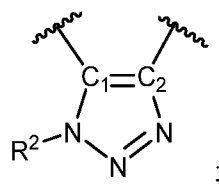
each R^{A2} and R^B is independently fluoro, chloro, cyano, C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl;

C₁₋₄ haloalkyl; C₁₋₄ alkoxy; C₁₋₄ hydroxyalkoxy; C₁₋₄ haloalkoxy; C₃₋₆ cycloalkyl; 7-9 membered heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; and

R² is independently hydrogen;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00275] In certain embodiments, the compound of Formula (XII) is that wherein: ring C is:



wherein the wavy lines ($\sim$) indicate the points of attachment of the C₁ carbon to Z, and the C₂ carbon to L;

L is O or S;

Z is -C(=O)H or -CH₂OY;

Y is hydrogen;

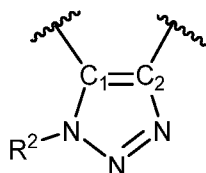
Ring A is C₅₋₇ cycloalkyl, piperidinyl, or phenyl;

Ring B is phenyl, optionally substituted with 1, 2, or 3 R^B groups;

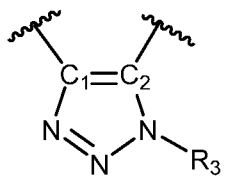
each R^{A2} and R^B is independently halo; C_{1-4} haloalkyl; C_{1-4} alkoxy; C_{1-4} haloalkoxy; C_{3-6} cycloalkyl; 7-9 membered heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; and R^2 is independently hydrogen; optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00276] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C_{3-7} cycloalkyl, 5-6 membered heterocycloalkyl, or phenyl. In certain embodiments, Ring A is C_{3-7} cycloalkyl. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl. In certain embodiments, Ring A is phenyl.

[00277] In certain embodiments, the compound of Formula (XII) is that wherein Ring C is:



[00278] In certain embodiments, the compound of Formula (XII) is that wherein Ring C is:



[00279] In certain embodiments, the compound of Formula (XII) is that wherein R^2 and R^3 are independently hydrogen. In certain embodiments, R^2 is hydrogen. In certain embodiments, R^3 is hydrogen.

[00280] In certain embodiments, the compound of Formula (XII) is that wherein L is a CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-O , or $O-CH_2$. In certain embodiments, L is a CF_2 , O, NR^L , or S. In certain embodiments, L is a CF_2 , O, S, $S(=O)$, or $C(=O)$. In certain embodiments, L is a CF_2 , O, or S. In certain embodiments, L is CF_2 . In certain embodiments, L is O. In certain embodiments, L is S. In certain embodiments, L is a CH_2-O . In certain embodiments, L is $O-CH_2$.

[00281] In certain embodiments, the compound of Formula (XII) is that wherein Z is -C(=O)H.

[00282] In certain embodiments, the compound of Formula (XII) is that wherein Z is -CH₂OY. In certain embodiments, Y is hydrogen. In certain embodiments, Y is W. In certain embodiments, W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵; -S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); or -SO₂NR⁵R⁶. In certain embodiments, W is -C(=O)R⁵ or -C(=O)OR⁵. In certain embodiments, W is -P(=O)(OR⁷)₂; -P(=O)(O⁻)₂; -P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-. In certain embodiments, W is -P(=O)(OR⁷)₂, wherein R⁷ is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl. In certain embodiments, W is -P(=O)(OR⁷)₂, wherein R⁷ is independently hydrogen or alkyl, for example, wherein R⁷ is independently hydrogen or C₁₋₄ alkyl, such as wherein W is -P(=O)(OH)₂, -P(=O)(OH)(O-C₁₋₄ alkyl), or -P(=O)(O-C₁₋₄ alkyl)₂. In certain embodiments, W is -P(=O)(OR⁷)(O⁻), wherein R⁷ is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl. In certain embodiments, W is -P(=O)(OR⁷)(O⁻), wherein R⁷ is independently hydrogen or alkyl, for example, wherein R⁷ is independently hydrogen or C₁₋₄ alkyl, such as wherein W is -P(=O)(OH)(O⁻) or -P(=O)(O-C₁₋₄ alkyl)(O⁻). In certain embodiments, W is methylene substituted with R⁴. In certain embodiments, W is methylene substituted with R⁴, wherein R⁴ is -O-P(=O)(O⁻)₂, -O-P(=O)(OR⁷)(O⁻), or -O-P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-. For example, in certain embodiments, W is methylene substituted with -O-P(=O)(OR⁷)(O⁻), wherein R⁷ is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl. In certain embodiments, W is methylene substituted with -O-P(=O)(OR⁷)(O⁻), wherein R⁷ is independently hydrogen or alkyl, for example, wherein R⁷ is independently hydrogen or C₁₋₄ alkyl, such as wherein W is methylene substituted with -O-P(=O)(OH)(O⁻) or -O-P(=O)(O-C₁₋₄ alkyl)(O⁻). It will be understood that phosphoric acids and phosphate esters, such as, e.g., -O-P(=O)(OH)₂ and -O-P(=O)(OR)(OH), where R is alkyl, aryl, etc., are ionizable groups, and can exist in equilibrium with their negatively charged or anionic forms, such as, e.g., -O-P(=O)(O⁻)₂ and -O-P(=O)(OR)(O⁻), respectively.

[00283] In certain embodiments, the compound of Formula (XII) is that wherein R⁴ is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, or alkoxycarbonyloxy.

For example, in certain embodiments, R^4 is C_{1-4} alkylcarbonyloxy, phenylcarbonyloxy, C_{5-7} cycloalkylcarbonyloxy, 5-7 membered heterocycloalkylcarbonyloxy, aminocarbonyloxy, C_{1-4} alkylaminocarbonyloxy, C_{1-4} dialkylaminocarbonyloxy, or C_{1-4} alkoxy carbonyloxy. For example, in certain embodiments, R^4 is C_{1-4} alkylcarbonyloxy, phenylcarbonyloxy, C_{5-7} cycloalkylcarbonyloxy, or C_{1-4} alkoxy carbonyloxy. For example, in certain embodiments, R^4 is 5-7 membered heterocycloalkylcarbonyloxy, aminocarbonyloxy, C_{1-4} alkylaminocarbonyloxy, or C_{1-4} dialkylaminocarbonyloxy. In certain embodiments, R^4 is $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, or $-N(R^{10})C(O)NR^{12}R^{13}$. For example, in certain embodiments, R^4 is $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, or $-N(R^{10})C(O)NR^{12}R^{13}$. For example, in certain embodiments, R^4 is $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO-$.

[00284] In certain embodiments, the compound of Formula (XII) is that wherein R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, $-N(R^9)C(=O)R^{14}$, $-N(R^9)C(=O)OR^{14}$, $-SO_2N(R^9)_2$, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl. For example, in certain embodiments, R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-OC(=O)R^9$, $-OC(=O)OR^9$, $-OC(=O)N(R^9)_2$, C_{1-4} alkyl, phenyl, C_{5-7} cycloalkyl, 5-7 membered heterocycloalkyl, or heteroaryl. For example, in certain embodiments, R^8 is independently hydrogen, fluoro, chloro, $-CN$, $-OR^9$, $-OC(=O)R^9$, $-OC(=O)OR^9$, C_{1-4} alkyl, phenyl, C_{5-7} cycloalkyl, 5-7 membered heterocycloalkyl, or heteroaryl. For example, in certain embodiments, R^8 is independently hydrogen, fluoro, chloro, $-CN$, $-OR^9$, $-OC(=O)R^9$, or $-OC(=O)OR^9$.

[00285] In certain embodiments, the compound of Formula (XII) is that wherein each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, alkyl, cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl. For example, in certain embodiments, each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, C_{1-4} alkyl, C_{5-7} cycloalkyl, phenyl, arylalkyl, 5-7 membered heterocycloalkyl, or heteroaryl. For example, in certain embodiments, each R^5 , R^6 , R^7 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} is independently hydrogen, C_{1-4} alkyl, C_{5-7} cycloalkyl, phenyl, or 5-7 membered heterocycloalkyl.

[00286] In certain embodiments, the compound of Formula (XII) is that wherein R^L is hydrogen. In certain embodiments, R^L is C_{1-4} alkyl optionally substituted with hydroxycarbonyl,

alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is hydrogen or C₁₋₄ alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is C₁₋₄ alkyl optionally substituted with hydroxycarbonyl. In certain embodiments, R^L is hydrogen or C₁₋₄ alkyl substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is C₁₋₄ alkyl substituted with hydroxycarbonyl, alkoxycarbonyl, hydroxycarbonylalkyl, or alkylcarbonyloxy. In certain embodiments, R^L is hydrogen or C₁₋₄ alkyl substituted with hydroxycarbonyl.

[00287] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C₃₋₁₀ cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[00288] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C₃₋₈ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiophenyl, pyridyl, phenyl, naphthyl, tetrahydronaphthalinyl, dihydronaphthalinyl, indanyl, indolyl, indolinyl, isoindolinyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, dihydrobenzodioxinyl, or tetrahydro-methanonaphthalenyl.

[00289] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C₅₋₇ cycloalkyl. In certain embodiments, the compound of Formula (XII) is that wherein Ring A is cyclopentyl or cyclohexyl.

[00290] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is heterocycloalkyl, pyrazolyl, triazolyl, thiazolyl, pyridyl, phenyl, naphthyl, tetrahydronaphthalinyl, dihydronaphthalinyl, indanyl, indolyl, isoindolinyl, benzothiazolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or dihydrobenzodioxinyl.

[00291] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is heterocycloalkyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, or dihydroisoquinolinyl.

[00292] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, pyrazolyl, thienyl, imidazolyl, triazolyl,

thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is pyrazolyl, thienyl, imidazolyl, triazolyl, thiazolyl, phenyl, naphthyl, indanyl, tetrahydronaphthalinyl, dihydronaphthalinyl, pyridyl, indolyl, benzothiazolyl, quinolinyl, isoquinolinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, or tetrahydro-methanonaphthalenyl. In certain embodiments, Ring A is cyclohexyl or phenyl,

[00293] In certain embodiments, the compound of Formula (XII) is that wherein Ring A is pyrrolidinyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, phenyl, pyridyl, or thienyl. In certain embodiments, Ring A is pyrrolidinyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, phenyl, or pyridyl. In certain embodiments, Ring A is thiazolyl, phenyl, or pyridyl. In certain embodiments, Ring A is thiazolyl or phenyl. In certain embodiments, Ring A is phenyl.

[00294] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present.

[00295] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is C₅₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is C₅₋₇ cycloalkyl, or aryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is C₅₋₇ cycloalkyl optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is aryl optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is aryl or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, Ring A is phenyl or heteroaryl, where each is optionally substituted with 1 or 2 R^{A1} groups. In certain embodiments, the compound of Formula (XII),

Ring A is unsubstituted. In certain embodiments, the compound of Formula (XII), Ring A is monosubstituted with 1 R^{A1} group. In certain embodiments, the compound of Formula (XII), Ring A is disubstituted with 2 R^{A1} groups.

[00296] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is optionally substituted with 1 or 2 R^{A1} groups, wherein each R^{A1} is independently selected from fluoro, chloro, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, nitro, hydroxy, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and C_{3-4} cycloalkyl. In certain embodiments, each R^{A1} is independently selected from fluoro, chloro, C_{1-4} alkyl, C_{1-4} alkoxy, cyano, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, and C_{3-4} cycloalkyl.

[00297] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is not present.

[00298] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is not present and Ring A is C_{5-7} cycloalkyl, 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is heterocycloalkyl, aryl, or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is aryl or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is heterocycloalkyl, phenyl, or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, Ring A is phenyl or heteroaryl, where each is optionally substituted with 1, 2, or 3 R^{A2} groups. In certain embodiments, the compound of Formula (XII), Ring A is unsubstituted. In certain embodiments, the compound of Formula (XII), Ring A is monosubstituted with 1 R^{A2} group. In certain embodiments, the compound of Formula (XII), Ring A is disubstituted with 2 R^{A2} groups. In certain embodiments, the compound of Formula (XII), Ring A is trisubstituted with 3 R^{A2} groups.

[00299] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is unsubstituted. In certain embodiments, the compound of Formula (XII) is that wherein Ring A is unsubstituted and Ring B is unsubstituted. In certain embodiments, the compound of Formula (XII) is that wherein Ring A is unsubstituted and Ring B is substituted. In

certain embodiments, the compound of Formula (XII) is that wherein Ring A is substituted and Ring B is unsubstituted. In certain embodiments, the compound of Formula (XII) is that wherein Ring A is substituted and Ring B is substituted. For example, in certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups, wherein each R^{A2} is independently selected from halo; cyano; C_{1-4} alkyl; C_{1-4} hydroxyalkyl; C_{1-4} haloalkyl; C_{1-4} alkoxy; C_{1-4} hydroxyalkoxy; C_{1-4} haloalkoxy; C_{1-4} alkylcarbonyl; C_{1-4} alkoxyalkoxy; C_{3-5} cycloalkyl; C_{5-6} heterocycloalkyl optionally substituted with one or two groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} alkoxyalkyl, and C_{1-4} hydroxycycloalkyl. In certain embodiments, the R^{A2} is independently selected from halo; cyano; C_{1-4} alkyl; C_{1-4} hydroxyalkyl; C_{1-4} haloalkyl; C_{1-4} alkoxy; C_{1-4} hydroxyalkoxy; C_{1-4} haloalkoxy; C_{1-4} alkylcarbonyl; C_{5-6} heterocycloalkyl optionally substituted with one or two groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkylcarbonyl. In certain embodiments, the R^{A2} is independently selected from fluoro; chloro; cyano; trifluoromethoxy; piperidinyl optionally substituted with one or two groups independently selected from halo, C_{1-4} alkyl, and C_{1-4} alkylcarbonyl.

[00300] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and is C_{3-8} cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups. In certain embodiments, Ring B is heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, aryl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, or heteroaryl. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is 5-6 membered heterocycloalkyl, phenyl, or quinoliny. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or heteroaryl. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or quinoliny. In certain embodiments, Ring B is phenyl, pyridyl, quinoliny, or isoquinoliny. In certain embodiments, Ring B is phenyl or quinoliny. In certain embodiments, Ring B is phenyl.

[00301] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and is heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups, wherein each R^B is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy,

cycloalkyloxy, heterocycloalkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl. In certain embodiments, Ring B is piperidinyl, piperazinyl, phenyl, or quinolinyl; each substituted with one or two R^B groups, where each R^B is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyloxy, heterocycloalkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl. In certain embodiments, each R^B is independently halo, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylcarbonyl, alkoxyalkoxy, alkylcarbonylaminoalkoxy, cycloalkyl, (cycloalkyl)alkyl, cycloalkyloxy, (cycloalkyl)alkoxy, cycloalkylcarbonyl, cycloalkylcarbonyloxy, heterocycloalkyl optionally substituted with alkyl or alkylcarbonyl, (5-6-membered heterocycloalkyl-one)alkyl, (heterocycloalkyl)alkyl, or heterocycloalkylcarbonyl.

[00302] In certain embodiments, the compound of Formula (XII) is that wherein Ring B is present and is piperidinyl, piperazinyl, phenyl, or quinolinyl; wherein each is optionally substituted with 1, 2, or 3 R^B groups, wherein each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxy, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is unsubstituted. In certain embodiments, Ring B is independently substituted with 1 R^B group. In certain embodiments, Ring B is independently substituted with 2 R^B groups. In certain embodiments, Ring B is independently substituted with 3 R^B groups. In certain embodiments, Ring B is phenyl or quinolinyl; each substituted with one or two R^B groups, where each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxy, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxy, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently fluoro, chloro, bromo, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, or piperidinyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently fluoro, chloro, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, or piperidinyl. In certain embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, trifluoromethyl, methoxy, trifluoromethoxy, or piperidinyl. In certain

embodiments, Ring B is phenyl substituted with one or two R^B groups, where each R^B is independently chloro, trifluoromethyl, methoxy, trifluoromethoxy, or piperidinyl.

[00303] In certain embodiments, the compound of Formula (XII) is selected from the group consisting of:

(4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol;
 (4-(((trans)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)oxy)-1H-1,2,3-triazol-5-yl)methanol;
 (4-(((cis)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)thio)-1H-1,2,3-triazol-5-yl)methanol;
 4-(((trans)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)oxy)-1H-1,2,3-triazole-5-carbaldehyde;
 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carbaldehyde;
 (4-((4'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol;
 (4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol;
 (4-((4'-chloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol;
 (4-((1-(3,5-dichlorophenyl)piperidin-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol;
 (4-((1-(3,5-dichlorophenyl)piperidin-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol;
 (4-((4'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol; and
 (4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol;

optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

[00304] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is (4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00305] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is (4-(((trans)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00306] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is (4-(((cis)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)thio)-1H-1,2,3-triazol-5-yl)methanol.

[00307] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-(((trans)-4-(4-(trifluoromethoxy)phenyl)cyclohexyl)oxy)-1H-1,2,3-triazole-5-carbaldehyde.

[00308] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carbaldehyde.

[00309] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((4'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol.

[00310] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00311] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((4'-chloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00312] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((1-(3,5-dichlorophenyl)piperidin-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00313] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((1-(3,5-dichlorophenyl)piperidin-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol.

[00314] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((4'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazol-5-yl)methanol.

[00315] In certain embodiments, the compound or pharmaceutically acceptable salt thereof of Formula (XII) is 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazol-5-yl)methanol.

[00316] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound from Table 1. In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1-168, or a single stereoisomer or mixture of stereoisomers thereof.

[00317] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25-1, 25-2, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58-1, 58-2, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 111-1, 111-2, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 152, 153, 154, 155, 156, 157, 158, 160, 161, 162, 163, 164, 165, 166, 167, and 168, or a single stereoisomer or mixture of stereoisomers thereof.

[00318] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25-1, 25-2, 26, 27, 28, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58-1, 58-2, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 111-1, 111-2, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, and 168, or a single stereoisomer or mixture of stereoisomers thereof.

[00319] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25-1, 25-2, 26, 27, 28, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58-1, 58-2, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 111-1, 111-2, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, and 168, or a single stereoisomer or mixture of stereoisomers thereof.

[00320] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 23, 24, 25-1, 25-2, 26, 27, 28, 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58-1, 58-2, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 111, 111-1, 111-2, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, and 168, or a single stereoisomer or mixture of stereoisomers thereof.

[00321] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 4-5, 14, 16, 21, 22, 30-33, 37, 38, 42, 45, 47, 51, 52, 54, 55, 58, 60, 62, 65-68, 72, 75, 81, 86, 87, 119, 126, 128-130, 139, 155-157, and 160-165, or a single stereoisomer or mixture of stereoisomers thereof.

[00322] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1-3, 8, 9, 11, 15, 17-19, 23-27, 29, 34, 39, 40, 43, 44, 53, 59, 61, 63, 64, and 124, or a single stereoisomer or mixture of stereoisomers thereof.

[00323] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 12, 20, and 145, or a single stereoisomer or mixture of stereoisomers thereof.

[00324] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 73, 90, 146, 149, and 150, or a single stereoisomer or mixture of stereoisomers thereof.

[00325] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 70, 71, and 74, or a single stereoisomer or mixture of stereoisomers thereof.

[00326] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1, 9, 11, 17, 19, 33, 37, 38, 40, 44, 45, 54, 55, 65, 72, 81, 93, 98, 107-110, 112, and 116, or a single stereoisomer or mixture of stereoisomers thereof.

[00327] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 54, 55, 37, 38, 81, and 107-109, or a single stereoisomer or mixture of stereoisomers thereof.

[00328] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 88, 91, 94, 95, 98, 100, 102-104, 112, and 131, or a single stereoisomer or mixture of stereoisomers thereof.

[00329] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound from Table 2. In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 169-375, or a single stereoisomer or mixture of stereoisomers thereof.

[00330] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound from Table 3. In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 294, 296, 366, 372 and 374, or a single stereoisomer or mixture of stereoisomers thereof.

[00331] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 185, 186, 187, 188, 189, 190, 194, 195, 196, 197, 198, 199, 200, 201, 203, 204, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272-1, 272-2, 273, 274, 275, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 295, 297, 298, 299, 300, 301, 303, 304, 305, 306, 307, 308-1, 308-2, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 367, 368, 369, 370, 373, and 375, or a single stereoisomer or mixture of stereoisomers thereof.

[00332] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 183, 197, 198, 199, 200, 201, 203, 216, 217, 220, 221, 222, 223, 224, 225, 227, 228, 230, 231, 232, 233, 234, 235, 236, 237, 238, 241, 242, 243,

247, 250, 253, 254, 255, 257, 259, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272-1, 272-2, 273, 274, 275, 277, 279, 280, 282, 283, 284, 285, 286, 287, 289, 290, 291, 292, 293, 295, 297, 298, 299, 300, 304, 308-1, 308-2, 309, 310, 311, 312, 314, 315, 316, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 367, 368, 369, 373, and 375, or a single stereoisomer or mixture of stereoisomers thereof.

[00333] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 169, 170, 172, 173, 175, 244, 247, 277, 278, 311, 313, 314, 315, 317, 318, 319, 320, 321, 323, 324, 325, 326, 327, 330, 331, 332, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 351, and 352, or a single stereoisomer or mixture of stereoisomers thereof.

[00334] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 1, 98, 110, 123, 142, 151, 159, 184, 191, 192, 193, 302, and 371, or a single stereoisomer or mixture of stereoisomers thereof.

[00335] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is compound 335, or a single stereoisomer or mixture of stereoisomers thereof.

[00336] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 171, 243, 312, 322, 328, 329, and 350, or a single stereoisomer or mixture of stereoisomers thereof.

[00337] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 174, 176, 177, 316, and 373, or a single stereoisomer or mixture of stereoisomers thereof.

[00338] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 220, 221, 222, 223, 224, 225, 226, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 245, 246, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 267, 268, 270, 271, 272-1, 272-2, 273, 275, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 295, 297, 301, 302, 303, 304, 305, 306, 307, 308-1, 308-2, 309, 310, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 367, 368, 370, 371, and 375, or a single stereoisomer or mixture of stereoisomers thereof.

[00339] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 227, 269, 274, 298, and 369, or a single stereoisomer or mixture of stereoisomers thereof.

[00340] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 264, 265, 266, 299, and 300, or a single stereoisomer or mixture of stereoisomers thereof.

[00341] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 181, 183, 186, and 190, or a single stereoisomer or mixture of stereoisomers thereof.

[00342] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 178, 179, 180, 184, 185, 187, 189, 193, 194, 195, 196, and 333, or a single stereoisomer or mixture of stereoisomers thereof.

[00343] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 178, 179, 180, and 333, or a single stereoisomer or mixture of stereoisomers thereof.

[00344] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound 182, or a single stereoisomer or mixture of stereoisomers thereof.

[00345] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 197, 198, 199, 200, and 201, or a single stereoisomer or mixture of stereoisomers thereof.

[00346] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 203, 204, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, and 334, or a single stereoisomer or mixture of stereoisomers thereof.

[00347] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compound 188, 191, and 192, or a single stereoisomer or mixture of stereoisomers thereof.

[00348] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound from Table 4 or 5. In certain embodiments, the compound or

pharmaceutically acceptable salt thereof is a compound selected from the compounds 376-486, or a single stereoisomer or mixture of stereoisomers thereof.

[00349] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 376, 377, 379, 380, 381, 382, 383, 384, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442-1, 442-2, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, and 486, or a single stereoisomer or mixture of stereoisomers thereof.

[00350] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 294, 296, 366, 372, 374, 378, and 385.

[00351] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the group consisting of compounds 4, 5, 21, 22, 30, 31, 47, 48, 276, and 376.

[00352] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound from Table 7. In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487-497, or a single stereoisomer or mixture of stereoisomers thereof.

[00353] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487, 488, 489, 490, 491, 492, 493-1, 493-2, 494, 495, 496, and 497, or a single stereoisomer or mixture of stereoisomers thereof.

[00354] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 490 and 491, or a single stereoisomer or mixture of stereoisomers thereof.

[00355] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487, 488, 489, 492, 493-1, 493-2, 494, 495, 496, and 497, or a single stereoisomer or mixture of stereoisomers thereof.

[00356] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487, 491, 492, 493-1, 493-2, 496, and 497, or a single stereoisomer or mixture of stereoisomers thereof.

[00357] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 488, 489, and 490, or a single stereoisomer or mixture of stereoisomers thereof.

[00358] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487, 488, 490, 491, 493-1, 493-2, 494, and 496, or a single stereoisomer or mixture of stereoisomers thereof.

[00359] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 489, 492, 495, and 497, or a single stereoisomer or mixture of stereoisomers thereof.

[00360] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 487, 488, 489, 490, 491, and 497, or a single stereoisomer or mixture of stereoisomers thereof.

[00361] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 493-1, 493-2, 494, and 495, or a single stereoisomer or mixture of stereoisomers thereof.

[00362] In certain embodiments, the compound or pharmaceutically acceptable salt thereof is a compound selected from the compounds 492 and 496, or a single stereoisomer or mixture of stereoisomers thereof.

Pharmaceutical Compositions

[00363] In certain embodiments, optionally in combination with any or all of the above various embodiments, provided herein is a pharmaceutical composition comprising of a compound disclosed herein, for example, a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00364] In certain embodiments, the pharmaceutical composition comprises a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or stereoisomers thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically

acceptable excipients. In certain embodiments, the pharmaceutical composition comprises a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00365] Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

[00366] Suitable excipients are well known to those skilled in the art. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art, including, but not limited to, the method of administration. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

Formulation and Administration

[00367] In another aspect, provided herein, a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, as disclosed herein, and a pharmaceutical composition comprising the same and a pharmaceutically acceptable excipient, may be used in the methods of use provided herein, such as used in the methods for treatment of the diseases or disorders provided herein, or such as used in the methods for preventing the diseases or disorders provided herein. In certain embodiments, the compounds and pharmaceutical compositions provided herein are for use as a medicament for the treatment or prevention of the diseases or disorders provided herein. For example, in certain embodiments, the compounds and pharmaceutical compositions provided herein are for use in a method for the treatment or prevention of a disease or disorder associated with a defect in glyoxylate metabolism. For example, in certain embodiments, the compounds and pharmaceutical compositions provided herein are for use in a method for the treatment or prevention of a disease or disorder that is mediated by the enzyme GO or associated with alterations in oxalate metabolism. For example, a disease or disorder that is mediated by the enzyme GO or associated with alterations in oxalate metabolism include those

disclosed in: Lorenzo, V., *et al.*, *Nefrologia*, **34**:398-412 (2014); Rumsby, G., *et al.*, *N Engl J Med.*, **369**:2163 (2013); Cramer, S.D., *et al.*, *Hum Mol Genet.*, **8**:2063–2069 (1999); Cregeen, D.P., *et al.*, *Hum Mutat.*, **22**:497 (2003); Belostotsky, R., *et al.*, *Am J Hum Genet.*, **87**:392–399 (2010); Liebow, A., *et al.*, *J. Am. Soc. Nephrol.*, **28**(2):494–503 (2017); Dutta, C., *et al.*, *Mol. Ther.*, **24**(4):770–778 (2016 Apr.); Selvam, R., *et al.*, *Indian J Exp Biol.*, **31**(11):882-7 (1993 Nov); Lindsjö, M., *et al.*, *Scand J Urol Nephrol.*, **23**(4):283-9 (1989); Worcester, E.M., *Endocrinol Metab Clin North Am.*, **31**:979–999 (2002); Lemann, J., *et al.*, *Kidney Int.*, **49**:200–208 (1996); Mittal, R.D., *et al.*, *J Endourol.*, **18**:418–424 (2004); Sidhu, H., *et al.*, *J Am Soc Nephrol.*, 10 Suppl **14**:S334–S340 (1999); Stapenhorst, L., *et al.*, *Pediatr Nephrol.*, **23**:2277–2279 (2008); Kraut, J.A., *et al.*, *Clin J Am Soc Nephrol.*, **3**:208–225 (2008); Nasr, S.H., *et al.*, *Kidney Int.*, **70**:1672 (2006); Canavese, C., *et al.*, *Am J Kidney Dis.*, **45**:540–549 (2005); Terribile, M., *et al.*, *Nephrol Dial Transplant.*, **21**:1870–1875 (2006); Hueppelshaeuser, R., *et al.*, *Pediatr Nephrol.*, **27**:1103–1109 (2012); Holmes, R.P., *et al.*, *Kidney Int.*, **59**:270–276 (2001); Holmes, R.P., *et al.*, *J Urol.*, **174**(3):943-947 (2005); Scales Jr., Charles, D., *et al.*, *European Urology*, **62**(1):160-165 (2012); Chadwick, V.S., *et al.*, *N Engl J Med.*, **289**:172–176 (1973); Demoulin, Nathalie, *et al.*, *Medicine*, **96**(19):e6758 (2017 May); Amin, R., *et al.*, *Kidney Int.*, **93**(5):1098-1107 (2018 May); Powell, C.R., *et al.*, *Urology*, **55**(6):825-30 (2000 Jun); Pini Prato, A., *et al.*, *Medicine (Baltimore)*, **88**(2):83-90 (2009 Mar); Nazzal, L., *et al.*, *Nephrology Dialysis Transplantation*, **31**(3):375–382 (2016 Mar); Robijn, S., *et al.*, *Kidney Int.*, **80**:1146–1158 (2011); Asplin, J.R., *et al.*, *J Urol.*, **177**(2):565-9 (2007 Feb); Whitson, J.M., *et al.*, *Int Urol Nephrol.*, **42**(2):369-74 (2010 Jun); Duffey, B.G., *et al.*, *J Am Coll Surg.*, **211**(1):8-15 (2010); Isakova, T., *et al.*, *Nephrol Dial Transplant.*, **26**(4):1258-1265 (2011); Eisner, B.H., *et al.*, *J Urol.*, **183**(6):2244-2248 (2010); Massey, L.K., *et al.*, *J Am Diet Assoc.*, **93**(8):901-906 (1993); Pak, C.Y., *et al.*, *Kidney Int.*, **68**(5):2264-2273 (2005); Jiang, Z., *et al.*, *Nat Genet.*, **38**:474–478 (2006); Freel, R.W., *et al.*, *Am J Physiol Gastrointest Liver Physiol.*, **290**:G719–G728 (2006); Knight, T.F., *et al.*, *Am J Physiol.*, **240**:F295–F298 (1981); Bergsland, K.J., *et al.*, *Am J Physiol Renal Physiol.*, **300**:F311–F318 (2011); Sikora, P., *et al.*, *Kidney Int.*, **73**:1181–1186 (2008); and Waikar, Sushru S., *et al.*, *JAMA Intern Med.*, **179**(4):542-551 (2019); each of which is incorporated by reference in its entirety. In certain embodiments, the compounds and pharmaceutical compositions provided herein are for use in a method for the treatment of a disease or disorder in which inhibition of the enzyme GO ameliorates or treats the disease or

disorder. In certain embodiments, a compound provided herein is a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof. In certain embodiments, provided is a method for treating any of the diseases or disorders described herein comprising administering to a subject in need of treatment thereof a compound according to any of the various embodiments described herein or a pharmaceutical composition according to any of the various embodiments described herein. The compounds and pharmaceutical compositions provided herein are for use in a method for the treatment of a disease or disorder that is mediated by the enzyme GO or associated with alterations in oxalate metabolism, or in which inhibition of the enzyme GO ameliorates or treats the disease or disorder. In certain embodiments, the compounds and pharmaceutical compositions provided herein are used in the preparation or manufacture of medicaments for the treatment of a disease or disorder that is mediated by the enzyme GO or associated with alterations in oxalate metabolism or in which inhibition of the enzyme GO ameliorates or treats the disease or disorder.

[00368] In certain embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00369] In certain embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Table 1, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the method comprises administering to a subject in need

thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Table 2, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Table 4, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the method comprises administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[00370] In certain embodiments, provided herein is a method of treating a disease or disorder associated with a defect in glyoxylate metabolism, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the disease or disorder is associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism. In certain embodiments, the disease or disorder is associated with the enzyme glycolate oxidase (GO). In certain embodiments, the disease or disorder is associated with alterations in oxalate metabolism. In certain embodiments, the disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism is characterized by high oxalate content in the urine. In certain embodiments, the disease or disorder associated with the enzyme glycolate oxidase (GO) is characterized by high oxalate content in the urine. In certain embodiments, the disease or disorder associated with alterations in oxalate metabolism is characterized by high oxalate content in the urine. In certain embodiments, the disease or disorder is characterized by high oxalate content in the urine. In certain embodiments, the disease or disorder is a disease or disorder associated with the enzyme GO misregulation. In certain embodiments, the disease or

disorder is treated or prevented by inhibition of the enzyme GO. In certain embodiments, the disease or disorder is treated by inhibition of the enzyme GO. In certain embodiments, the disease or disorder is prevented by inhibition of the enzyme GO. In certain embodiments, the disease or disorder is characterized by a deficiency in the enzyme alanine: glyoxylate aminotransferase (AGT). In certain embodiments, the disease or disorder is characterized by a disruption of oxalate metabolic pathway. In certain embodiments, the disease or disorder is an enteric hyperoxaluria. In certain embodiments, the disease or disorder is a dietary hyperoxaluria. In certain embodiments, the disease or disorder is an idiopathic hyperoxaluria. In certain embodiments, the disease or disorder is a pharmacologically induced hyperoxaluria. In certain embodiments, the disease or disorder is a kidney disease.

[00371] In certain embodiments, provided herein is a method of treating a disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the disease or disorder is characterized by high oxalate content in the urine. In certain embodiments, the disease or disorder results from a disruption of the oxalate metabolic pathway. In certain embodiments, the disease or disorder is selected from the group consisting of: hyperoxaluria, genetic or environmental vitamin B6 deficiency, genetic or environmental abnormal calcium metabolism, abnormal collagen metabolism, abnormal function of oxalate transporters, and genetic kidney disease. In certain embodiments, the disease or disorder is hyperoxaluria. In certain embodiments, the disease or disorder hyperoxaluria is a primary hyperoxaluria (“PH”) or is a secondary hyperoxaluria. In specific embodiments, the disease or disorder is a primary hyperoxaluria (“PH”). In certain embodiments, the disease or disorder is a primary hyperoxaluria selected from the group consisting of: Primary hyperoxaluria type 1 (“PH1”), Primary hyperoxaluria type 2 (“PH2”), and Primary hyperoxaluria type 3 (“PH3”). In a specific embodiment, the primary hyperoxaluria is Primary hyperoxaluria type 1 (“PH1”). In a specific embodiment, the primary hyperoxaluria is Primary hyperoxaluria type 2 (“PH2”). In a specific

embodiment, the primary hyperoxaluria is Primary hyperoxaluria type 3 (“PH3”). In a specific embodiment, the hyperoxaluria is secondary hyperoxaluria. In a specific embodiment, the disease or disorder is a genetic or environmental vitamin B6 deficiency. In certain embodiments, the disease or disorder is a genetic or environmental abnormal calcium metabolism. In certain embodiments, the genetic or environmental abnormal calcium metabolism is hypercalciuria or hyperparathyroidism. In a specific embodiment, the genetic or environmental abnormal calcium metabolism is hypercalciuria. In a specific embodiment, the genetic or environmental abnormal calcium metabolism is hyperparathyroidism. In a specific embodiment, the disease or disorder is an abnormal collagen metabolism. In a specific embodiment, the disease or disorder is an abnormal function of oxalate transporters. In a specific embodiment, the disease or disorder is a genetic kidney disease. In a specific embodiment, the genetic kidney disease is Hirschsprung’s disease.

[00372] In certain embodiments, provided herein is a method of treating a disease or disorder characterized by high oxalate content in the urine is an enteric hyperoxaluria, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the disease or disorder is an enteric hyperoxaluria selected from the group consisting of: fat malabsorption, steatorrhea, inflammatory bowel disease (“IBD”), pancreatic insufficiency, biliary cirrhosis, short-bowel syndrome, bariatric surgery, jejunioileal bypass, Crohn’s disease, ulcerative colitis, cystic fibrosis, high blood pressure, diabetes, obesity, absence of the gastrointestinal tract-dwelling bacterium *Oxalobacter formigenes*, and ileal dysfunction. In a specific embodiment, the enteric hyperoxaluria is fat malabsorption. In a specific embodiment, the enteric hyperoxaluria is steatorrhea. In a specific embodiment, the enteric hyperoxaluria is inflammatory bowel disease (“IBD”). In a specific embodiment, the enteric hyperoxaluria is pancreatic insufficiency. In a specific embodiment, the enteric hyperoxaluria is biliary cirrhosis. In a specific embodiment, the enteric hyperoxaluria is short-bowel syndrome. In a specific embodiment, the enteric hyperoxaluria is bariatric surgery. In a specific embodiment, the enteric hyperoxaluria is

jejunoileal bypass. In a specific embodiment, the enteric hyperoxaluria is Crohn's disease. In a specific embodiment, the enteric hyperoxaluria is ulcerative colitis. In a specific embodiment, the enteric hyperoxaluria is cystic fibrosis. In a specific embodiment, the enteric hyperoxaluria is high blood pressure. In a specific embodiment, the enteric hyperoxaluria is diabetes. In a specific embodiment, the enteric hyperoxaluria is obesity. In a specific embodiment, the enteric hyperoxaluria is an absence of the gastrointestinal tract-dwelling bacterium *Oxalobacter formigenes*. In a specific embodiment, the enteric hyperoxaluria is an ileal dysfunction.

[00373] In certain embodiments, provided herein is a method of treating a disease or disorder characterized by high oxalate content in the urine is a dietary hyperoxaluria, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the dietary hyperoxaluria is associated with and/or the result of one or more of a high oxalate diet, a high protein diet, a high oxalate precursor diet, and a low calcium diet. In a specific embodiment, the dietary hyperoxaluria is associated with and/or the result of a high oxalate diet. In a specific embodiment, the dietary hyperoxaluria is associated with and/or the result of a high protein diet. In a specific embodiment, the dietary hyperoxaluria is associated with and/or the result of a high oxalate precursor diet. In a specific embodiment, the dietary hyperoxaluria is associated with and/or the result of a low calcium diet.

[00374] In certain embodiments, provided herein is a method of treating a disease or disorder characterized by high oxalate content in the urine is an idiopathic hyperoxaluria, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the idiopathic hyperoxaluria is undefined elevated hyperoxaluria.

[00375] In certain embodiments, provided herein is a method of treating a disease or disorder characterized by high oxalate content in the urine is a pharmacologically induced hyperoxaluria, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmacologically induced hyperoxaluria is associated with and/or the result of ingestion of compounds that metabolize to oxylate. In certain embodiments, the pharmacologically induced hyperoxaluria is the result of ingestion of ethylene glycol or hydroxylproline. In certain embodiments, the pharmacologically induced hyperoxaluria is the result of ingestion of ethylene glycol. In certain embodiments, the pharmacologically induced hyperoxaluria is the result of ingestion of hydroxylproline.

[00376] In certain embodiments, provided herein is a method of treating a disease or disorder associated with a defect in glyoxylate metabolism, associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism, and/or characterized by high oxalate content in the urine, is a kidney disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In certain embodiments, the kidney disease is selected from the group consisting of: primary hyperoxaluria, dietary hyperoxaluria, kidney stones (nephrolithiasis), recurrent kidney stones, progressive kidney failure, nephrocalcinosis, urinary tract infections, end stage renal disease, chronic kidney disease (“CKD”), end-stage kidney disease (“ESKD”), hypertension, diabetes, urolithiasis, and systemic oxalosis. In a specific embodiment, the kidney disease is primary hyperoxaluria. In a specific embodiment, the kidney disease is a dietary hyperoxaluria. In a specific embodiment, the kidney disease is kidney stones (nephrolithiasis). In a specific embodiment, the kidney disease is recurrent kidney stones. In a specific embodiment, the kidney

disease is progressive kidney failure. In a specific embodiment, the kidney disease is nephrocalcinosis. In a specific embodiment, the kidney disease is urinary tract infections. In a specific embodiment, the kidney disease is end stage renal disease. In a specific embodiment, the kidney disease is chronic kidney disease (“CKD”). In a specific embodiment, the disease or disorder is end-stage kidney disease (“ESKD”). In a specific embodiment, the kidney disease is hypertension. In a specific embodiment, the kidney disease is diabetes. In a specific embodiment, the kidney disease is urolithiasis. In a specific embodiment, the kidney disease is systemic oxalosis. In certain embodiments, the disease or disorder is nephropathy. In a specific embodiment, the nephropathy is oxalate nephropathy. In a specific embodiment, the nephropathy is chronic calcium-oxalate nephropathy. In a specific embodiment, the disease or disorder is systemic oxalosis. In a specific embodiment, the disease or disorder is urolithiasis. In a specific embodiment, the disease or disorder is nephrocalcinosis. In a specific embodiment, the disease or disorder is calcium oxalate (CaOx) stone disease. In a specific embodiment, the disease or disorder is nephrolithiasis. In a specific embodiment, the nephrolithiasis is calcium oxalate (CaOx) nephrolithiasis. In a specific embodiment, the disease or disorder is renal failure.

[00377] In certain embodiments, provided herein is a method of treating a disease or disorder associated with a defect in glyoxylate metabolism, associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism, and/or characterized by high oxalate content in the urine, is selected from the group consisting of hyperoxaluria, chronic kidney disease (“CKD”), end-stage kidney disease (“ESKD”), nephropathy, systemic oxalosis, urolithiasis, nephrocalcinosis, calcium oxalate (CaOx) stone disease, nephrolithiasis, and renal failure, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In a specific embodiment, the disease or disorder is hyperoxaluria. In a specific embodiment, the hyperoxaluria is a primary hyperoxaluria. In a specific embodiment, the hyperoxaluria is PH1. In a specific embodiment, the hyperoxaluria is PH2. In a specific embodiment, the hyperoxaluria is PH3. In a specific embodiment, the hyperoxaluria is a secondary hyperoxaluria. In a specific embodiment, the disease or disorder is

chronic kidney disease (“CKD”). In a specific embodiment, the disease or disorder is end-stage kidney disease (“ESKD”). In a specific embodiment, the disease or disorder is nephropathy. In a specific embodiment, the disease or disorder is systemic oxalosis. In a specific embodiment, the disease or disorder is urolithiasis. In a specific embodiment, the disease or disorder is nephrocalcinosis. In a specific embodiment, the disease or disorder is calcium oxalate (CaOx) stone disease. In a specific embodiment, the disease or disorder is nephrolithiasis. In a specific embodiment, the disease or disorder is renal failure.

[00378] In certain embodiments, provided herein is a method of treating a disease or disorder associated with a defect in glyoxylate metabolism, associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism, and/or characterized by high oxalate content in the urine, is selected from the group consisting of idiopathic hyperoxaluria, primary hyperoxaluria (“PH”), secondary hyperoxaluria, idiopathic hyperoxaluria, enteric hyperoxaluria, chronic kidney disease (“CKD”), end-stage kidney disease (“ESKD”), oxalate nephropathy, chronic calcium-oxalate nephropathy, systemic oxalosis, urolithiasis, nephrocalcinosis, calcium oxalate (CaOx) stone disease, calcium oxalate (CaOx) nephrolithiasis, and renal failure, the method comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), or (XII), or a compound of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7, or stereoisomers thereof, and additionally optionally a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients. In a specific embodiment, the disease or disorder is idiopathic hyperoxaluria. In a specific embodiment, the disease or disorder is primary hyperoxaluria (“PH”). In a specific embodiment, the primary hyperoxaluria is PH1. In a specific embodiment, the primary hyperoxaluria is PH2. In a specific embodiment, the primary hyperoxaluria is PH3. In a specific embodiment, the disease or disorder is secondary hyperoxaluria. In a specific embodiment, the disease or disorder is idiopathic hyperoxaluria. In a specific embodiment, the disease or disorder is enteric hyperoxaluria. In a specific embodiment, the disease or disorder is chronic kidney disease (“CKD”). In a specific embodiment, the disease or disorder is end-stage kidney disease (“ESKD”). In a specific embodiment, the disease or disorder is oxalate nephropathy. In a specific embodiment, the disease or disorder is chronic calcium-oxalate nephropathy. In a specific embodiment, the

disease or disorder is systemic oxalosis. In a specific embodiment, the disease or disorder is urolithiasis. In a specific embodiment, the disease or disorder is nephrocalcinosis. In a specific embodiment, the disease or disorder is calcium oxalate (CaOx) stone disease. In a specific embodiment, the disease or disorder is calcium oxalate (CaOx) nephrolithiasis. In a specific embodiment, the disease or disorder is renal failure.

[00379] In another aspect, provided herein is a method of inhibiting the enzyme GO comprising administering to a subject in need thereof a therapeutically effective amount of the compounds and pharmaceutical compositions described herein.

[00380] The compounds or compositions disclosed herein can be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. The compounds are typically administered as pharmaceutical compositions by any route which makes the compound bioavailable. In certain embodiments, the composition is a solid formulation adapted for oral administration. In certain embodiments, the composition is a tablet, powder, or capsule; or the composition is a tablet. In certain embodiments, the composition is a liquid formulation adapted for oral administration. In certain embodiments, the composition is a liquid formulation adapted for parenteral administration. In certain embodiments, the composition is a solution, suspension, or emulsion; or the composition is a solution. In certain embodiments, solid form compositions can be converted, shortly before use, to liquid form compositions for either oral or parenteral administration. These particular solid form compositions are provided in unit dose form and as such are used to provide a single liquid dosage unit. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*See, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd ed.; Rathbone *et al.*, Eds.; Marcel Dekker, Inc.: New York, NY, 2008).

[00381] The dosages may be varied depending on the requirement of the patient, the severity of the disease or disorder being treating and the particular compound and/or composition being employed. Determination of the proper dosage can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery. In certain embodiments, the compounds are administered to a subject at a daily dosage of between 0.01 to about 50 mg/kg of body weight.

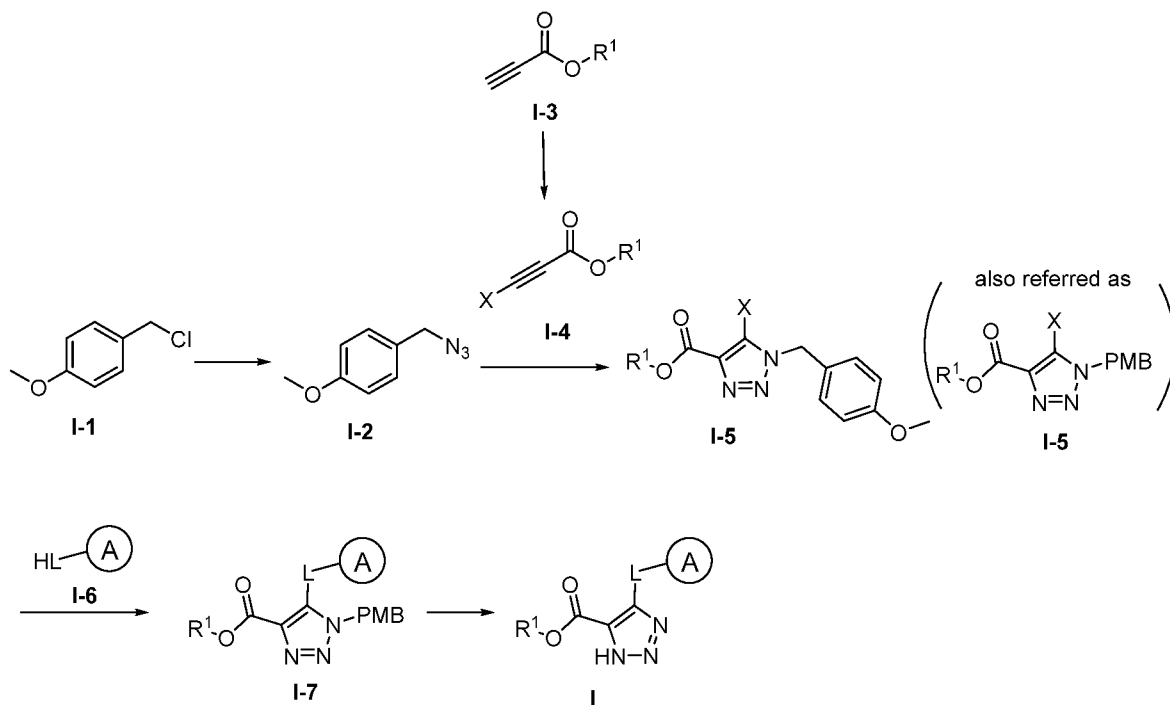
In other embodiments, the dose is from 1 to 1000 mg/day. In certain embodiments, the daily dose is from 1 to 750 mg/day; or from 10 to 500 mg/day.

[00382] In certain embodiments, the pharmaceutical composition is in unit dosage form. The composition can be subdivided into unit doses containing appropriate quantities of the active component(s). The unit dosage form can be a tablet, capsule, or powder in a vial or ampule, or it may be the appropriate number of any of these in a packaged form. The unit dosage form can be a packaged form, the package containing discrete quantities of composition such as packeted tablets, capsules, or powders in vials or ampules. The quantity of active compound(s) in a unit dose of the composition may be varied or adjusted from about 1 mg to about 100 mg, or from about 1 mg to about 50 mg, or from about 1 mg to about 25 mg.

[00383] The compounds or pharmaceutical compositions disclosed herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

PREPARATION OF COMPOUNDS

[00384] The following are illustrative schemes and examples of how the compounds described herein can be prepared and tested. Although the examples can represent only some embodiments, it should be understood that the following examples are illustrative and not limiting. All substituents, unless otherwise specified, are as previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art. The specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare the compounds described herein.

[00385] General Scheme 1

[00386] A compound of Formula **(I)** can be prepared according to General Scheme 1, wherein R^1 can be, for example, alkyl or cycloalkyl group. In certain embodiments, R^1 is methyl, or ethyl.

[00387] Compound **I-2** can be prepared from Compound **I-1** using standard azide substitution conditions. More specifically, Compound **I-1** can react with NaN_3 in a solvent such as DMF, or THF, and at ambient temperature or up to 50 °C.

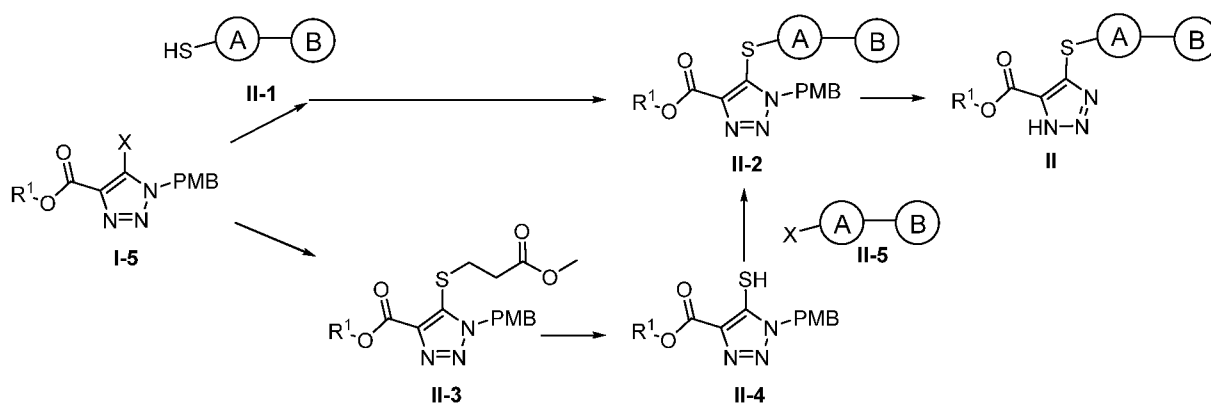
[00388] Compound **I-4** can be prepared from corresponding unsubstituted acetylene **I-3** using standard halogenation conditions, wherein X is, for example, Cl, Br or I. More specifically, Compound **I-3** can reaction with a halogenation reagent, such as NBS (*N*-Bromosuccinimide) or NIS (*N*-iodosuccinimide), in a solvent such as acetone or THF, in the presence of a silver salt such as AgNO_3 , to yield Compound **I-4**.

[00389] Intermediate **I-5** can be prepared from Compounds **I-2** and **I-4** using standard click reaction conditions. More specifically, Compound **I-2** can reaction with Compound **I-4** optionally in the presence of copper salts, for example, a mixture of Cu(I) and Cu(II) salts such as CuI and $\text{Cu}(\text{OAc})_2$ in a solvent such as THF, to yield Intermediate **I-5**.

[00390] Compound **I-7** can be prepared using standard substitution conditions. More specifically, Compound **I-5** can be reacted with Compound **I-6**, in a solvent such as DMF or THF, in the presence of a base such as Na_2CO_3 or K_2CO_3 , to yield Compound **I-7**.

[00391] Compound **I** can be prepared using standard PMB (*p*-Methoxybenzyl) deprotection conditions. More specifically, Compound **I-7** can be treated in acidic conditions, such as in TFA (trifluoroacetic acid) as the solvent, at ambient temperature or up to 50 °C to afford Compound **I**.

[00392] **General Scheme 2**



[00393] Compound **I** or **II** of Formula (**I**) can be also prepared using General Scheme 2.

[00394] Compound **II-2** can be prepared using standard substitution conditions. More specifically, Intermediate **I-5** can be reacted with Compound **II-1**, in a solvent such as DMF or THF, in the presence of a base such as Na_2CO_3 or K_2CO_3 , to yield Compound **II-2**.

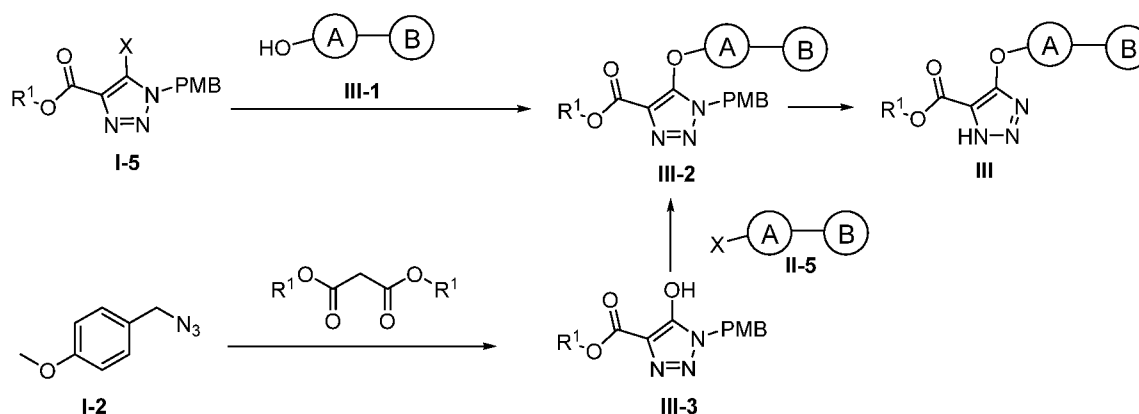
[00395] Compound **II-3** can be prepared using standard coupling conditions. More specifically, Intermediate **I-5** can be reacted with methyl 3-mercaptopropanoate, in a solvent such as 1,4-dioxane or THF, in the presence of a base such as DIPEA (*N,N*-diisopropylethylamine), a palladium salt such as $\text{Pd}_2(\text{dba})_3$, and a phosphine such as Xantphos, and to yield Compound **II-3**.

[00396] Compound **II-3** can be treated in basic condition to afford Compound **II-4**. More specifically, Compound **II-3** can be reacted with potassium tert-butoxide, in a solvent such as THF at -78 °C and warmed up to ambient temperature, and to yield Compound **II-4**.

[00397] Compound **II-2** can also be prepared using standard substitution conditions. More specifically, Compound **II-4** can be reacted with Compound **II-5**, in a solvent such as DMF or THF, in the presence of a base such as Na_2CO_3 or K_2CO_3 , to yield Compound **II-2**.

[00398] Compound **II** can be prepared using standard PMB (*p*-Methoxybenzyl) deprotection conditions. More specifically, Compound **II-2** can be treated in acidic conditions, such as in TFA (trifluoroacetic acid) as the solvent, at ambient temperature or up to 50 °C to afford Compound **II**.

[00399] **General Scheme 3**



[00400] Compound **III** of **Formula (I)** can be also prepared using General Scheme 3.

[00401] Compound **III-2** can be prepared using standard substitution conditions. More specifically, Intermediate **I-5** can be reacted with Compound **III-1**, in a solvent such as DMF or THF, in the presence of a base such as Na_2CO_3 or K_2CO_3 , to yield Compound **III-2**.

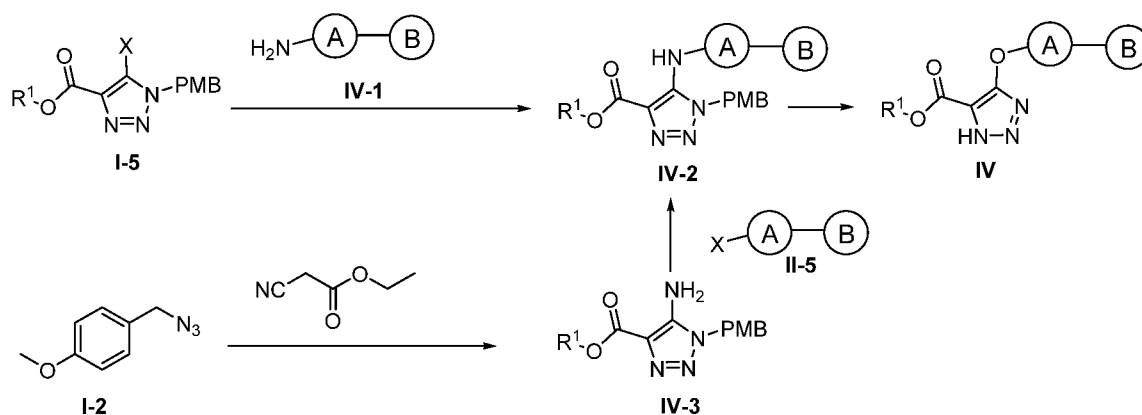
[00402] Compound **III-3** can be prepared using standard click reaction conditions. More specifically, Compound **I-2** can be reacted with dialkyl malonate, in a solvent such as 1,4-dioxane or THF, optionally in the presence of copper salts, for example, a mixture of Cu(I) and Cu(II) salts such as CuI and Cu(OAc)₂ in a solvent such as THF, to yield Intermediate **III-3**.

[00403] Compound **III-2** can also be prepared using standard substitution conditions. More specifically, Compound **III-3** can be reacted with Compound **II-5**, in a solvent such as DMF or THF, in the presence of a base such as Na_2CO_3 or K_2CO_3 , to yield Compound **III-2**.

[00404] Compound **III** can be prepared using standard PMB (*p*-Methoxybenzyl) deprotection conditions. More specifically, Compound **III-2** can be treated in acidic conditions,

such as in TFA (trifluoroacetic acid) as the solvent, at ambient temperature or up to 50 °C to afford Compound **III**.

[00405] General Scheme 4



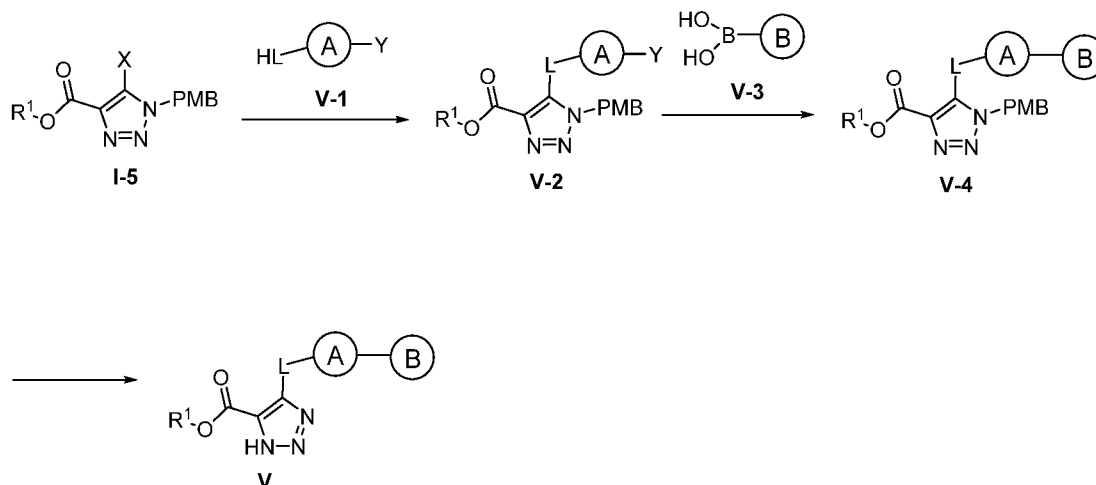
[00406] Compound **IV** of Formula **(I)** can be also prepared using General Scheme 4.

[00407] Compound **IV-2** can be prepared using standard substitution conditions. More specifically, Intermediate **I-5** can be reacted with Compound **IV-1**, in a solvent such as DMF or THF, in the presence of a base such as Na₂CO₃ or K₂CO₃, to yield Compound **IV-2**.

[00408] Compound **IV-3** can be prepared using standard click reaction conditions. More specifically, Compound **I-2** can be reacted with ethyl 2-cyanoacetate, in a solvent such as 1,4-dioxane or THF, optionally in the presence of copper salts, for example, a mixture of Cu(I) and Cu(II) salts such as CuI and Cu(OAc)₂ in a solvent such as THF, to yield Intermediate **IV-3**.

[00409] Compound **IV-2** can also be prepared using standard substitution conditions. More specifically, Compound **IV-3** can be reacted with Compound **II-5**, in a solvent such as DMF or THF, in the presence of a base such as Na₂CO₃ or K₂CO₃, to yield Compound **IV-2**.

[00410] Compound **IV** can be prepared using standard PMB (*p*-Methoxybenzyl) deprotection conditions. More specifically, Compound **IV-2** can be treated in acidic conditions, such as in TFA (trifluoroacetic acid) as the solvent, at ambient temperature or up to 50 °C to afford Compound **IV**.

[00411] General Scheme 5

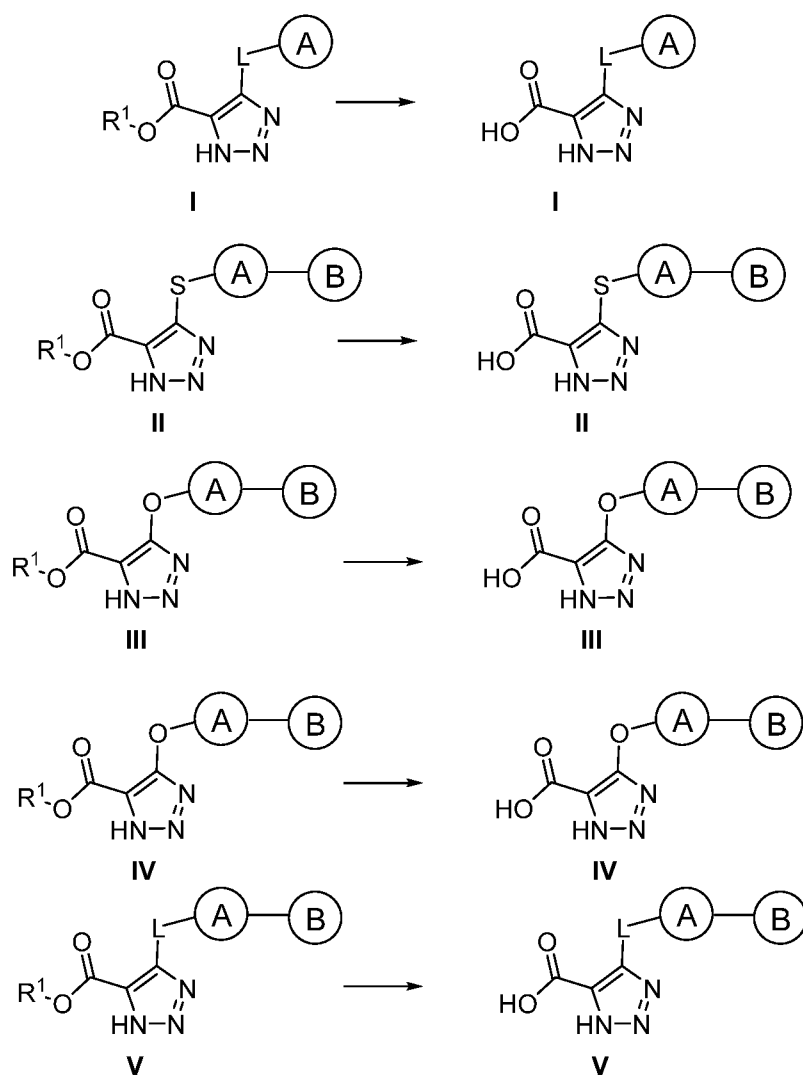
[00412] Compound **V** of **Formula (I)** can be also prepared using General Scheme 5, wherein Y is a halo group for example, Cl, Br, or I.

[00413] Compound **V-2** can be prepared using standard substitution conditions. More specifically, Intermediate **I-5** can be reacted with Compound **V-1**, in a solvent such as DMF or THF, in the presence of a base such as Na₂CO₃ or K₂CO₃, to yield Compound **V-2**.

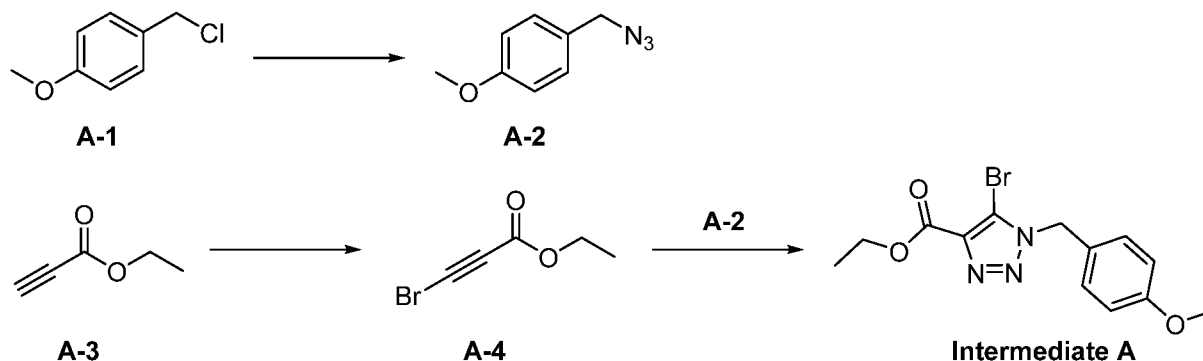
[00414] Compound **V-4** can be prepared using standard Suzuki-Miyaura coupling reaction conditions. More specifically, Compound **V-2** can be reacted with boronic acid Compound **V-3**, in a solvent such as toluene/EtOH/H₂O or toluene/H₂O, in the presence of a palladium salt such as Pd(PPh₃)₄ and a base such as Na₂CO₃ or K₃PO₄·7H₂O, to yield Intermediate **V-4**.

[00415] Compound **V** can be prepared using standard PMB (*p*-Methoxybenzyl) deprotection conditions. More specifically, Compound **V-4** can be treated in acidic conditions, such as in TFA (trifluoroacetic acid) as the solvent, at ambient temperature or up to 50 °C to afford Compound **V**.

[00416] General Scheme 6



[00417] Compounds of **Formula (I)** can be also prepared using General Scheme 6. Compounds **I**, **II**, **III**, **IV**, or **V** can be prepared using standard hydrolysis conditions. More specifically, Compounds **I**, **II**, **III**, **IV**, or **V**, respectively, can be treated in basic conditions, such as in the presence of NaOH or LiOH·H₂O in a solvent such as THF, at ambient temperature to afford the corresponding hydrolyzed Compound **I**, **II**, **III**, **IV**, or **V**, respectively.

[00418] Intermediate A**[00419] Synthesis of ethyl 5-bromo-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate**

[00420] To a solution of NaN₃ (25.0 g, 0.38 mol) in DMF (300 mL) was slowly added 1-(chloromethyl)-4-methoxybenzene (**A-1**) (49.7 mL, 0.37 mol) and stirred at 50 °C overnight. After cooling down to room temperature, the mixture was diluted with water (1000 mL) and extracted with ethyl acetate (500 mL x 3). The combined extracts were washed with water (500 mL x 4) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Intermediate **A-2**. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.82 (s, 3H), 4.27 (s, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H).

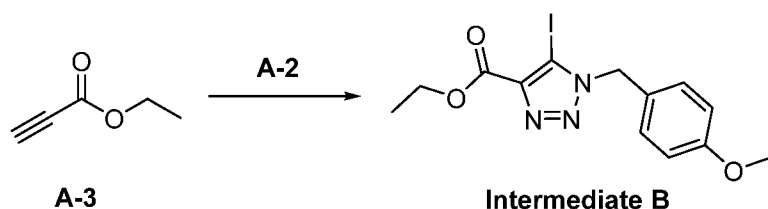
[00421] To a solution of ethyl propionate (**A-3**) (26.3 g, 0.268 mol) and AgNO₃ (4.56 g, 26.8 mmol) in anhydrous acetone (300 mL) was added NBS (52.6 g, 0.295 mol) in several small portions at 0 °C and stirred at room temperature overnight. The mixture was filtered. The filtrate was diluted with H₂O (500 mL) and extracted with n-hexane (500 mL x 3). The combined extracts were washed with an aqueous HCl solution (10%, 500 mL x 2) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure at room temperature (< 20 °C) to furnish Intermediate **A-4** as a white solid. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.32 (t, *J* = 7.2 Hz, 3H), 4.25 (q, *J* = 7.2 Hz, 2H).

[00422] A mixture of Intermediate **A-2** (23.0 g, 0.14 mol), Intermediate **A-4** (27.4 g, 0.155 mol), CuI (1.34 g, 7 mmol), and Cu(OAc)₂ (1.27 g, 7 mmol) in anhydrous THF (500 mL) was stirred at 50 °C for 16 hours. After cooling down to room temperature, the mixture was filtered,

the filtrate was concentrated under reduced pressure, and the residue was diluted with H₂O (500 mL) and extracted with dichloromethane (500 mL x 2). The combined extracts were washed with saturated aqueous NaHCO₃ solution (500 mL x 2) and brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a product. The product was slurred in petroleum ether (300 mL), filtered, and dried under vacuum to afford Intermediate A. LC-MS (ESI) m/z: 701 [2M+Na]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.42 (t, J = 7.2 Hz, 3H), 3.80 (s, 3H), 4.44 (q, J = 7.2 Hz, 2H), 5.55 (s, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H).

[00423] Intermediate B

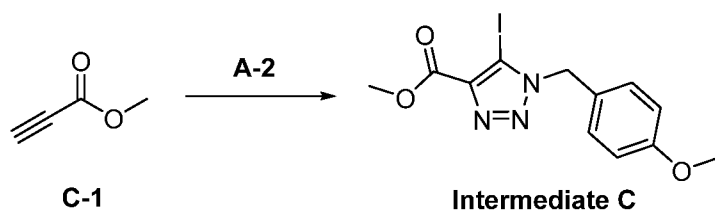
[00424] Synthesis of ethyl 5-iodo-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate



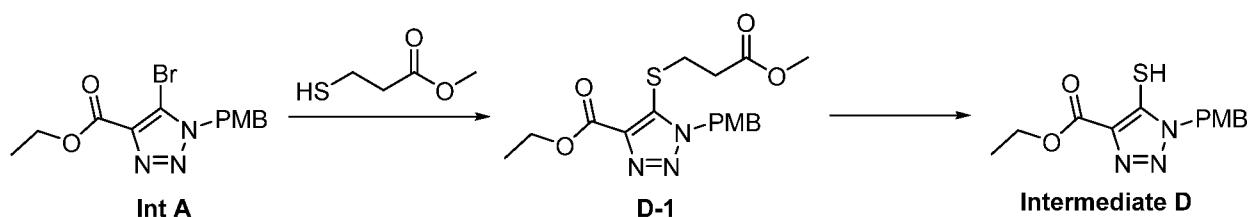
[00425] A mixture of Intermediate A-2 (840 mg, 5.1 mmol), ethyl propiolate (A-3) (402 mg, 5.1 mmol), CuI (970 mg, 5.1 mmol), NIS (908 mg, 5.1 mmol), and *N,N*-diisopropylethylamine (658 mg, 5.1 mmol) in THF (10 mL) was stirred at room temperature for 16 hours. The mixture was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 17% v/v) to afford Intermediate B. LC-MS (ESI) m/z: 388 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.43 (t, J = 6.8 Hz, 3H), 3.79 (s, 3H), 4.43 (q, J = 6.8 Hz, 2H), 5.60 (s, 2H), 6.86 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H).

[00426] Intermediate C

[00427] Synthesis of methyl 5-iodo-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate

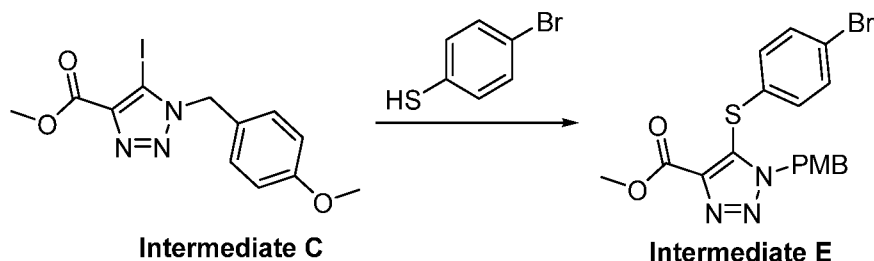


[00428] Intermediate C was synthesized by employing the procedure described for Intermediate B using Intermediate C-1 in lieu of Intermediate A-3, LC-MS (ESI) m/z: 374 [M+H]⁺.

[00429] Intermediate D**[00430] Synthesis of ethyl 5-mercapto-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate**

[00431] To a solution of Intermediate **A** (1 g, 2.9 mmol) and methyl 3-mercaptopropanoate (418 mg, 3.48 mmol) in 1,4-dioxane (8 mL) was added *N,N*-diisopropylethylamine (748 mg, 5.8 mmol), $\text{Pd}_2(\text{dba})_3$ (133 mg, 0.145 mmol), and Xantphos (168 mg, 0.29 mmol). The mixture was purged with nitrogen for 2 minutes and heated in a microwave oven at 120 °C for 30 minutes. The reaction mixture was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0% to 60% v/v) to yield Intermediate **D-1**. LC-MS (ESI) *m/z*: 380 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.42 (t, $J = 7.2$ Hz, 3H), 2.43 (t, $J = 7.2$ Hz, 2H), 3.17 (t, $J = 6.8$ Hz, 2H), 3.65 (s, 3H), 3.77 (s, 3H), 4.34 (q, $J = 7.2$ Hz, 2H), 5.59 (s, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 8.8$ Hz, 2H).

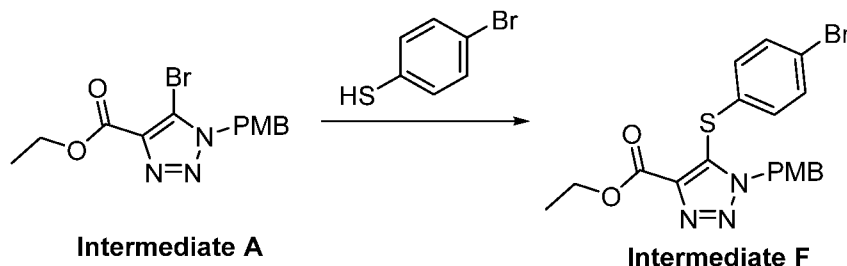
[00432] To a solution of Intermediate **D-1** (0.8 g, 2.1 mmol) in dry THF (10 mL) was added potassium *tert*-butoxide (235 mg, 2.1 mmol) at -78 °C. The mixture was stirred at -78 °C under nitrogen for 30 minutes. After slowly warming to room temperature, the mixture was diluted with water (4 mL), acidified to pH 6 with a concentrated HCl solution, and concentrated under reduced pressure. The residue was purified with reverse phase chromatography using eluents (methanol in H_2O , from 0% to 60% v/v) to afford Intermediate **D**. LC-MS (ESI) *m/z*: 294 $[\text{M}+\text{H}]^+$.

[00433] Intermediate E**[00434] Synthesis of methyl 5-((4-bromophenyl)thio)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate**

[00435] Intermediate **E** was synthesized by employing the procedure described for Compound **1E** using 4-bromobenzenethiol and Intermediate **C** in lieu of Compound **1D** and Intermediate **B**, LC-MS (ESI) m/z : 434 $[M+H]^+$.

[00436] Intermediate **F**

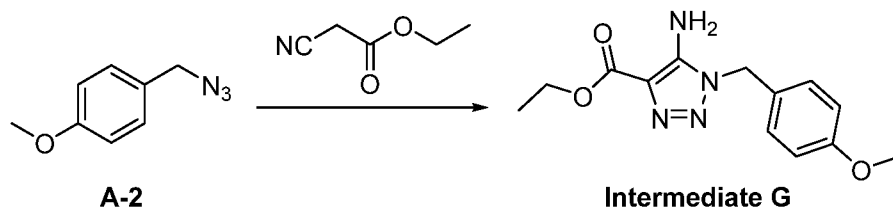
[00437] Synthesis of ethyl 5-((4-bromophenyl)thio)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate



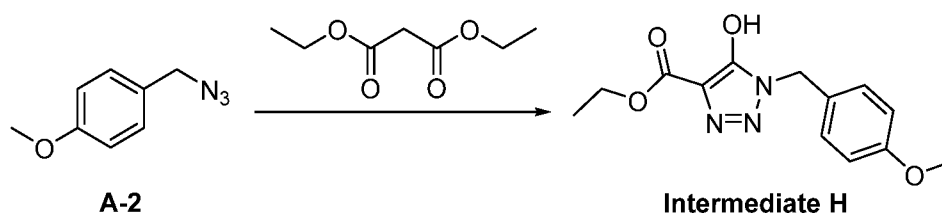
[00438] Intermediate **F** was synthesized by employing the procedure described for Compound **1E** using 4-bromobenzenethiol and Intermediate **A** in lieu of Compound **1D** and Intermediate **B**, LC-MS (ESI) m/z : 448 $[M+H]^+$.

[00439] Intermediate **G**

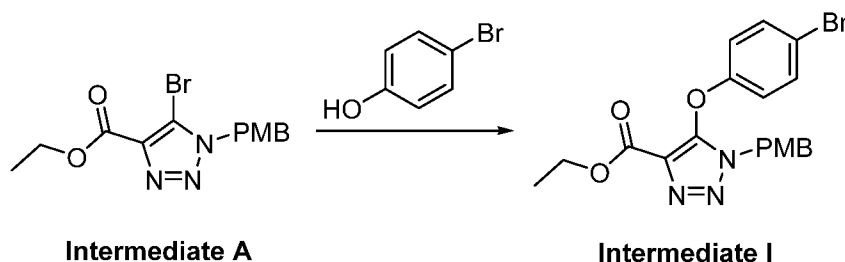
[00440] Synthesis of ethyl 5-amino-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate



[00441] A mixture of ethyl 2-cyanoacetate (2.4 mL, 22.3 mmol), Intermediate **A-2** (3.64 g, 22.3 mmol), and EtONa (1.5 g, 22.3 mmol) in EtOH (50 mL) was stirred at 80 °C for 5.5 hours. The mixture was concentrated under reduced pressure. The residue was diluted with water (300 mL) and filtered. The cake was washed with water (100 mL x 2) and slurred in petroleum ether (20 mL) for 15 minutes. The resulting solid was collected and dried under vacuum to afford Intermediate **G**. LC-MS (ESI) m/z : 277 $[M+H]^+$; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.27 (t, J = 7.2 Hz, 3H), 3.72 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 5.35 (s, 2H), 6.57 (s, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H).

[00442] Intermediate H**[00443] Synthesis of ethyl 5-hydroxy-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate**

[00444] To anhydrous EtOH (45 mL) at room temperature was added sodium (600 mg, 26 mmol) in small pieces and stirred at room temperature until sodium was dissolved. To the solution was added diethyl malonate (2.08 g, 1.98 mL, 13 mmol) and stirred at room temperature for 30 minutes. To the mixture was dropped a solution of Intermediate **A-2** (2.12 g, 13 mmol) in EtOH (5 mL) and heated at reflux for 18 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was diluted with H₂O (100 mL) and washed with ethyl acetate (50 mL x 2). The aqueous layer was adjusted to pH 3-4 with a diluted HCl solution (2 N) and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to afford Intermediate **H**. LC-MS (ESI) *m/z*: 278 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.40 (t, *J* = 7.2 Hz, 3H), 3.79 (s, 3H), 4.42 (q, *J* = 7.2 Hz, 2H), 5.31 (s, 2H), 6.85-6.88 (m, 2H), 7.29-7.31 (m, 2H).

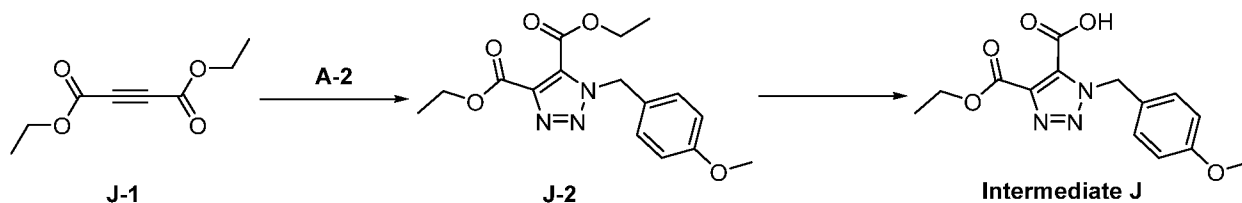
[00445] Intermediate I**[00446] Synthesis of ethyl 5-(4-bromophenoxy)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate**

[00447] A mixture of 4-bromophenol (610 mg, 3.53 mmol), Intermediate **A** (1 g, 2.94 mmol), and K₂CO₃ (608 mg, 4.41 mmol) in DMF (20 mL) was stirred at 90 °C for 4 hours. The reaction mixture was cooled down to room temperature, diluted with water (50 mL), and extracted with EtOAc (50 mL x 3). The combined extracts were washed with water (100 mL),

dried over anhydrous Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 40% v/v) to afford Intermediate I LC-MS (ESI) m/z : 432 $[\text{M}+\text{H}]^+$.

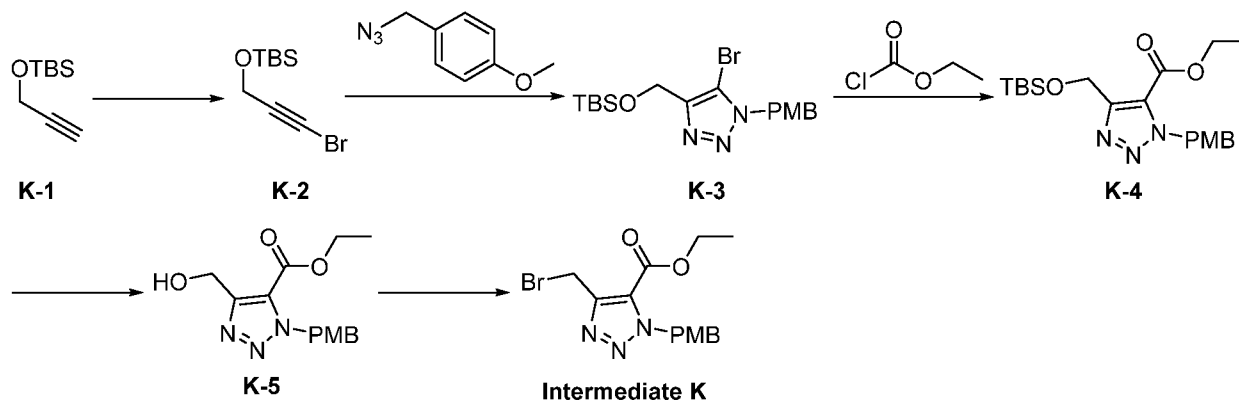
[00448] Intermediate J

[00449] Synthesis of a mixture of 4-(ethoxycarbonyl)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-5-carboxylic acid and 5-(ethoxycarbonyl)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylic acid



[00450] A mixture of Intermediate J-1, diethyl but-2-ynedioate, (1.0 g, 5.9 mmol), CuI (2.25 g, 11.8 mmol), and Intermediate A-2 (963 mg, 5.9 mmol) in DMSO (20 mL) was stirred at room temperature under nitrogen overnight. The mixture was diluted with EtOAc (50 mL), washed with brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Intermediate J-2. LC-MS (ESI) m/z : 334 $[\text{M}+\text{H}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 1.31 (t, $J = 7.2$ Hz, 3H), 1.60 (t, $J = 7.2$ Hz, 3H), 3.79 (s, 3H), 4.33 (q, $J = 7.2$ Hz, 2H), 4.42 (q, $J = 7.2$ Hz, 2H), 5.73 (s, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H).

[00451] A mixture of Intermediate J-2 (5 g, 15 mmol) and potassium hydroxide (840 mg, 15 mmol) in water (25 mL) and EtOH (25 mL) was stirred at room temperature for 16 hours. The mixture was adjusted to pH 6 with a diluted aqueous HCl solution (1 N) and a solid was precipitated. The solid was collected by filtration and dried under vacuum to give Intermediate J. LC-MS (ESI) m/z : 328 $[\text{M}+\text{Na}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 1.49 (t, $J = 7.2$ Hz, 3H), 3.76 (s, 3H), 4.57-4.59 (m, 2H), 6.00 (s, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H).

[00452] Intermediate K

[00453] Intermediates **K-2** and **K-3** were synthesized by employing the procedures described for Intermediates **A-4** and **A** using Intermediates **K-1** and **K-2** in lieu of Intermediates **A-3** and **A-4**. Intermediate **K-2**: LC-MS (m/z): Non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.05 (s, 6H), 0.84 (s, 9H), 4.27 (s, 2H). Intermediate **K-3**: LC-MS (m/z): 412 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 0.09 (s, 6H), 0.89 (s, 9H), 3.79 (s, 3H), 4.74 (s, 2H), 5.47 (s, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.8$ Hz, 2H).

[00454] To a solution of Intermediate **K-3** (14.02 g, 33.4 mmol) in dry THF (250 mL) at -78°C under nitrogen was dropped a solution of *n*-BuLi in *n*-hexane (2.5 *N*, 15 mL, 37.4 mmol) and stirred at -78°C for 0.5 hour, followed by addition of ethyl carbonochloridate (11 mL, 112.2 mmol). The mixture was stirred at -78°C for 0.5 hour, quenched with saturated aqueous NH_4Cl solution (150 mL), and extracted with ethyl acetate (250 mL x 2). The combined organic layers was washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Intermediate **K-4**. LC-MS (m/z): 406 $[\text{M}+\text{H}]^+$.

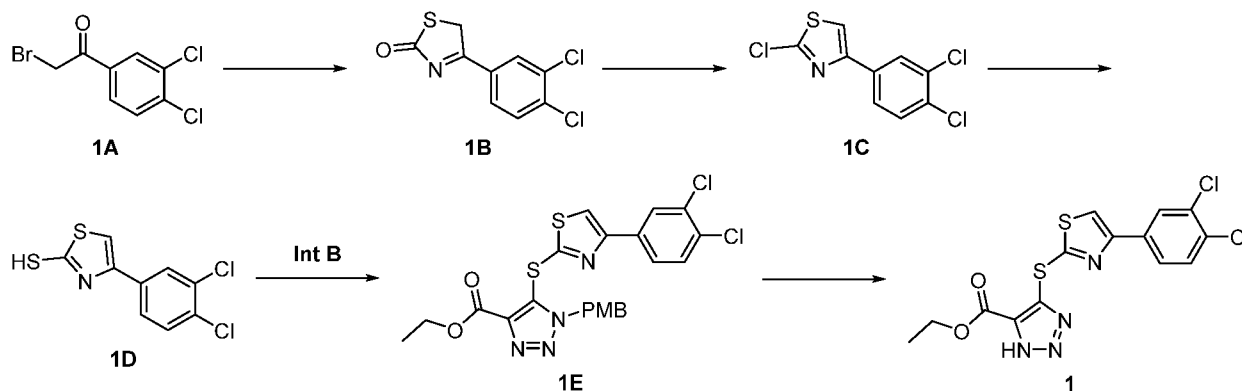
[00455] To a solution of Intermediate **K-4** (13.5 g, 33.4 mmol) in dry THF (20 mL) was dropped a solution of Bu_4NF in THF (1 *N*, 16.7 mL, 16.7 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 50% v/v) to give Intermediate **K-5**. LC-MS (m/z): 292 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ (ppm) 1.38 (t, $J = 7.0$ Hz, 3H), 3.78 (s, 3H), 4.39 (q, $J = 7.0$ Hz, 2H), 4.91 (s, 2H), 5.82 (s, 2H), 6.84 (d, $J = 9.0$ Hz, 2H), 7.26 (d, $J = 9.0$ Hz, 2H).

[00456] To a solution of Intermediate **K-5** (1.0 g, 3.44 mmol) in THF (40 mL) was added PBr_3 (1.38 g, 5.16 mmol). The mixture was stirred at room temperature for 4 hours, quenched with water (10 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers

was washed with water (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Intermediate **K**. LC-MS (ESI) m/z : 354 $[M+H]^+$.

[00457] Example 1

[00458] Synthesis of ethyl 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (1)



[00459] A mixture of 2-bromo-1-(3,4-dichlorophenyl)ethanone (Compound **1A**) (1.5 g, 5.6 mmol) and carbamodithioic acid ammonia salt (677 mg, 6.1 mmol) in EtOH (5 mL) was stirred at 60 °C for 10 minutes. The reaction mixture was concentrated. The residue was washed with water (20 mL) and dried under vacuum to give Compound **1B**. LC-MS (ESI) m/z : 246 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 4.66 (s, 2H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.75-7.78 (m, 1H), 8.03 (d, $J = 2.0$ Hz, 1H).

[00460] A mixture of Compound **1B** (1150 mg, 4.7 mmol) and POCl_3 (5 mL) was stirred at 100 °C for 1 hour. The mixture was concentrated to give Compound **1C**. LC-MS (ESI) m/z : 264 $[M+H]^+$.

[00461] A mixture of Compound **1C** (1.2 g, 4.5 mmol) and thiourea (686 mg, 9.0 mmol) in EtOH (10 mL) was stirred at 80 °C for 16 hours. After cooling down to room temperature, the mixture was diluted with water (60 mL) and filtered. The cake was dried under vacuum to afford Compound **1D**. LC-MS (ESI) m/z : 262 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.63 (s, 1H), 7.69-7.78 (m, 2H), 8.11 (s, 1H), 13.75 (brs, 1H).

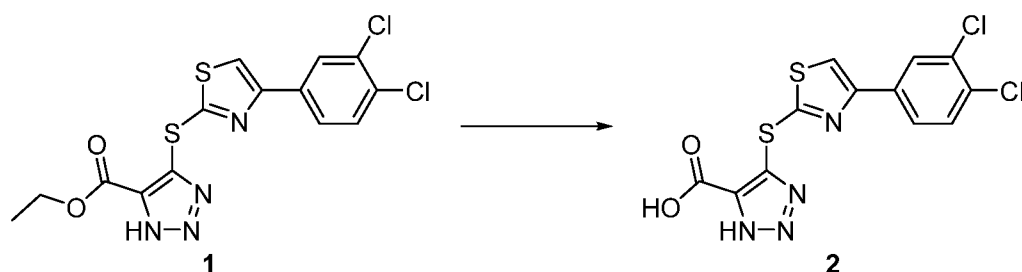
[00462] A mixture of Compound **1D** (300 mg, 0.77 mmol), Intermediate **B** (407 mg, 1.55 mmol), and K_2CO_3 (214 mg, 1.55 mmol) or Na_2CO_3 in DMF (5 mL) was stirred at 50 °C for 16 hours. The mixture was concentrated and purified with flash column chromatography on silica

gel (ethyl acetate in petroleum ether, 17% v/v) to afford Compound **1E**. LC-MS (ESI) m/z : 521 $[M+H]^+$.

[00463] A mixture of Compound **1E** (300 mg, 0.58 mmol) in TFA (5 mL) was stirred at 50 °C for 16 hours. The mixture was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to afford Compound **1**. LC-MS (ESI) m/z : 401 $[M+H]^+$.

[00464] **Example 2**

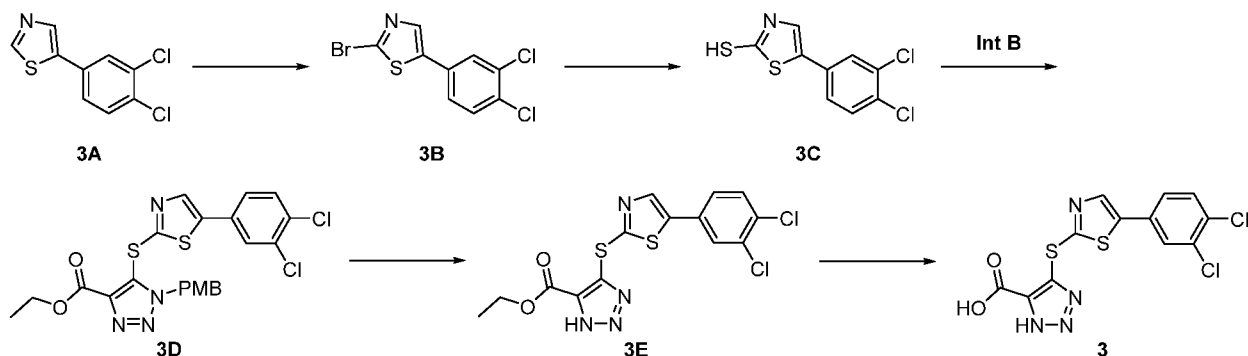
[00465] **Synthesis of 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (2)**



[00466] A mixture of Compound **1** (100 mg, 0.25 mmol) and NaOH (100 mg, 2.5 mmol) in THF (20 mL) and H₂O (2 mL) was stirred at room temperature for 16 hours. The mixture was concentrated and the residue was purified with preparative HPLC to afford Compound **2**. LC-MS (ESI) m/z : 373 $[M+H]^+$. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.14 (brs, 2H), 7.68-7.71 (m, 1H), 7.89-7.92 (m, 1H), 8.15-8.18 (m, 2H).

[00467] **Example 3**

[00468] **Synthesis of 4-((5-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (3)**



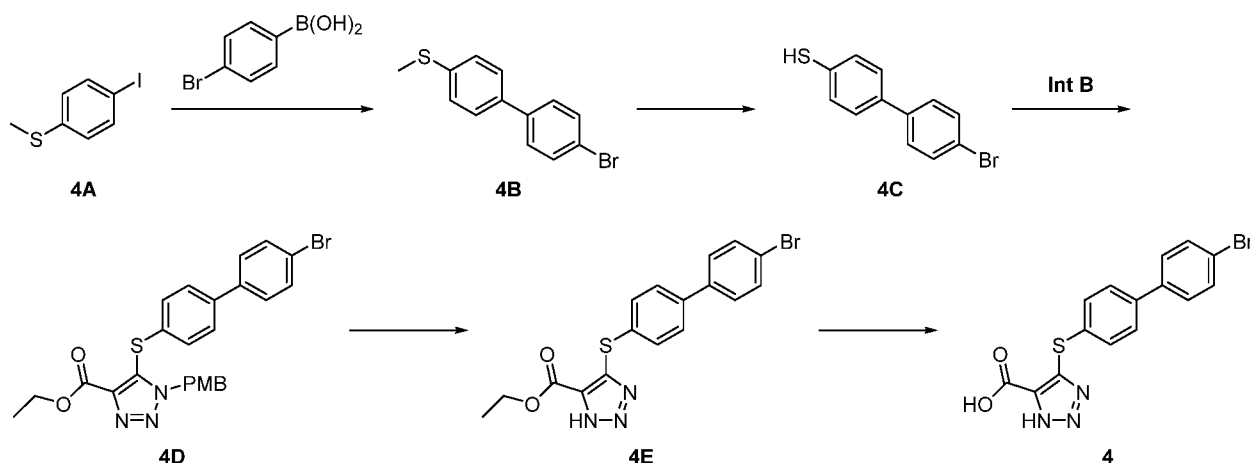
[00469] To a solution of 5-(3,4-dichlorophenyl)thiazole (Compound **3A**) (2.3 g, 10 mmol) in anhydrous THF (20 mL) was dropped *n*-BuLi solution (2.5 *M* in *n*-hexane, 12 mL, 30 mmol)

at -78 °C under nitrogen. After stirring at -78 °C for 30 minutes, to the mixture was added Br₂ (3.2 g, 20 mmol) and stirred at -78 °C for 30 minutes. The reaction mixture was quenched with water (2 mL), concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 17% v/v) to give Compound **3B**. LC-MS (ESI) m/z: 308 [M+H]⁺.

[00470] Compounds **3C**, **3D**, **3E**, and **3** were synthesized by employing the procedures described for Compounds **1D**, **1E**, **1**, and **2** using Compounds **3B**, **3C**, **3D**, and **3E** in lieu of Compounds **1C**, **1D**, **1E**, and **1**. Compound **3C**: LC-MS (ESI) m/z: 262 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.43-7.46 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.99 (s, 1H), 13.50 (brs, 1H). Compound **3D**: LC-MS (ESI) m/z: 521 [M+H]⁺. Compound **3E**: LC-MS (ESI) m/z: 401 [M+H]⁺. Compound **3**: LC-MS (ESI) m/z: 373 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.13 (brs, 2H), 7.51-7.55 (m, 1H), 7.62-7.64 (m, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 8.20 (s, 1H).

[00471] **Reference Example 4**

[00472] **Synthesis of 4-((4'-bromo-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (4)**



[00473] A mixture of (4-iodophenyl)(methyl)sulfane (Compound **4A**) (500 mg, 2 mmol), 4-bromophenylboronic acid (400 mg, 2 mmol), Na₂CO₃ (636 mg, 6 mmol), and Pd(PPh₃)₄ (115 mg, 0.1 mmol) in toluene/EtOH/H₂O (20/10/4 mL) was stirred at 80 °C under nitrogen overnight. The mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **4B**. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. ¹H-

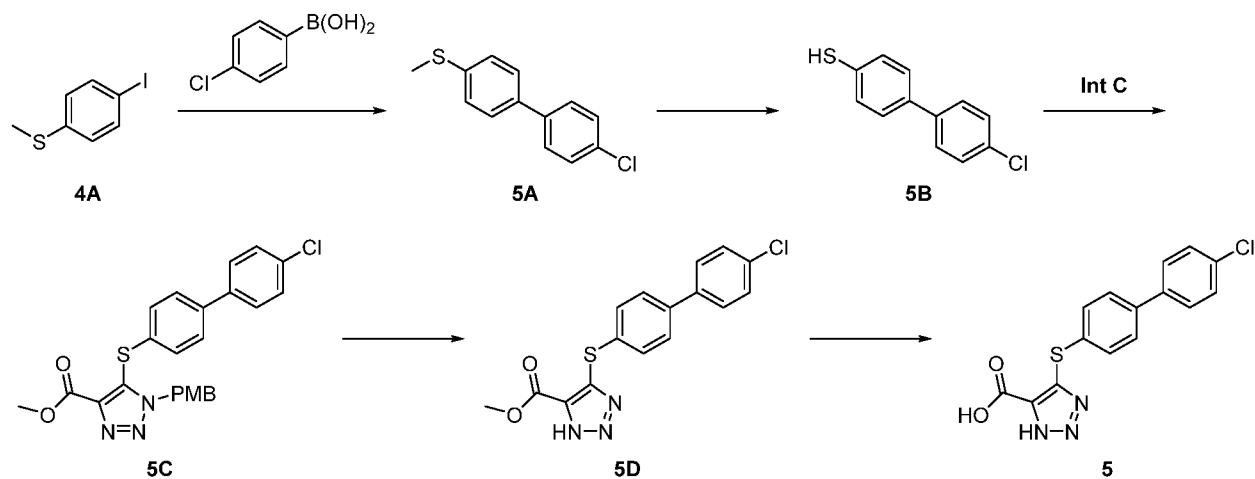
NMR (CDCl₃, 500 MHz): δ (ppm) 2.52 (s, 3H), 7.32 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H).

[00474] To a solution of Compound **4B** (278 mg, 1 mmol) in dichloromethane (10 mL) was added *m*-CPBA (258 mg, 1.5 mmol) at 0 °C. After the mixture was stirred at room temperature for 30 minutes, Ca(OH)₂ (238 mg, 1.7 mmol) was added. The mixture was stirred at room temperature for 5 minutes and filtered. To the filtrate was added trifluoroacetoanhydride (440 mg, 2.1 mmol) and heated at reflux for 1 hour. The mixture was evaporated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **4C**. LC-MS (ESI) m/z : 263 [M-H]⁻; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 5.64 (s, 1H), 7.41-7.55 (m, 8H).

[00475] Compounds **4D**, **4E**, and **4** were synthesized by employing the procedures described for Compounds **1E**, **1**, and **2** using Compounds **4C**, **4D**, and **4E** in lieu of Compounds **1D**, **1E**, and **1**. Compound **4D**: LC-MS (ESI) m/z : 524 [M+H]⁺. Compound **4E**: LC-MS (ESI) m/z : 404 [M+H]⁺. Compound **4**: LC-MS (ESI) m/z : 376 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 7.18-7.50 (m, 2H), 7.56-7.60 (m, 6H).

[00476] Example 5

[00477] Synthesis of 4-((4'-chloro-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (5**)**

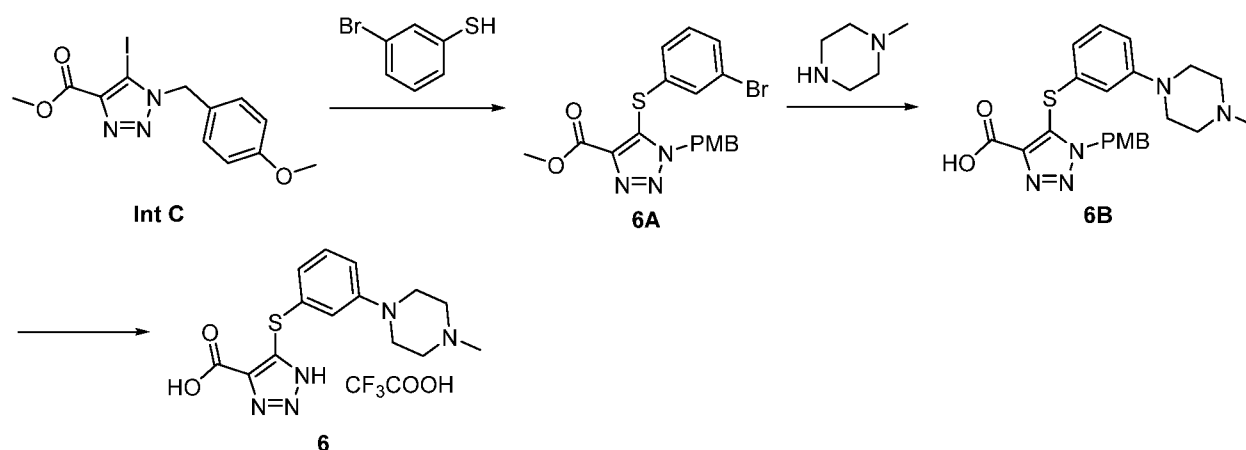


[00478] Compounds **5A**, **5B**, **5C**, **5D**, and **5** were synthesized by employing the procedures described for Compounds **4B**, **4C**, **1E**, **1**, and **2** using 4-chlorophenylboronic acid, Compounds **5A**, **5B**, Intermediate C, **5C**, and **5D** in lieu of 4-bromophenylboronic acid, Compounds **4B**, **1D**, Intermediate B, **1E**, and **1**. Compound **5A**: LC-MS (ESI) m/z : non-ionizable

compound under routine conditions used. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.52 (s, 3H), 7.31-7.33 (m, 2H), 7.38-7.40 (m, 2H), 7.47-7.50 (m, 4H). Compound **5B**: LC-MS (ESI) m/z : 219 $[\text{M-H}]^-$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 500 MHz): δ (ppm) 5.96 (s, 1H), 7.58-7.73 (m, 8H). Compound **5C**: LC-MS (ESI) m/z : 466 $[\text{M+H}]^+$. Compound **5D**: LC-MS (ESI) m/z : 346 $[\text{M+H}]^+$. Compound **5**: LC-MS (ESI) m/z : 332 $[\text{M+H}]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 7.42-7.48 (m, 4H), 7.56-7.62 (m, 4H).

[00479] Example 6

[00480] Synthesis of 5-((3-(4-methylpiperazin-1-yl)phenyl)thio)-1H-1,2,3-triazole-4-carboxylic acid 2,2,2-trifluoroacetate (6**)**



[00481] Compound **6A** was synthesized by employing the procedure described for Compound **1E** using 3-bromobenzenethiol and Intermediate **C** in lieu of Compound **1D** and Intermediate **B**, LC-MS (ESI) m/z : 434 $[\text{M+H}]^+$.

[00482] To a solution of Compound **6A** (138 mg, 0.32 mmol) in toluene (4 mL) was added N-methylpiperazine (160 mg, 1.6 mmol), $t\text{-BuONa}$ (61 mg, 0.64 mmol), $\text{Pd}_2(\text{dba})_3$ (29 mg, 0.032 mmol), and Xantphos (37 mg, 0.064 mmol) and heated in a microwave oven at 120 °C for 2 hours. The mixture was concentrated and purified by reverse phase column chromatography to afford Compound **6B**. LC-MS (ESI) m/z : 440 $[\text{M+H}]^+$.

[00483] Compound **6** was synthesized by employing the procedure described for Compound **1** using Compound **6B** in lieu of Compound **1E**, LC-MS (ESI) m/z : 320 $[\text{M+H}]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.85 (s, 3H), 3.00-3.20 (br, 2H), 3.24-3.95 (br, 6H), 6.92-6.94 (m, 2H), 7.07 (s, 1H), 7.17-7.21 (m, 1H).

[00484] Example 7

[00489] A mixture of 2,4-dibromothiazole (Compound **8A**) (3.9 g, 16 mmol), 3,4-dichlorophenylboronic acid (3.05 g, 16 mol), Pd(dppf)Cl₂ (0.7 g, 0.87 mmol), and cesium carbonate (15 g, 46 mmol) in DME (120 mL) and water (10 mL) was heated at reflux under nitrogen overnight. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (200 mL x 2). The combined extracts were washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to yield Compound **8B**. LC-MS (ESI) m/z: 308 [M+H]⁺.

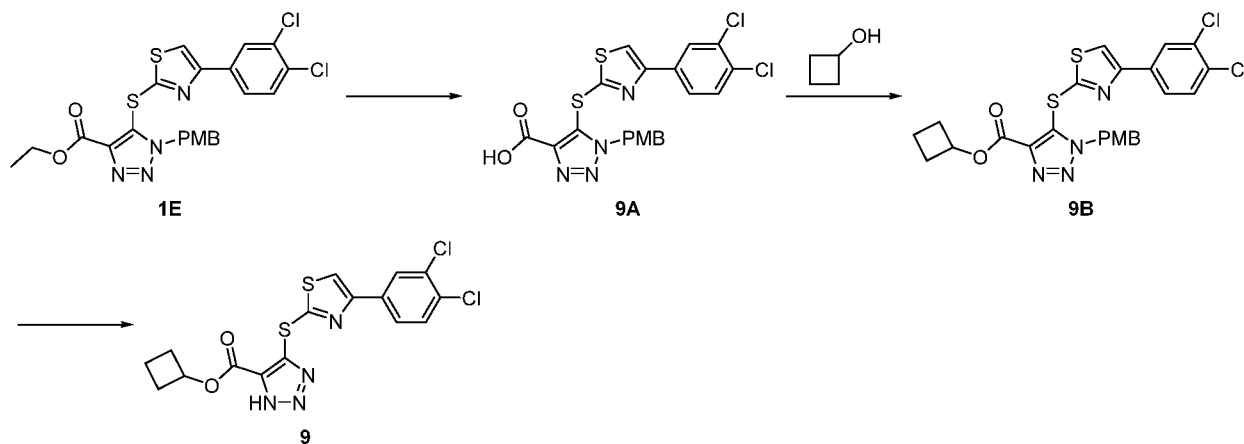
[00490] Compounds **8C**, **8D**, and **8E** were synthesized by employing the procedures described for Intermediates **D-1**, **D**, and Compound **1E** using Compounds **8B**, **8C**, and **8D** in lieu of Intermediates **A**, **D-1**, and Compound **1D**. Compound **8C**: LC-MS (ESI) m/z: 348 [M+H]⁺. Compound **8D**: LC-MS (ESI) m/z: 262 [M+H]⁺. Compound **8E**: LC-MS (ESI) m/z: 521 [M+H]⁺.

[00491] To a solution of Compound **8E** (220 mg, 0.42 mmol) in THF (40 mL) and water (8 mL) was added LiOH·H₂O (110 mg, 2.62 mmol). The mixture was stirred at room temperature for 2 hours and concentrated to furnish Compound **8F**, which was used directly for next step without further purification. LC-MS (ESI) m/z: 493.

[00492] Compound **8** was synthesized by employing the procedure described for Compound **1** using Compound **8F** in lieu of Compound **1E**, LC-MS (ESI) m/z: 373 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.65 (d, *J* = 8.4 Hz, 1H), 7.85-7.88(m, 2H), 8.13 (d, *J* = 2.0 Hz, 1H).

[00493] Example 9

[00494] Synthesis of cyclobutyl 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (**9**)



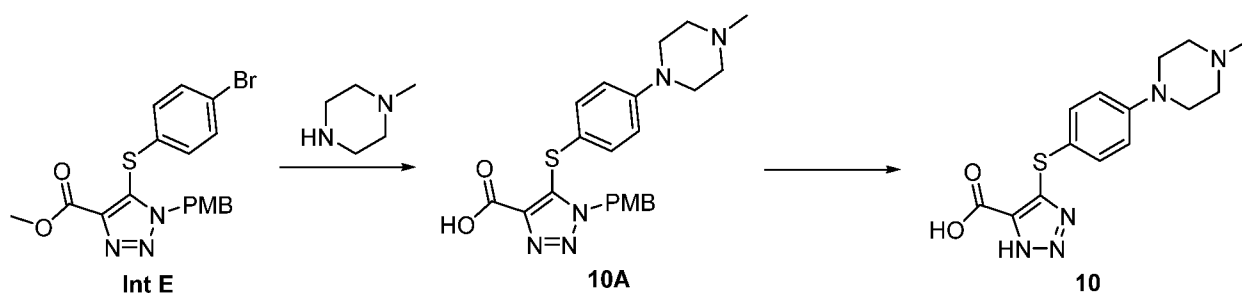
[00495] Compound **9A** was synthesized by employing the procedure described for Compound **2** using Compound **1E** in lieu of Compound **1**, LC-MS (ESI) m/z : 493 $[M+H]^+$.

[00496] A mixture of Compound **9A** (200 mg, 0.4 mmol), cyclobutanol (86 mg, 1.2 mmol), and HBTU (456 mg, 1.2 mmol) in dichloromethane (10 mL) was stirred at room temperature for 16 hours. The mixture was evaporated under reduced pressure and the residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **9B**. LC-MS (ESI) m/z : 547 $[M+H]^+$.

[00497] Compound **9** was synthesized by employing the procedure described for Compound **1** using Compound **9B** in lieu of Compound **1E**, LC-MS (ESI) m/z : 427 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 1.59-1.73 (m, 2H), 1.99-2.05 (m, 2H), 2.26-2.33 (m, 2H), 5.03-5.07 (m, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.89-7.92 (m, 1H), 8.15 (d, $J = 2.0$ Hz, 1H), 8.24 (s, 1H).

[00498] **Example 10**

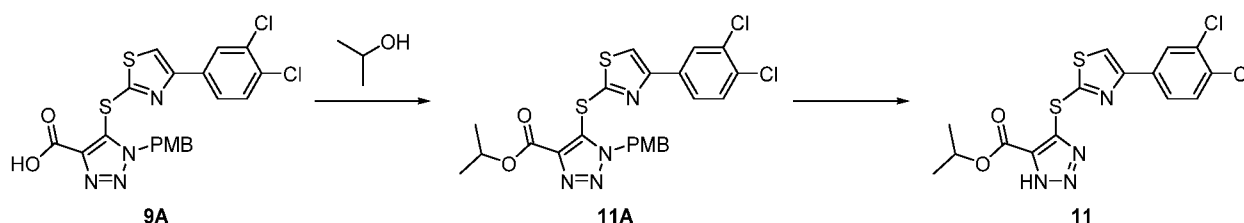
[00499] **Synthesis of 4-((4-(4-methylpiperazin-1-yl)phenyl)thio)-1H-1,2,3-triazole-5-carboxylic acid (10)**



[00500] Compounds **10A** and **10** were synthesized by employing the procedures described for Compounds **6B** and **1** using N-methylpiperazine, Intermediate **E**, and Compound **10A** in lieu of 1-methylpiperazine, Compounds **6A**, and **1E**. Compound **10A**: LC-MS (ESI) m/z : 440 $[M+H]^+$. Compound **10**: LC-MS (ESI) m/z : 320 $[M+H]^+$; $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ (ppm) 2.27 (s, 3H), 2.48-2.50 (m, 4H), 3.17-3.19 (m, 4H), 6.92 (d, $J=8.8$ Hz, 2H), 7.31 (d, $J=8.8$ Hz, 2H).

[00501] **Example 11**

[00502] **Synthesis of isopropyl 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (11)**

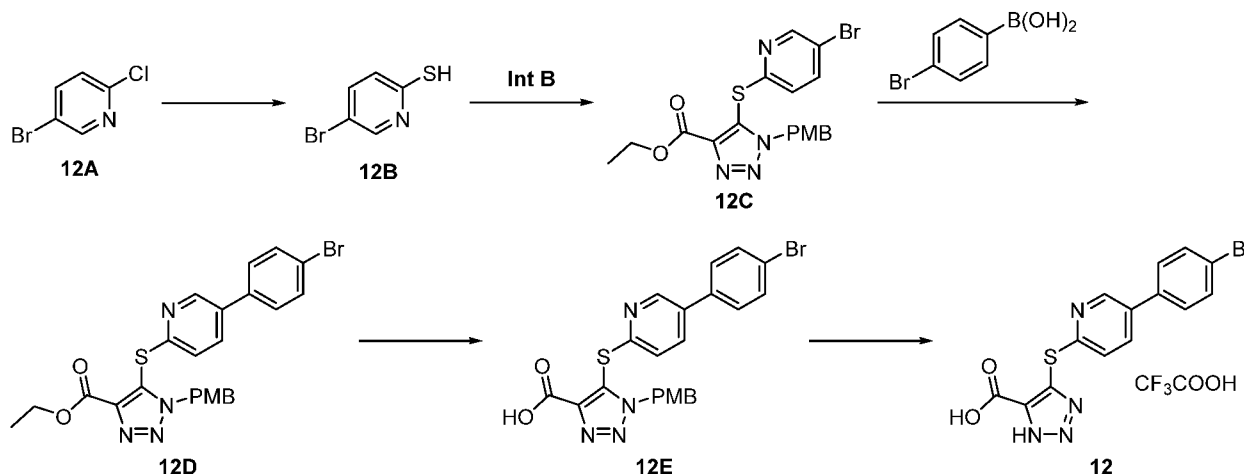


[00503] A mixture of Compound **9A** (400 mg, 0.8 mmol) and SOCl_2 (960 mg, 8.0 mmol) in propan-2-ol (5 mL) was stirred at 60 °C for 16 hours. The mixture was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **11A**. LC-MS (ESI) m/z : 535 $[\text{M}+\text{H}]^+$.

[00504] Compound **11** was synthesized by employing the procedure described for Compound **1** using Compound **11A** in lieu of Compound **1E**, LC-MS (ESI) m/z : 415 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 500 MHz): δ (ppm) 1.18 (d, J = 6.0 Hz, 6H), 4.97-5.00 (m, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.89-7.91 (m, 1H), 8.09 (s, 1H), 8.14 (d, J = 2.0 Hz, 1H).

[00505] Example 12

[00506] Synthesis of 4-((5-(4-bromophenyl)pyridin-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (12**)**



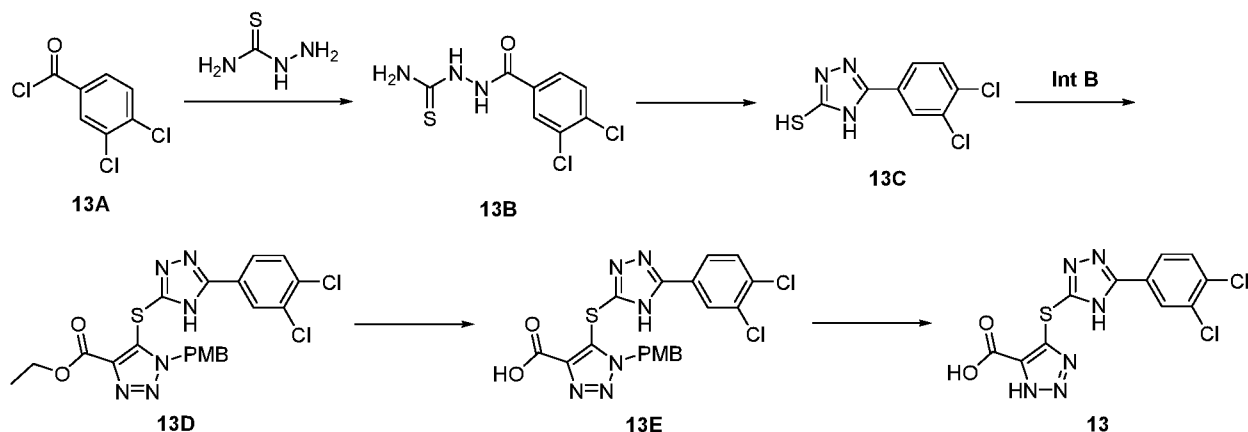
[00507] To a solution of Compound **12A** (1.92 g, 10 mmol) in DMF (20 mL) was added NaHS (560 mg, 10.0 mmol). The reaction mixture was stirred at 70 °C under nitrogen for 14 hours. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **12B**. LC-MS (ESI) m/z : 190 $[\text{M}+\text{H}]^+$.

[00508] Compounds **12C**, **12D**, **12E**, and **12** were synthesized by employing the procedures described for Compounds **1E**, **4B**, **8F**, and **1** using Compounds **12B**, **12C**, **12D**, and

12E in lieu of Compounds **1D**, **4A**, **8E**, and **1E**. Compound **12C**: LC-MS (ESI) m/z : 449 $[M+H]^+$. Compound **12D**: LC-MS (ESI) m/z : 525 $[M+H]^+$. Compound **12E**: LC-MS (ESI) m/z : 497 $[M+H]^+$. Compound **12**: LC-MS (ESI) m/z : 377 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 7.36 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.97 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 8.66 (d, $J = 2.0$ Hz, 1H).

[00509] Example 13

[00510] Synthesis of 4-((5-(3,4-dichlorophenyl)-4H-1,2,4-triazol-3-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (13**)**



[00511] A mixture of 3,4-dichlorobenzoyl chloride (Compound **13A**) (832 mg, 4 mmol) and hydrazinecarbothioamide (910 mg, 10 mmol) in THF (50 mL) was stirred at room temperature overnight. The mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **13B**. LC-MS (ESI) m/z : 264 $[M+H]^+$.

[00512] To a mixture of Compound **13B** (526 mg, 2 mmol) in ethanol (10 mL) was added aqueous NaOH solution (4 N, 10 mL). The mixture was stirred at 80 °C overnight. The mixture was adjusted to pH 4 with acetic acid (20 mL) and a solid was precipitated. The resulting solid was filtered and dried under vacuum to afford Compound **13C**. LC-MS (ESI) m/z : 246 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.79-7.89 (m, 2H), 8.14-8.15 (m, 1H), 13.84 (brs, 1H).

[00513] A mixture of Compound **13C** (369 mg, 1.5 mmol), Intermediate **B** (388 mg, 1 mmol), $t\text{-BuONa}$ (144 mg, 1.5 mmol), 2,9-dimethyl-1,10-phenanthroline (21 mg, 0.1 mmol), and CuI (20 mg, 0.1 mmol) in DMF (20 mL) was stirred at 110 °C under nitrogen overnight. The mixture was concentrated under reduced pressure. The residue was purified with flash column

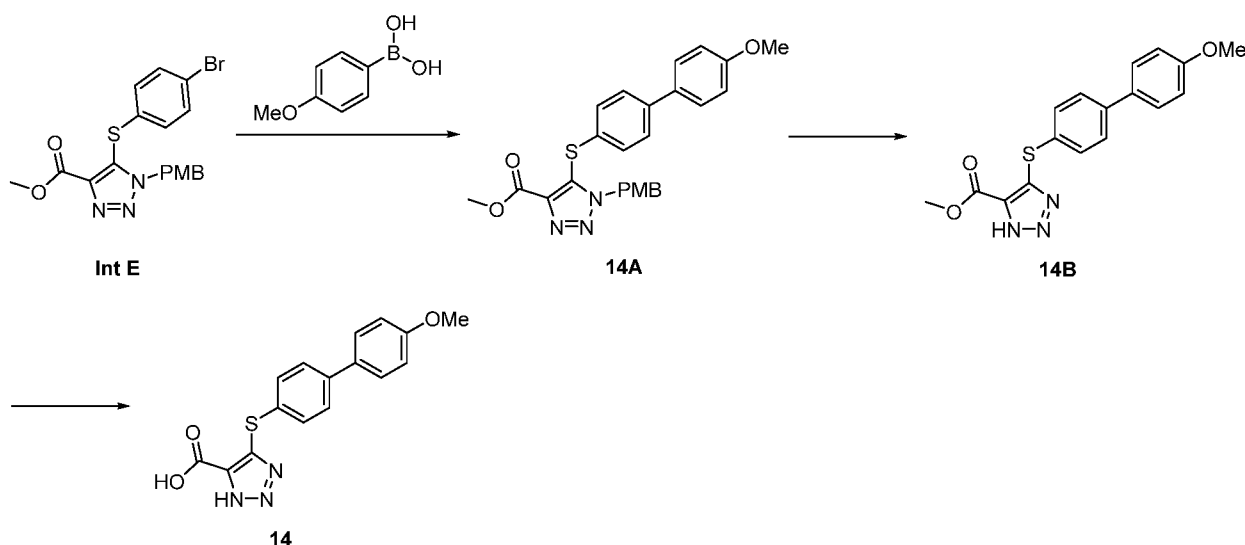
chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **13D**. LC-MS (ESI) m/z : 505 $[M+H]^+$.

[00514] Compounds **13E** and **13** were synthesized by employing the procedures described for Compounds **2** and **1** using Compounds **13D** and **13E** in lieu of Compounds **1** and **1E**.

Compound **13E**: LC-MS (ESI) m/z : 477 $[M+H]^+$. Compound **13**: LC-MS (ESI) m/z : 357 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 7.66 (d, $J = 8.8$ Hz, 1H), 7.91 (dd, $J = 8.8$, 2.0 Hz, 1H), 8.15 (d, $J = 2.0$ Hz, 1H).

[00515] Example 14

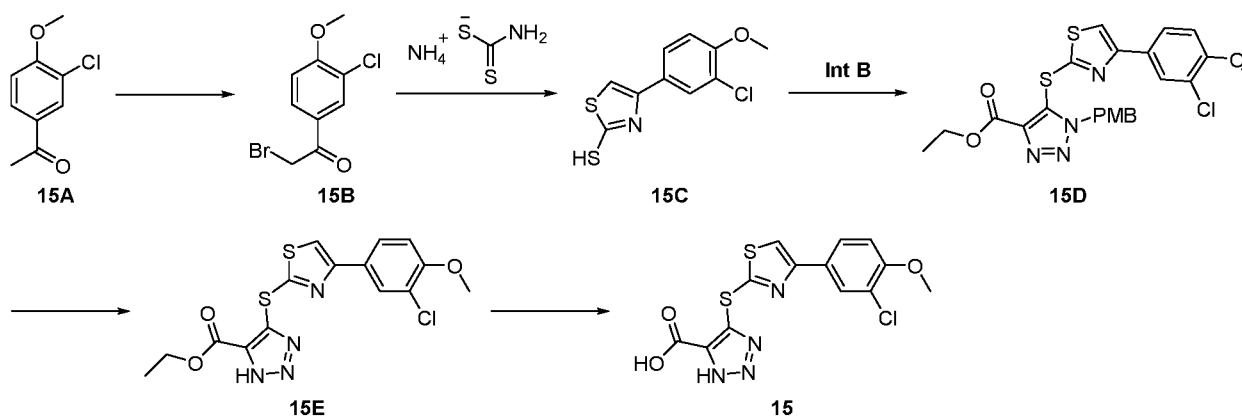
[00516] Synthesis of 4-((4'-methoxy-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (14)



[00517] Compounds **14A**, **14B**, and **14** were synthesized by employing the procedures described for Compounds **4B**, **1**, and **8F** using 4-methoxyphenylboronic acid, Intermediate **E**, Compounds **14A**, and **14B** in lieu of (4-bromophenyl)boronic acid, Compounds **4A**, **1E**, and **8E**. Compound **14A**: LC-MS (ESI) m/z : 462 $[M+H]^+$. Compound **14B**: LC-MS (ESI) m/z : 342 $[M+H]^+$. Compound **14**: LC-MS (ESI) m/z : 328 $[M+H]^+$. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 3.80 (s, 3H), 7.01-7.06 (m, 2H), 7.48-7.52 (m, 2H), 7.61-7.66 (m, 4H).

[00518] Example 15

[00519] Synthesis of 4-((4-(3-chloro-4-methoxyphenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (15)



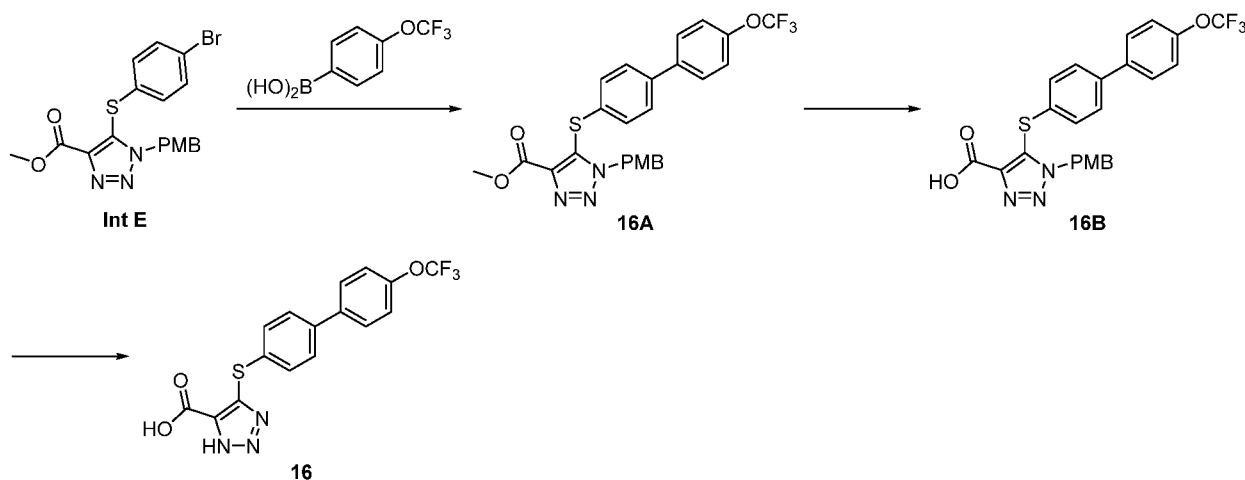
[00520] To a solution of 1-(3-chloro-4-methoxyphenyl)ethanone (Compound **15A**) (500 mg, 2.7 mmol) and *N*-bromosuccinimide (482 mg, 2.7 mmol) in acetonitrile (10 mL) was added trimethylsilyl trifluoromethanesulfonate (600 mg, 2.7 mmol). The mixture was stirred at 40 °C overnight, diluted with ethyl acetate (30 mL), washed with H₂O (10 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **15B**, which was used directly in the next step without further purification. LC-MS (ESI) *m/z*: 263 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.00 (s, 3H), 4.39 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H).

[00521] A mixture of Compound **15B** (700 mg, 1.90 mmol) and ammonium carbamodithioate (209 mg, 1.90 mmol) in ethanol (20 mL) was stirred at 80 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was slurred in mixed solvents (petroleum ether/EtOAc, 1/2, v/v, 15 mL) and filtered. The solid was dried under vacuum to give Compound **15C**. LC-MS (ESI) *m/z*: 258 [M+H]⁺.

[00522] Compounds **15D**, **15E**, and **15** were synthesized by employing the procedures described for Compounds **1E**, **1**, and **8F** using Compounds **15C**, **15D**, and **15E** in lieu of Compounds **1D**, **1E**, and **8E**. Compound **15D**: LC-MS (ESI) *m/z*: 517 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.36 (t, *J* = 6.8 Hz, 3H), 3.70 (s, 3H), 3.95 (s, 3H), 4.41 (q, *J* = 6.8 Hz, 2H), 5.72 (s, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 1H), 7.24 (d, *J* = 5.6 Hz, 3H), 7.63 (dd, *J* = 5.6, 2.0 Hz, 1H), 7.78 (d, *J* = 2.0 Hz, 1H). Compound **15E**: LC-MS (ESI) *m/z*: 397 [M+H]⁺. Compound **15**: LC-MS (ESI) *m/z*: 369 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 3.92 (s, 3H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.92 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.04 (d, *J* = 2.4 Hz, 1H).

[00523] **Example 16**

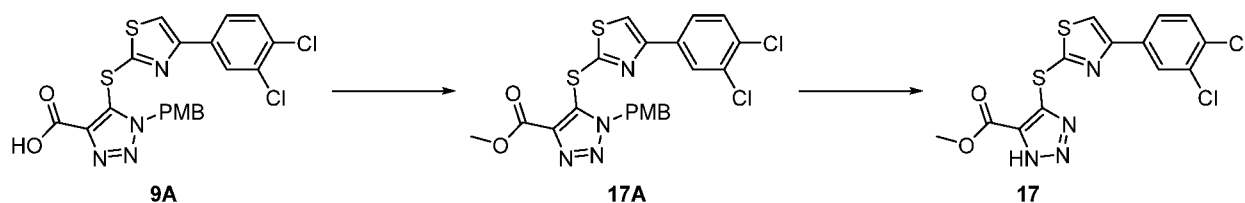
[00524] Synthesis of 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (16)



[00525] Compounds **16A**, **16B**, and **16** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using 4-(trifluoromethoxy)phenylboronic acid, Intermediate **E**, Compounds **16A**, and **16B** in lieu of (4-bromophenyl)boronic acid, Compounds **4A**, **8E**, and **1E**. Compound **16A**: LC-MS (ESI) m/z : 516 $[\text{M}+\text{H}]^+$. Compound **16B**: LC-MS (ESI) m/z : 502. Compound **16**: LC-MS (ESI) m/z : 382 $[\text{M}+\text{H}]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 7.35 (s, 1H), 7.38 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 8.4$ Hz, 2H), 7.73 (s, 1H), 7.75 (s, 1H).

[00526] Example 17

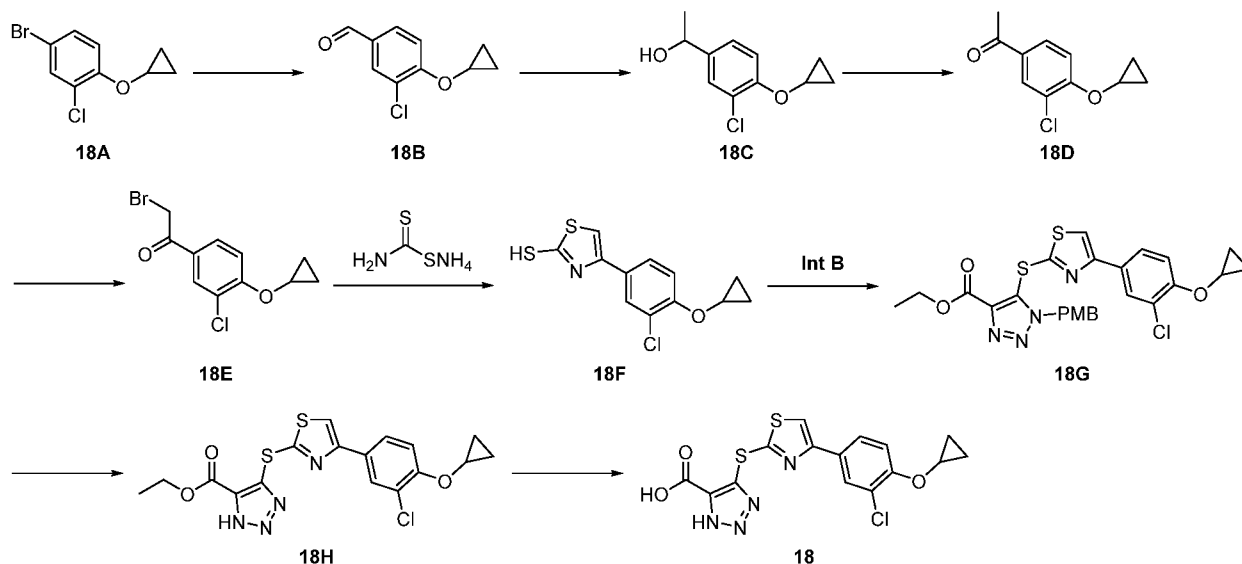
[00527] Synthesis of methyl 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (17)



[00528] Compounds **17A** and **17** were synthesized by employing the procedures described for Compounds **11A** and **1** using methanol and Compound **17A** in lieu of isopropanol and Compound **1E**. Compound **17A**: LC-MS (ESI) m/z : 507 $[\text{M}+\text{H}]^+$. Compound **17**: LC-MS (ESI) m/z : 387 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 3.85 (s, 3H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 8.16 (d, $J = 1.6$ Hz, 1H), 8.39 (s, 1H).

[00529] Example 18

[00530] Synthesis of 4-((4-(3-chloro-4-cyclopropoxyphenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (18)



[00531] To a solution of 4-bromo-2-chloro-1-cyclopropoxybenzene (Compound **18A**) (7.42 g, 30 mmol) in anhydrous THF (50 mL) was dropped a solution of *n*-BuLi in *n*-hexane (2.5 *M*, 13.2 mL, 33 mmol) over 15 minutes at -78 °C under nitrogen and stirred at -78 °C for 30 minutes. To the mixture was added anhydrous DMF (2.78 mL, 36 mmol), stirred at -78 °C for 30 minutes, quenched with saturated NH₄Cl solution (50 mL), and extracted with ethyl acetate (100 mL). The extract was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **18B**. LC-MS (ESI) *m/z*: 197 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.90-0.92 (m, 4H), 3.88-3.92 (m, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 9.87 (s, 1H).

[00532] To a solution of Compound **18B** (5.21 g, 26.5 mmol) in anhydrous THF (50 mL) was dropped a MeMgBr solution (3 *M* in ether, 9.72 mL, 29.2 mmol) over 10 minutes at -20 °C and stirred at -20 °C for 30 minutes and at room temperature for 3 hours. The reaction mixture was quenched with a saturated NH₄Cl aqueous solution (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **18C**. LC-MS (ESI) *m/z*: 195 [M-OH]⁺.

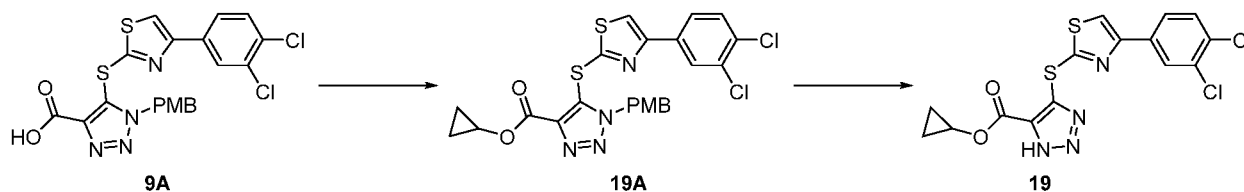
[00533] To a solution of Compound **18C** (5.52 g, 26.0 mmol) in dichloromethane (100 mL) was added Dess-Martin periodinane (13.2 g, 31.2 mmol) in several portions at 0 °C and

stirred at room temperature for 30 minutes. The mixture was quenched with a saturated $\text{Na}_2\text{S}_2\text{O}_3$ aqueous solution (150 mL), stirred at room temperature for 15 minutes, and extracted with dichloromethane (100 mL x 2). The combined extracts were washed with saturated NaHCO_3 solution (100 mL x 2) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **18D**. LC-MS (ESI) m/z : 211 $[\text{M}+\text{H}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 0.88-0.89 (m, 4H), 2.56 (s, 3H), 3.85-3.89 (m, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 7.87 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.97 (d, $J = 2.4$ Hz, 1H).

[00534] Compounds **18E**, **18F**, **18G**, **18H**, and **18** were synthesized by employing the procedures described for Compounds **15B**, **15C**, **1E**, **1**, and **8F** using Compounds **18D**, **18E**, **18F**, **18G**, and **18H** in lieu of Compounds **15A**, **15B**, **1D**, **1E**, and **8E**. Compound **18E**: LC-MS (ESI) m/z : 289 $[\text{M}+\text{H}]^+$. Compound **18F**: LC-MS (ESI) m/z : 284 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 0.71-0.75 (m, 2H), 0.83-0.89 (m, 2H), 4.00-4.03 (m, 1H), 7.31 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 1H), 7.73-7.76 (m, 1H), 7.89 (s, 1H), 13.61 (s, 1H). Compound **18G**: LC-MS (ESI) m/z : 543 $[\text{M}+\text{H}]^+$. Compound **18H**: LC-MS (ESI) m/z : 423 $[\text{M}+\text{H}]^+$. Compound **18**: LC-MS (ESI) m/z : 395 $[\text{M}+\text{H}]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.77-0.80 (m, 2H), 0.82-0.87 (m, 2H), 3.91-3.92 (m, 1H), 7.44 (d, $J = 8.8$ Hz, 1H), 7.78 (s, 1H), 7.81 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.90 (d, $J = 2.0$ Hz, 1H).

[00535] Example 19

[00536] Synthesis of cyclopropyl 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (19)

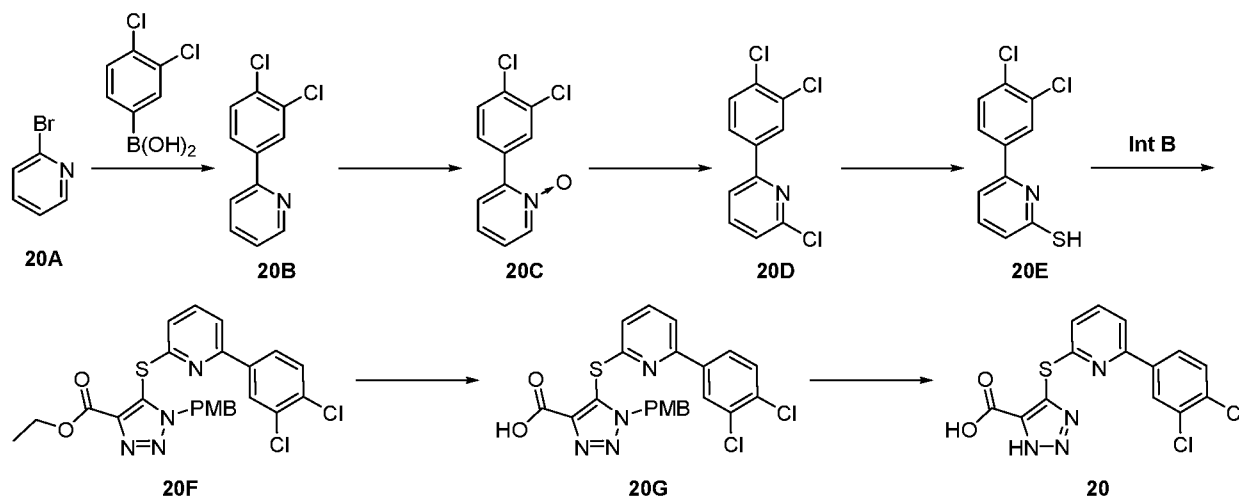


[00537] A mixture of Compound **9A** (20 mg, 0.04 mmol), cyclopropanol (23 mg, 0.4 mmol), HATU (23 mg, 0.06 mmol), and DIPEA (10 mg, 0.08 mmol) in DMF (5 mL) was stirred at room temperature for 16 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with water (20 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **19A**. LC-MS (ESI) m/z : 533 $[\text{M}+\text{H}]^+$.

[00538] Compound **19** was synthesized by employing the procedure described for Compound **1** using Compound **19A** in lieu of Compound **1E**, LC-MS (ESI) m/z : 413 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.75-0.79 (m, 4H), 4.35-4.40 (m, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8$ Hz, 1H), 7.99 (s, 1H), 8.08(s, 1H).

[00539] **Example 20**

[00540] **Synthesis of 4-((6-(3,4-dichlorophenyl)pyridin-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (20)**



[00541] Compound **20B** was synthesized by employing the procedure described for Compound **4B** using (3,4-dichlorophenyl)boronic acid and Compound **20A** in lieu of (4-bromophenyl)boronic acid and Compound **4A**, LC-MS (ESI) m/z : 224 $[M+H]^+$. ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.25-7.29 (m, 1H), 7.51-7.54 (m, 1H), 7.67-7.70 (m, 1H), 7.74-7.79 (m, 1H), 7.81-7.84 (m, 1H), 8.13 (d, $J = 2.0$ Hz, 1H), 8.68 (d, $J = 4.4$ Hz, 1H).

[00542] A mixture of Compound **20B** (1.12 g, 5 mmol) and *m*-CPBA (1.3 g, 6.5 mmol) in dichloromethane (15 mL) was stirred at 20 °C for 5 hours. The mixture was poured into a saturated $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (50 mL x 2). The combined extracts were washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **20C**. LC-MS (ESI) m/z : 240 $[M+H]^+$.

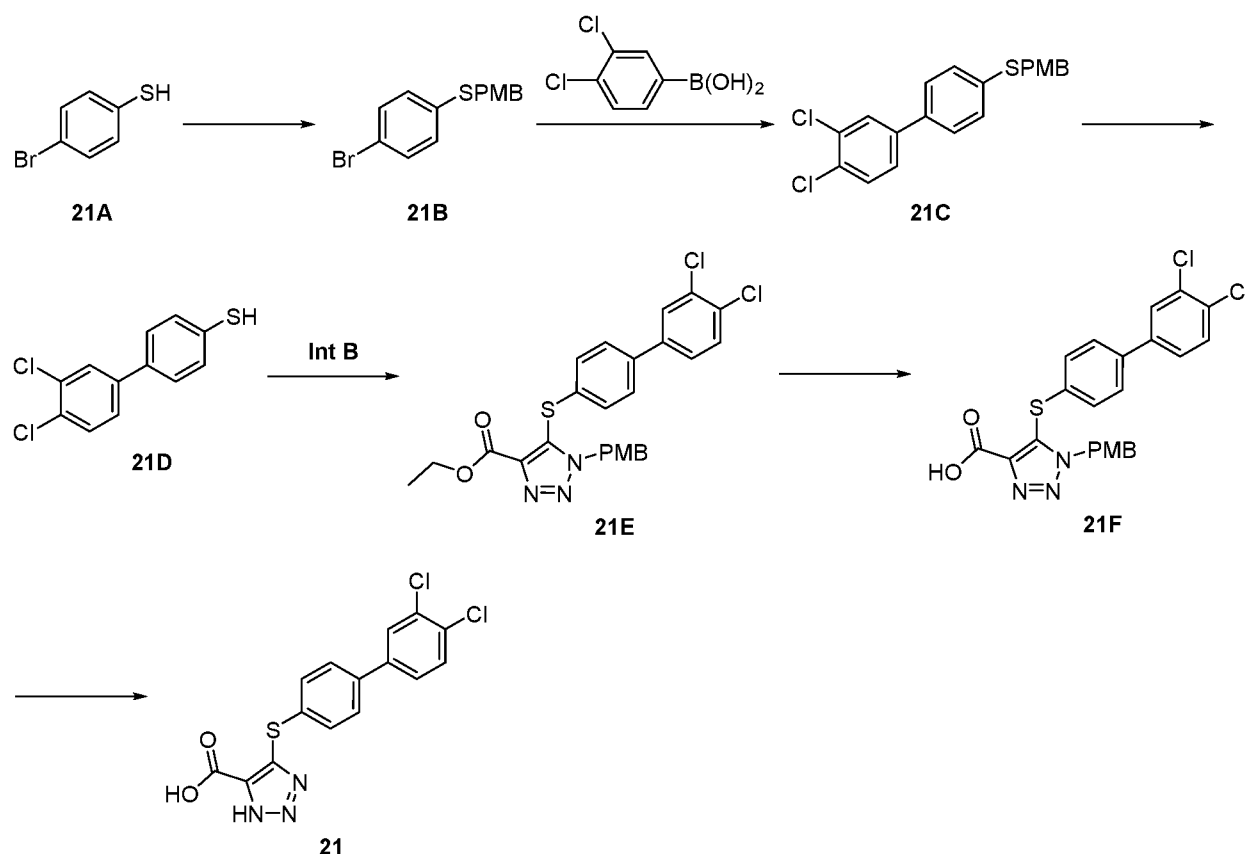
[00543] A mixture of Compound **20C** (840 mg, 3.5 mmol) and $POCl_3$ (9 mL) was stirred at 80 °C for 15 hour. The mixture was concentrated under reduced pressure. The residue was diluted with NaOH solution (6 N, 100 mL) and extracted with dichloromethane (50 mL x 2). The combined extracts were washed with water (50 mL x 2) and brine (50 mL), dried over anhydrous

sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 17% v/v) to afford Compound **20D**. LC-MS (ESI) m/z : 258 $[M+H]^+$.

[00544] Compounds **20E**, **20F**, **20G**, and **20** were synthesized by employing the procedures described for Compounds **12B**, **1E**, **8F**, and **1** using Compounds **20D**, **20E**, **20F**, and **20G** in lieu of Compounds **12A**, **1D**, **8E**, and **1E**. Compound **20E**: LC-MS (ESI) m/z : 256 $[M+H]^+$. Compound **20F**: LC-MS (ESI) m/z : 515 $[M+H]^+$. Compound **20G**: LC-MS (ESI) m/z : 487 $[M+H]^+$. Compound **20**: LC-MS (ESI) m/z : 367 $[M+H]^+$. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.17 (brs, 1H), 7.75 (d, $J = 8.8$ Hz, 1H), 8.05-8.08 (m, 2H), 8.32 (d, $J = 2$ Hz, 1H), 8.53 (d, $J = 5.2$ Hz, 1H).

[00545] Example 21

[00546] Synthesis of 4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (21)



[00547] To a degassed solution of Compound **21A** (1.89 g, 10 mmol) in DMF (15 mL) was added K_2CO_3 (1.38 g, 10 mmol). The mixture was stirred under nitrogen for 10 minutes,

followed by addition of 1-(chloromethyl)-4-methoxybenzene (1.56 g, 10 mmol) dropwise. The mixture was stirred at room temperature for 12 hours and at 100 °C for 1 hour. The reaction was slowly quenched with water (25 mL) and a solid precipitated gradually. The solid was collected by filtration and recrystallized from methanol to give Compound **21B**. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.78 (s, 3H), 4.04 (s, 2H), 6.80-6.83 (m, 2H), 7.13-7.15 (m, 2H), 7.17-7.19 (m, 2H), 7.35-7.37 (m, 2H).

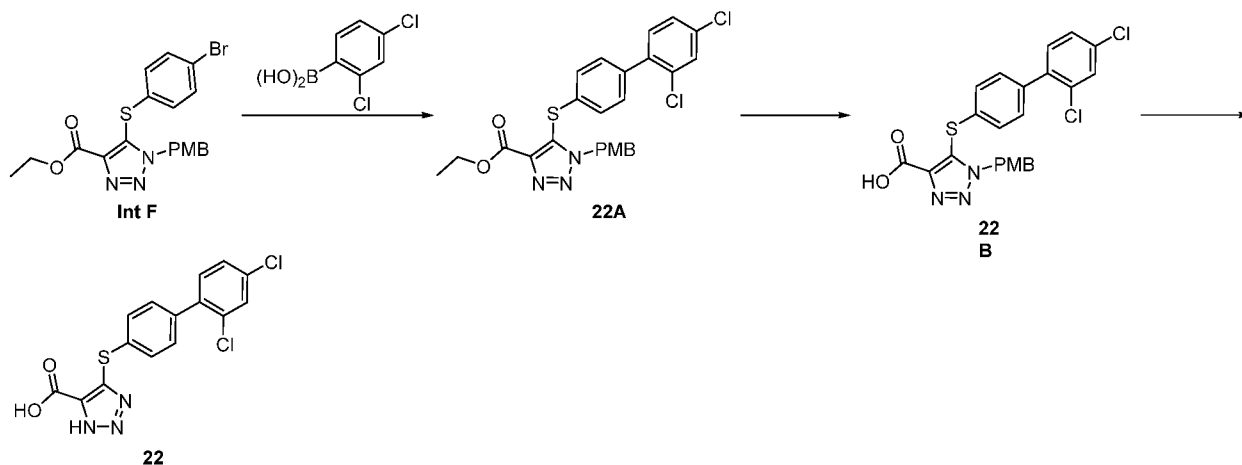
[00548] Compound **21C** was synthesized by employing the procedure described for Compound **4B** using (3,4-dichlorophenyl)boronic acid and Compound **21B** in lieu of (4-bromophenyl)boronic acid and Compound **4A**, LC-MS (ESI) m/z: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.79 (s, 3H), 4.12 (s, 2H), 6.82-6.84 (m, 2H), 7.23-7.25 (m, 2H), 7.34-7.38 (m, 3H), 7.42-7.44 (m, 2H), 7.47-7.50 (m, 1H), 7.64 (d, *J* = 2.4 Hz, 1H).

[00549] A mixture of compound **21C** (188 mg, 0.5 mmol) and TFA (3 mL) was stirred at 80 °C for 4 hours and concentrated under reduced pressure. The residue was partitioned between CH₂Cl₂ (5 mL) and water (5 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to furnish compound **21D**. LC-MS (ESI) m/z: 253 [M-H]⁻.

[00550] Compounds **21E**, **21F**, and **21** were synthesized by employing the procedures described for Compounds **13D**, **8F**, and **1** using Compounds **21D**, **21E**, and **21F** in lieu of Compounds **13C**, **8E**, and **1E**. Compound **21E**: LC-MS (ESI) m/z: 514 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.32 (t, *J* = 5.6 Hz, 3H), 3.79 (s, 3H), 4.37 (q, *J* = 5.6 Hz, 2H), 5.58 (s, 2H), 6.71-6.73 (m, 2H), 7.00-7.02 (m, 2H), 7.13-7.15 (m, 2H), 7.31-7.33 (m, 3H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.57 (d, *J* = 1.6 Hz, 1H). Compound **21F**: LC-MS (ESI) m/z: 486 [M+H]⁺. Compound **21**: LC-MS (ESI) m/z: 366 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 7.45-7.47 (m, 2H), 7.56-7.59 (m, 4H), 7.79 (d, *J* = 1.2 Hz, 1H).

[00551] **Example 22**

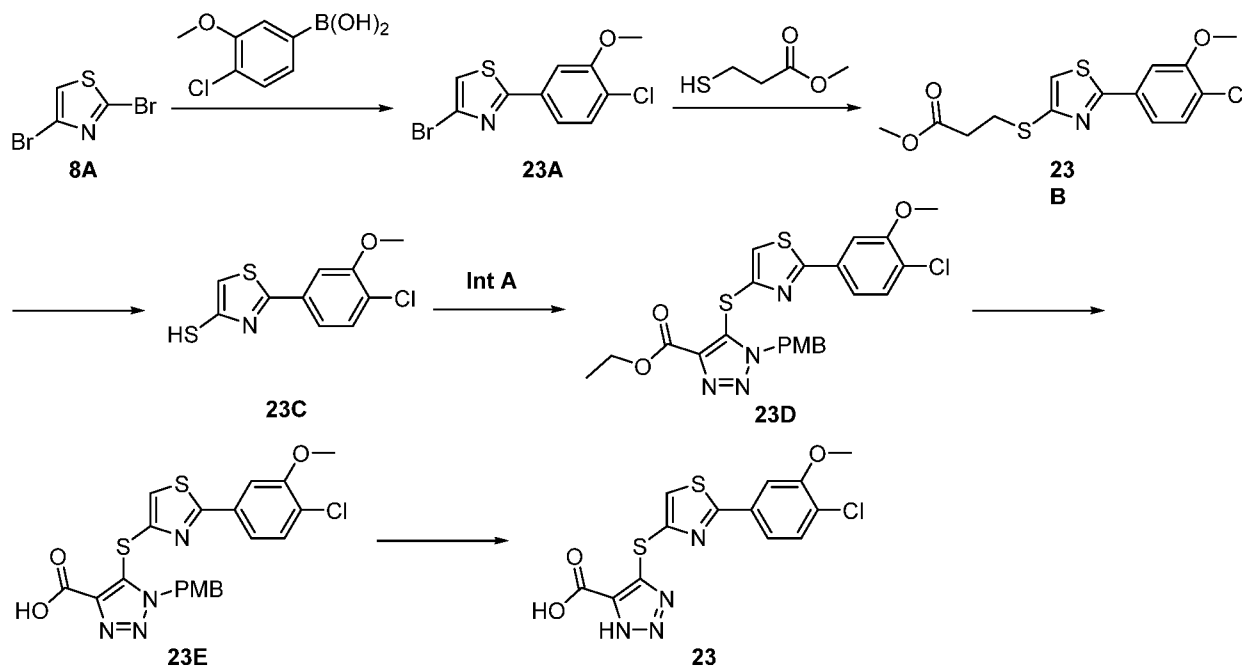
[00552] **Synthesis of 4-((2',4'-dichloro-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (22)**



[00553] Compounds **22A**, **22B**, and **22** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using Intermediate **F**, 2,4-dichlorophenylboronic acid, Compounds **22A**, and **22B** in lieu of Compounds **4A**, (4-bromophenyl)boronic acid, **8E**, and **1E**. Compound **22A**: LC-MS (ESI) m/z : 514 $[M+H]^+$. Compound **22B**: LC-MS (ESI) m/z : 486 $[M+H]^+$. Compound **22**: LC-MS (ESI) m/z : 366 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.43-7.47 (m, 3H), 7.52 (d, $J = 8.4$ Hz, 3H), 7.75 (s, 1H).

[00554] Example 23

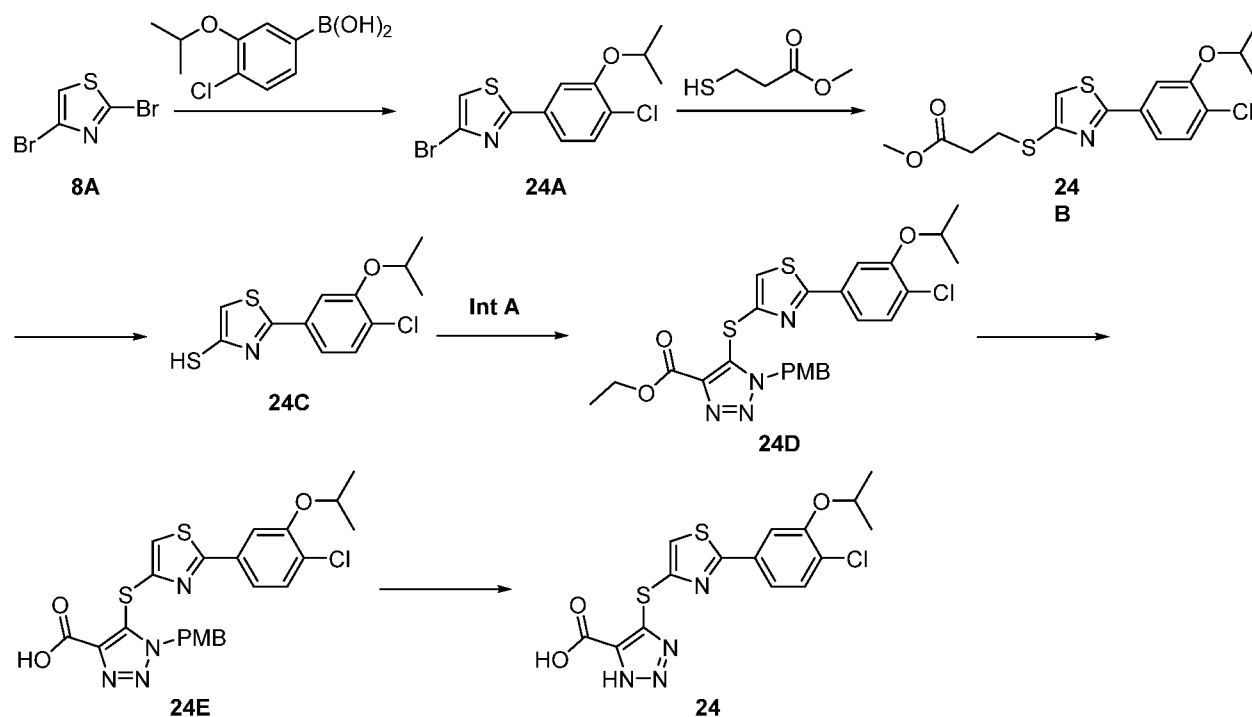
[00555] Synthesis of 4-((2-(4-chloro-3-methoxyphenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (**23**)



[00556] Compounds **23A**, **23B**, **23C**, **23D**, **23E**, and **23** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using 4-chloro-3-methoxyphenylboronic acid, Compounds **23A**, **23B**, **23C**, Intermediate **A**, **23D**, and **23E** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, Compounds **1D**, Intermediate **B**, **8E**, and **1E**. Compound **23A**: LC-MS (ESI) m/z : 304 $[M+H]^+$. Compound **23B**: LC-MS (ESI) m/z : 344 $[M+H]^+$. Compound **23C**: LC-MS (ESI) m/z : 258 $[M+H]^+$. Compound **23D**: LC-MS (ESI) m/z : 517 $[M+H]^+$. Compound **23E**: LC-MS (ESI) m/z : 489 $[M+H]^+$. Compound **23**: LC-MS (ESI) m/z : 369 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 3.97 (s, 3H), 7.48 (s, 2H), 7.67 (s, 1H), 7.86 (s, 1H).

[00557] **Example 24**

[00558] **Synthesis of 4-((2-(4-chloro-3-isopropoxyphenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (**24**)**



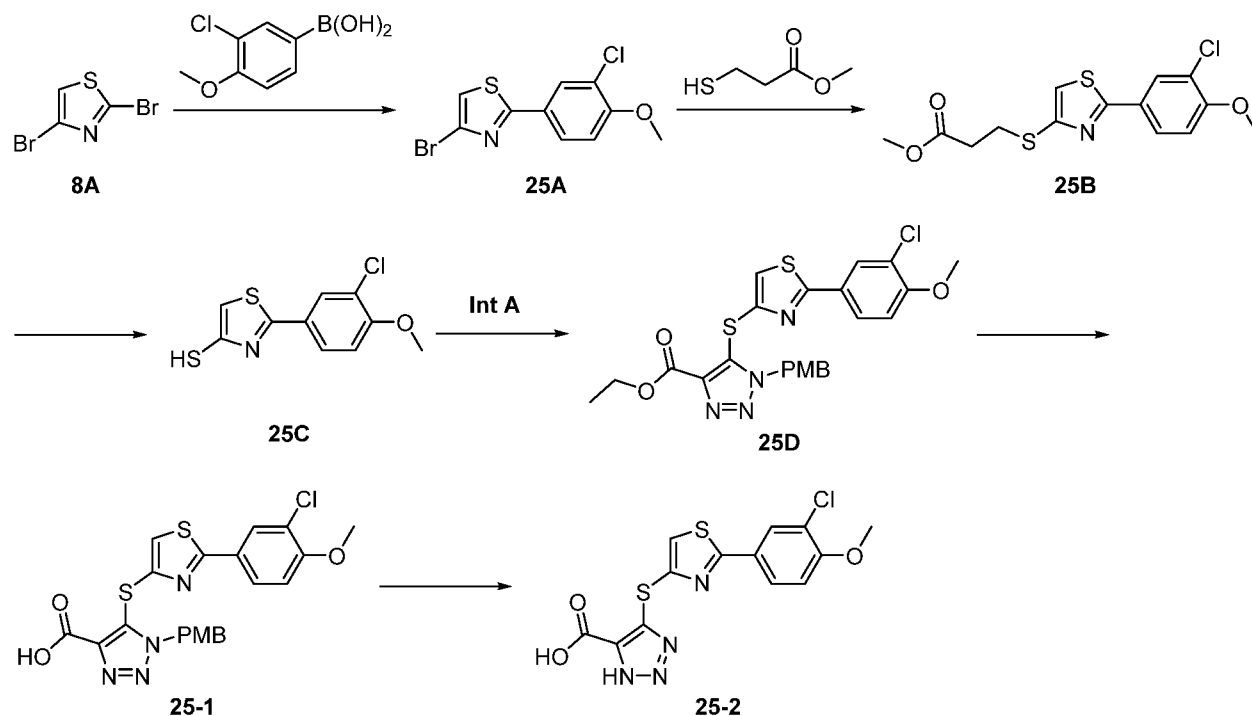
[00559] Compounds **24A**, **24B**, **24C**, **24D**, **24E**, and **24** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using 4-chloro-3-methoxyphenylboronic acid, Compounds **24A**, **24B**, **24C**, Intermediate **A**, **24D**, and **24E** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, Compounds **1D**, Intermediate **B**, **8E**, and **1E**. Compound **24A**: LC-MS (ESI) m/z : 332 $[M+H]^+$. Compound **24B**: LC-MS (ESI) m/z : 372 $[M+H]^+$. Compound **24C**: LC-MS (ESI) m/z : 286 $[M+H]^+$. Compound

24D: LC-MS (ESI) m/z: 545 [M+H]⁺. Compound **24E**: LC-MS (ESI) m/z: 517 [M+H]⁺.

Compound **24**: LC-MS (ESI) m/z: 397 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 1.38 (d, *J* = 6.4 Hz, 6H), 4.75 (m, 1H), 7.47 (m, 2H), 7.66 (s, 1H), 7.85 (s, 1H).

[00560] Example 25

[00561] Synthesis of 5-((2-(3-chloro-4-methoxyphenyl)thiazol-4-yl)thio)-1-(4-methoxybenzyl)-1H-1,2,3-triazole-4-carboxylic acid (25-1) and 4-((2-(3-chloro-4-methoxyphenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (25-2)

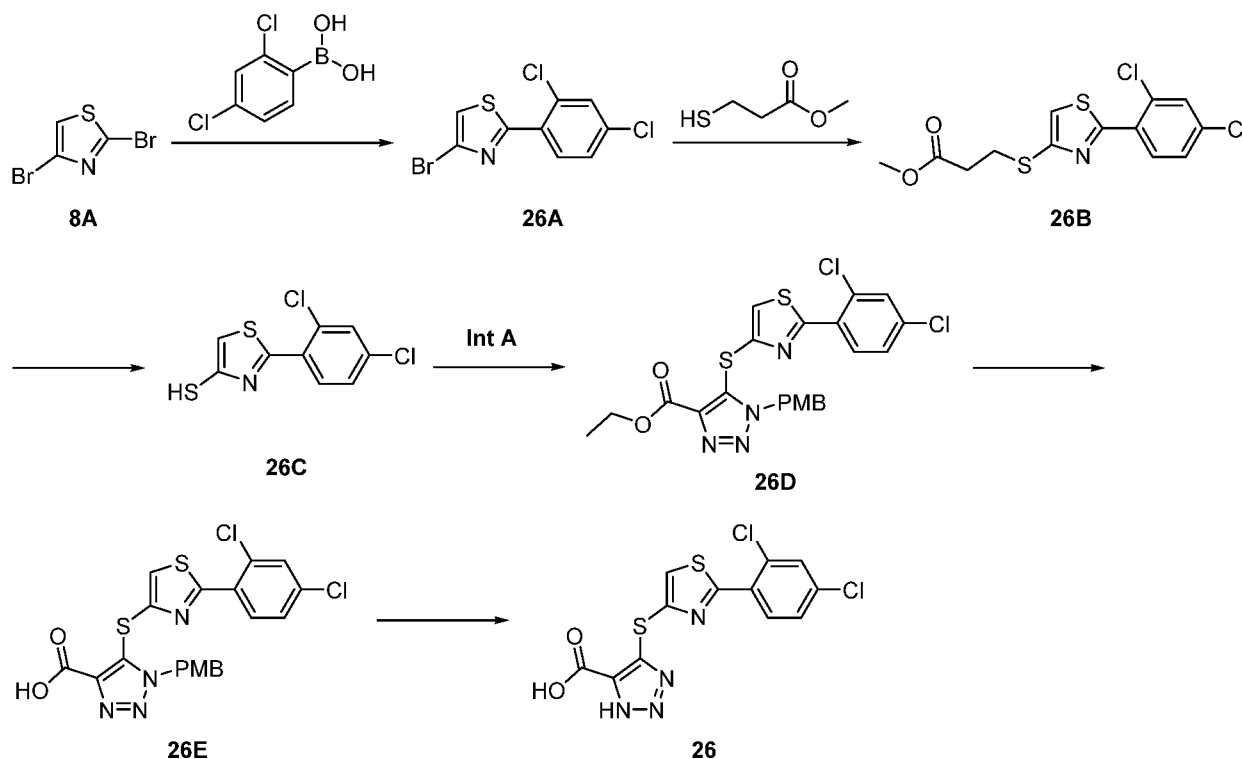


[00562] Compounds **25A**, **25B**, **25C**, **25D**, **25-1**, and **25-2** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using 4-chloro-3-methoxyphenylboronic acid, Compounds **25A**, **25B**, **25C**, Intermediate **A**, **25D**, and **25-1** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, Compounds **1D**, Intermediate **B**, **8E**, and **1E**. Compound **25A**: LC-MS (ESI) m/z: 304 [M+H]; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.96 (s, 3H), 6.97 (d, *J* = 8.8 Hz, 1H), 7.17 (s, 1H), 7.80 (dd, *J*₁ = 8.4 Hz, *J*₂ = 2.4 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H). Compound **25B**: LC-MS (ESI) m/z: 344 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.77 (t, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 3.97 (s, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 7.07 (s, 1H), 7.81 (dd, *J*₁ = 8.8 Hz, *J*₂ = 2.0 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H). Compound **25C**: LC-MS (ESI) m/z: 258 [M+H]⁺. Compound **25D**: LC-MS (ESI) m/z: 517 [M+H]⁺. Compound **25-1**: LC-MS (ESI) m/z: 489 [M+H]⁺; ¹H-NMR

(CDCl₃, 400 MHz): δ (ppm) 3.76 (s, 3H), 3.97 (s, 3H), 5.76 (s, 2H), 6.80-6.82 (m, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 7.14 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.69 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.79 (d, $J = 2.0$ Hz, 1H). Compound **25-2**: LC-MS (ESI) m/z : 369 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.92 (s, 3H), 7.27 (d, $J = 8.8$ Hz, 1H), 7.86 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 7.92 (d, $J = 2.0$ Hz, 1H), 7.94 (s, 1H).

[00563] Example 26

[00564] Synthesis of 4-((2-(2,4-dichlorophenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (26)

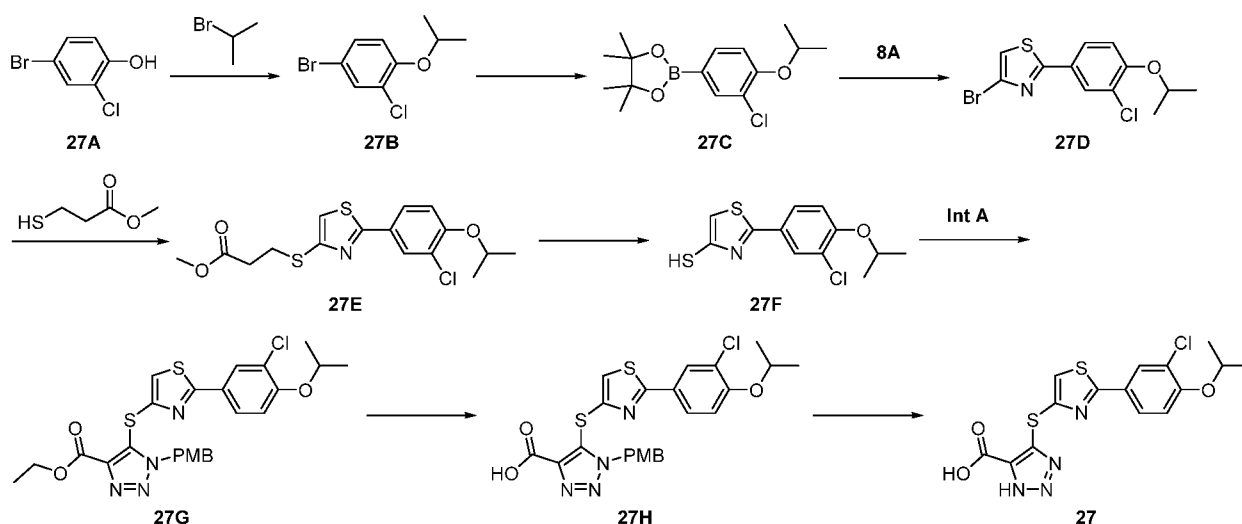


[00565] Compounds **26A**, **26B**, **26C**, **26D**, **26E**, and **26** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using 4-chloro-3-methoxyphenylboronic acid, Compounds **26A**, **26B**, **26C**, Intermediate **A**, **26D**, and **26E** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, Compounds **1D**, Intermediate **B**, **8E**, and **1E**. Compound **26A**: LC-MS (ESI) m/z : 308 [M+H]⁺. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.35-7.39 (m, 2H), 7.51 (d, $J = 1.6$ Hz, 1H), 8.28 (d, $J = 8.8$ Hz, 1H). Compound **26B**: LC-MS (ESI) m/z : 348 [M+H]⁺. ¹H-NMR (CDCl₃, 400 MHz): δ 2.77 (t, $J = 7.2$ Hz, 2H), 3.35 (t, $J = 7.2$ Hz, 2H), 3.70 (s, 3H), 7.26 (s, 1H), 7.36 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 8.25 (d, $J = 8.8$ Hz, 1H). Compound **26C**: LC-MS (ESI) m/z : 262 [M+H]⁺.

Compound **26D**: LC-MS (ESI) m/z: 521. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.35 (t, $J = 7.2$ Hz, 3H), 3.72 (s, 3H), 4.39 (q, $J = 7.2$ Hz, 2H), 5.73 (s, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 7.18 (s, 1H), 7.23 (d, $J = 8.8$ Hz, 2H), 7.31 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.96 (d, $J = 8.4$ Hz, 1H). Compound **26E**: LC-MS (ESI) m/z: 493 $[\text{M}+\text{H}]^+$. Compound **26**: LC-MS (ESI) m/z: 373 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.60 (dd, $J = 2.0, 8.4$ Hz, 1H), 7.87 (d, $J = 2.0$ Hz, 1H), 8.16-8.18 (m, 2H).

[00566] Example 27

[00567] Synthesis of 4-((2-(3-chloro-4-isopropoxyphenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (27)



[00568] To a solution of 4-bromo-2-chlorophenol (Compound **27A**) (5.0 g, 24.1 mmol) in DMF (100 mL) was added K_2CO_3 (10.0 g, 72.5 mmol) and 2-bromopropane (7.5 g, 61.5 mmol) and stirred at 100 °C for 16 hours. The mixture was diluted with water (400 mL) and extracted with a mixture of ethyl acetate in petroleum ether (15% v/v, 300 mL x 3). The combined extracts were washed with brine (300 mL x 4), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **27B**. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used.

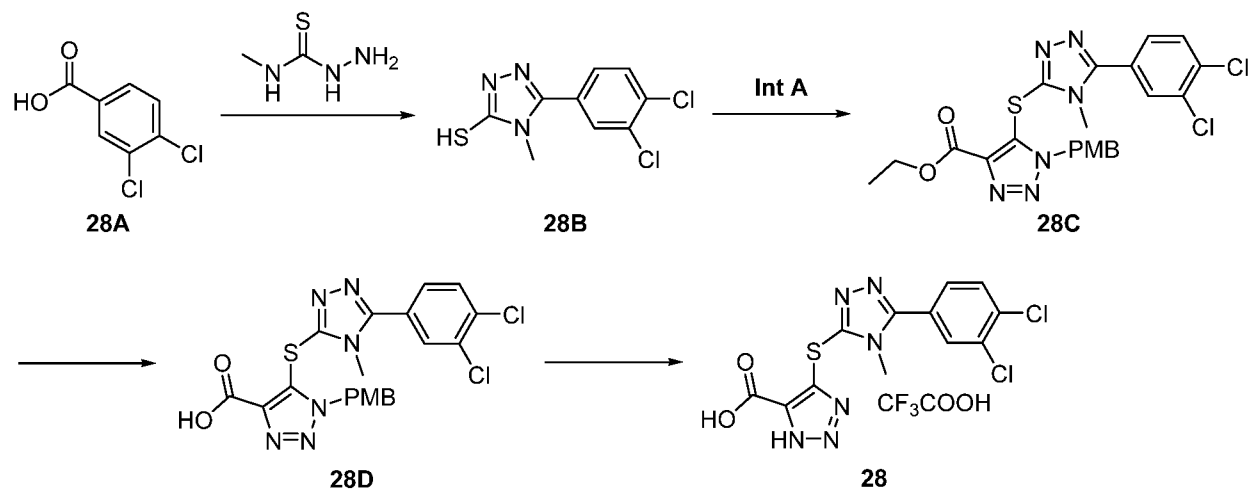
[00569] A mixture of Compound **27B** (1.35 g, 5.4 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.35 g, 0.43 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.09 g, 8.22 mmol), and potassium acetate (1.62 g, 16.5 mmol) in 1,4-dioxane (50 mL) was heated at 80 °C for 16 hours. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (200 mL x 2). The

combined extracts were washed with water (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 10% v/v) to furnish Compound **27C**. LC-MS (ESI) *m/z*: non-ionizable compound under routine conditions used.

[00570] Compounds **27D**, **27E**, **27F**, **27G**, **27H**, and **27** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using Compounds **27C**, **27D**, **27E**, **27F**, Intermediate **A**, **27G**, and **27H** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, Compounds **1D**, Intermediate **B**, **8E**, and **1E**. Compound **27D**: LC-MS (ESI) *m/z*: 332. Compound **27E**: LC-MS (ESI) *m/z*: 372 [M+H]⁺. Compound **27F**: LC-MS (ESI) *m/z*: 286 [M+H]⁺. Compound **27G**: LC-MS (ESI) *m/z*: 545 [M+H]⁺. Compound **27H**: LC-MS (ESI) *m/z*: 517 [M+H]⁺. Compound **27**: LC-MS (ESI) *m/z*: 397 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.33 (d, *J* = 6.0 Hz, 6H), 4.77-4.80 (m, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 7.82 (dd, *J*₁ = 2.0 Hz, *J*₂ = 8.4 Hz, 1H), 7.92-7.94 (m, 2H).

[00571] **Example 28**

[00572] **Synthesis of 4-((5-(3,4-dichlorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**28**)**



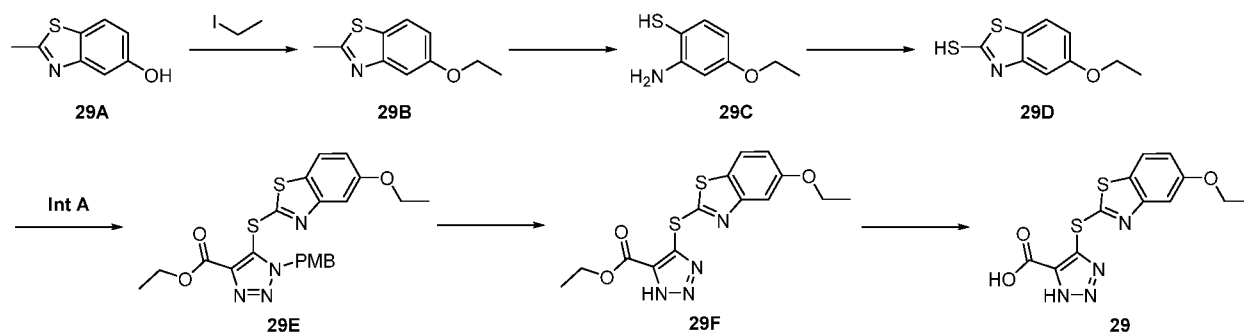
[00573] To a solution of 3,4-dichlorobenzoic acid (**28A**) (500 mg, 2.62 mmol), *N*-methylhydrazinecarbothioamide (302 mg, 2.88 mmol), and DIPEA (606 mg, 4.7 mmol) in DMF (5 mL) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T_3P , 1.25 g, 3.93 mmol) and stirred at room temperature for 30 minutes. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined extracts were concentrated under reduced pressure. The residue was diluted with a mixture of water (10

mL) and DMF (2 mL), adjusted to pH 8 with aqueous NaOH solution (4 M) and heated to 70 °C for 16 hours. The mixture was acidified to pH 5 with concentrated HCl solution. The resulting solid was collected and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0% to 100% v/v) to furnish Compound **28B**. LC-MS (ESI) m/z: 260 [M+H]⁺.

[00574] Compounds **28C**, **28D**, and **28** were synthesized by employing the procedures described for Compounds **1E**, **8F**, and **1** using Intermediate **A**, Compounds **28B**, **28C**, and **28D** in lieu of Intermediate **B**, Compounds **1D**, **8E**, and **1E**. Compound **28C**: LC-MS (ESI) m/z: 519 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 1.35 (t, *J* = 7.2 Hz, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.84 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 2.0 Hz, 1H). Compound **28D**: LC-MS (ESI) m/z: 491 [M+H]⁺. Compound **28**: LC-MS (ESI) m/z: 371 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.70 (s, 3H), 7.78 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H).

[00575] Example 29

[00576] Synthesis of 4-((5-ethoxybenzo[d]thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (29)



[00577] A mixture of 2-methylbenzo[d]thiazol-5-ol (Compound **29A**) (2 g, 12.1 mmol), iodoethane (2.8 g, 18.2mmol), and potassium carbonate (3.4 g, 24.2mmol) in acetonitrile (40 mL) was stirred at 70 °C overnight. The mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with H₂O (10 mL x 3), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 9% v/v) to give Compound **29B**. LC-MS (ESI) m/z: 194 [M+H]⁺.

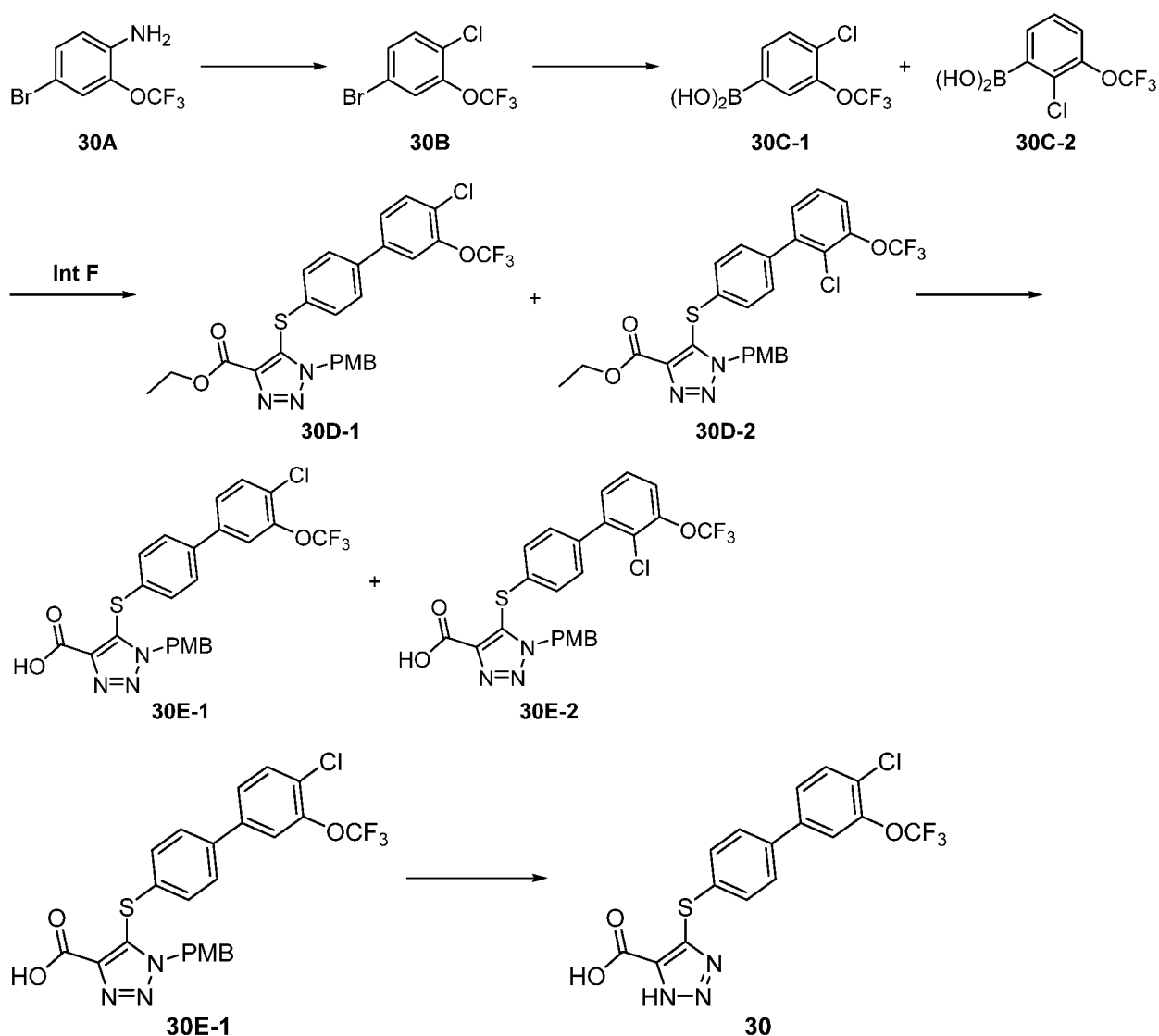
[00578] To a solution of Compound **29B** (500 mg, 2.59 mmol) in ethylene glycol (3 mL) was added an aqueous sodium hydroxide solution (50% w/w, 6 g, 75 mmol) and stirred at 140 °C for 3 hours. The mixture was poured into ice-water (50 mL), acidified to pH 3 with an aqueous hydrochloric acid solution (2 *N*), and extracted with dichloromethane (20 mL x 4). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated to give Compound **29C**, which was used directly in next step without further purification. LC-MS (ESI) *m/z*: 170 [*M* + *H*]⁺.

[00579] A mixture of Compound **29C** (400 mg, 2.36 mmol), carbon disulfide (450 mg, 5.9 mmol), and sodium hydroxide (236 mg, 5.9 mmol) in ethanol (10 mL) was heated at reflux for 2 hours. After cooled to room temperature, the mixture was filtered. The filtrate was diluted with ice-water (30 mL) and acidified to pH 3 with an aqueous hydrochloric acid solution (2 *N*). The resulting solid was collected and dried under vacuum to give Compound **29D**. LC-MS (ESI) *m/z*: 212 [*M* + *H*]⁺.

[00580] Compounds **29E**, **29F**, and **29** were synthesized by employing the procedures described for Compounds **1E**, **1**, and **8F** using Intermediate **A**, Compounds **29D**, **29E**, and **29F** in lieu of Intermediate **B**, Compounds **1D**, **1E**, and **8E**. Compound **29E**: LC-MS (ESI) *m/z*: 471 [*M* + *H*]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.33 (t, *J* = 7.2 Hz, 3H), 1.47 (t, *J* = 7.2 Hz, 3H), 3.63 (s, 3H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 5.67 (s, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H). Compound **29F**: LC-MS (ESI) *m/z*: 351 [*M* + *H*]⁺. Compound **29**: LC-MS (ESI) *m/z*: 323 [*M* + *H*]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.34 (t, *J* = 7.2 Hz, 3H), 4.08 (q, *J* = 7.2 Hz, 2H), 7.01 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H).

[00581] **Example 30**

[00582] **Synthesis of 4-((4'-chloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (30)**



[00583] A mixture of isoamyl nitrite (4 mL, 30 mmol), copper (II) chloride (3.22 g, 24 mmol) and 4-bromo-2-(trifluoromethoxy)aniline (Compound **30A**) (5.1 g, 20 mmol) in acetonitrile (80 mL) was heated at 70 °C for 3 hours. The mixture was poured into an aqueous HCl solution (0.5 M, 50 mL) and extracted with ethyl acetate (50 mL x 2). The combined extracts were washed with water (50 mL x 4) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (petroleum ether) to afford Compound **30B**. LC-MS (ESI) *m/z*: non-ionizable compound under routine conditions used. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.33-7.35 (m, 1H), 7.37-7.40 (m, 1H), 7.48 (t, *J* = 1.6 Hz, 1H).

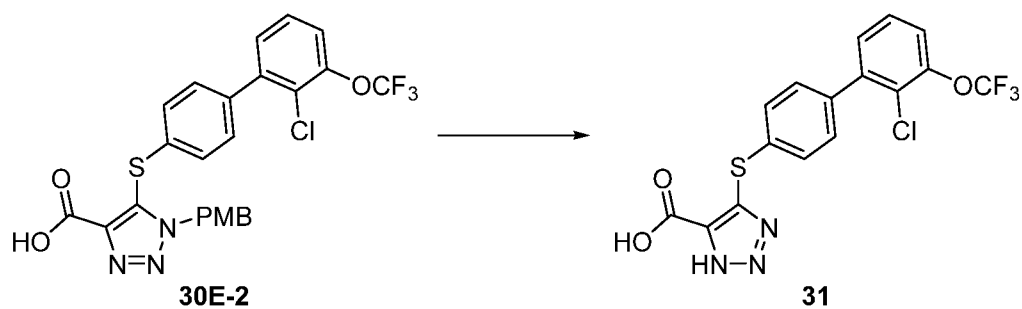
[00584] To Compound **30B** (1.7 g, 6.2 mmol) in anhydrous THF (30 mL) at -78 °C was dripped *n*-BuLi solution (2.5 M in hexanes, 3.15 mL, 6.25 mmol) and stirred at -78 °C for 30

minutes. To the mixture was added triisopropyl borate (1.44 mL, 6.25 mmol) and was gradually allowed to warm to room temperature and stirred at room temperature for 2 hours. The mixture was poured into water (100 mL), acidified to pH 4 with aqueous HCl solution (1 M), and extracted with ethyl acetate (100 mL x 2). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield a mixture of Compound **30C-1** and **30C-2**. LC-MS (ESI) *m/z*: non-ionizable compound under routine conditions used.

[00585] Mixture of **30D-1** and **30D-2**, Compounds **30E-1**, **30E-2**, and **30** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using Intermediate **F**, Mixtures of **30C-1** and **30C-2**, **30D-1** and **30D-2**, and Compound **30E-1** in lieu of Intermediate **B**, Compounds **4A**, **8E**, and **1E**. Mixture of **30D-1** and **30D-2**: LC-MS (ESI) *m/z*: 564 [M+H]⁺. Compound **30E-1**: LC-MS (ESI) *m/z*: 536 [M+H]⁺. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.62 (s, 3H), 5.62 (s, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 4H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.69-7.78 (m, 3H), 13.36 (s, 1H). Compound **30E-2**: LC-MS (ESI) *m/z*: 536 [M+H]⁺. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.66 (s, 3H), 5.63 (d, *J* = 14 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.10-7.16 (m, 4H), 7.32-7.71 (m, 5H), 13.39 (s, 1H). Compound **30**: LC-MS (ESI) *m/z*: 416 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.53 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.79 (s, 2H), 7.86 (s, 1H).

[00586] Example 31

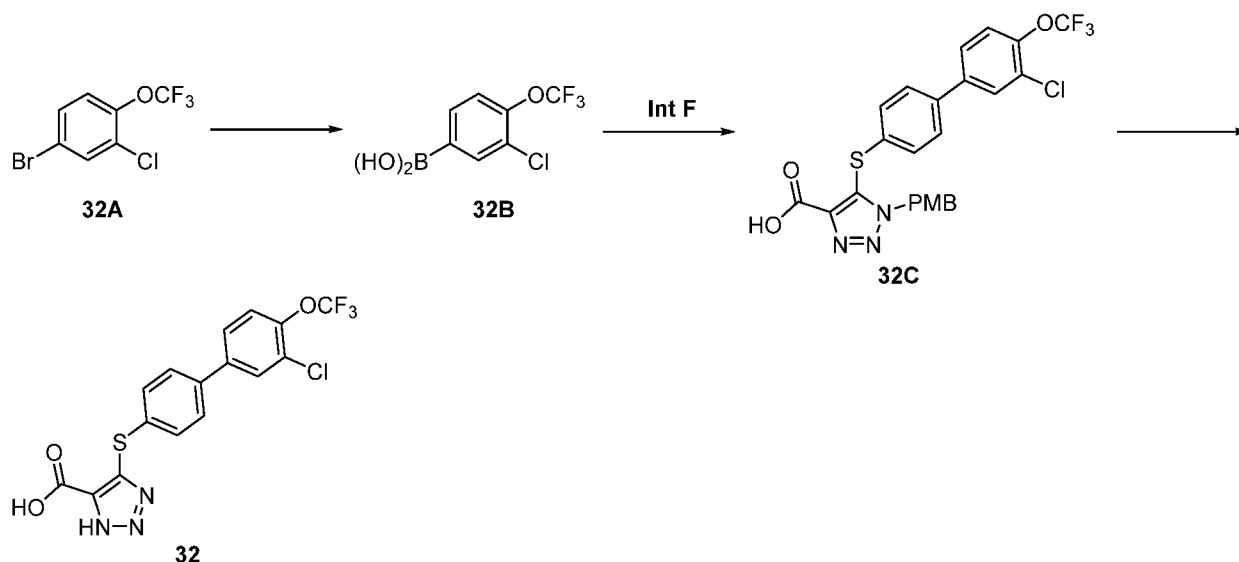
[00587] Synthesis of 4-((2'-chloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (31)



[00588] Compound **31** was synthesized by employing the procedure described for Compound **1** using Compound **30E-2** in lieu of Compound **1E**, LC-MS (ESI) *m/z*: 416 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.45-7.71 (m, 7H).

[00589] Example 32

[00590] Synthesis of 4-((3'-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (32)



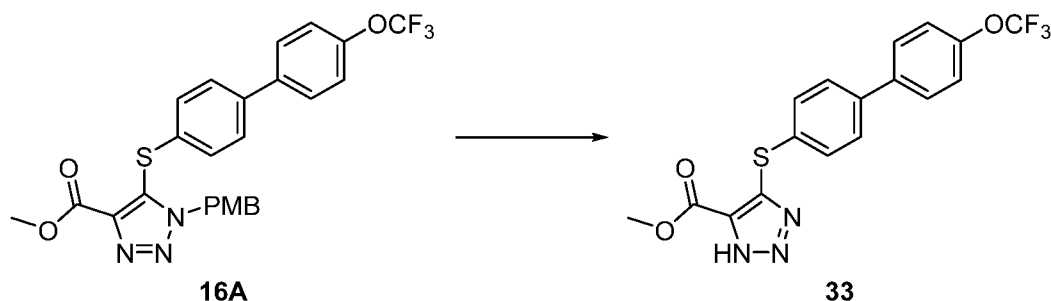
[00591] Compound **32B** was synthesized by employing the procedure described for Compound **30C-1** using Compound **32A** in lieu of Compound **30B**, LC-MS: (ESI) m/z : 239 $[M-H]^-$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.47-7.49 (m, 1H), 8.11-8.14 (m, 1H), 8.26 (d, $J = 1.6$ Hz, 1H).

[00592] A mixture of Compound **32B** (150 mg, 0.34 mmol), Intermediate **F** (129 mg, 0.54 mmol), $Pd(PPh_3)_4$ (39 mg, 0.03 mmol), and K_2CO_3 (187 mg, 1.36 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was stirred at 90 °C under nitrogen for 4 hours. After the mixture was cooled down to room temperature, a solution of $LiOH \cdot H_2O$ (21 mg, 0.53 mmol) in H_2O (1 mL) was added and stirred at 40 °C for 2 hours. The reaction mixture was concentrated and purified with reverse phase chromatography using eluents (acetonitrile in water, from 0% to 90% v/v) to furnish Compound **32C**. LC-MS: (ESI) m/z : 536 $[M+H]^+$.

[00593] Compound **32** was synthesized by employing the procedure described for Compound **1** using Compound **32C** in lieu of Compound **1E**, LC-MS (ESI) m/z : 416 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 77.53 (d, $J = 8.4$ Hz, 2H), 7.64-7.67 (m, 1H), 7.74-7.78 (m, 2H), 7.79-7.81 (m, 1H), 8.02 (d, $J = 2.4$ Hz, 1H).

[00594] Example 33

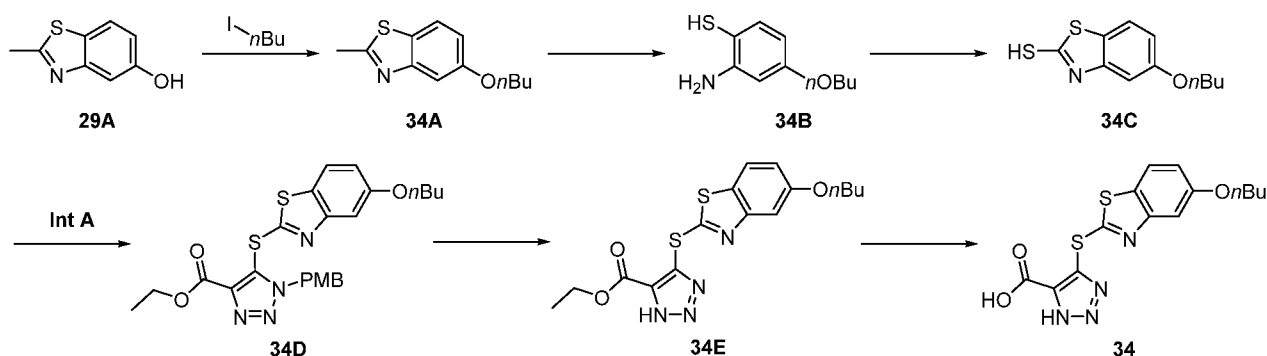
[00595] Synthesis of methyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (33)



[00596] Compound **33** was synthesized by employing the procedure described for Compound **1** using Compound **16A** in lieu of Compound **1E**, LC-MS (ESI) m/z : 396 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.85 (s, 3H), 7.47 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H).

[00597] **Example 34**

[00598] **Synthesis of 4-((5-butoxybenzo[d]thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (**34**)**

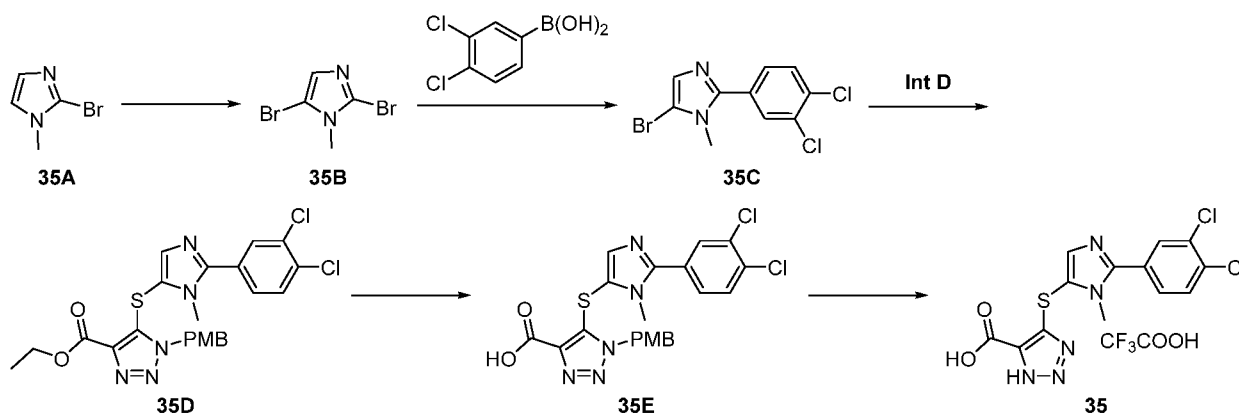


[00599] Compounds **34A**, **34B**, **34C**, **34D**, **34E**, and **34** were synthesized by employing the procedures described for Compounds **29B**, **29C**, **29D**, **1E**, **1**, and **8F** using 1-iodobutane, Compounds **34A**, **34B**, Intermediate **A**, **34C**, **34D**, and **34E** in lieu of iodoethane, Compounds **29B**, **29C**, Intermediate **B**, Compounds **1D**, **1E**, and **8E**. Compound **34A**: LC-MS (ESI) m/z : 222 $[M+H]^+$. Compound **34B**: LC-MS (ESI) m/z : 198 $[M+H]^+$. Compound **34C**: LC-MS (ESI) m/z : 240 $[M+H]^+$. Compound **34D**: LC-MS (ESI) m/z : 499 $[M+H]^+$; ^1H -NMR (CDCl₃, 400 MHz): δ (ppm) 1.00 (t, J = 7.6 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.50-1.56 (m, 2H), 1.79-1.84 (m, 2H), 3.63 (s, 3H), 4.01 (q, J = 7.2 Hz, 2H), 4.39 (q, J = 7.2 Hz, 2H), 5.67 (s, 2H), 6.67 (dd, J = 6.8, 2.0 Hz, 2H), 6.97 (dd, J = 8.8, 2.4 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H). Compound **34E**: LC-MS (ESI) m/z : 379 $[M+H]^+$. Compound **34**: LC-MS (ESI) m/z : 351 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.93 (t, J = 7.6 Hz, 3H),

1.44 (m, 2H), 1.71 (m, 2H), 4.03 (t, $J = 6.4$ Hz, 2H), 7.01 (dd, $J = 8.8$, $J = 2.4$ Hz, 1H), 7.42 (d, $J = 2.4$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 1H).

[00600] Example 35

[00601] Synthesis of 4-((2-(3,4-dichlorophenyl)-1-methyl-1H-imidazol-5-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (35**)**



[00602] To a solution of 2-bromo-1-methyl-1H-imidazole **35A** (5 g, 31.05 mmol) in chloroform (50 mL) was added NBS (5.53 g, 31.05 mmol) in several portions at 65 °C and stirred for 2 hours. The mixture was cooled down to room temperature, diluted with water (50 mL), and extracted with dichloromethane (30 mL). The organic phase was washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a product, which was slurred in dichloromethane/petroleum (50 mL, 2:3 in volume) to furnish Compound **35B**. LC-MS (ESI) m/z : 239 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.60 (s, 3H), 7.00 (s, 1H).

[00603] Compound **35C** was synthesized by employing the procedure described for Compound **8B** using Compound **35B** in lieu of Compound **8A**, LC-MS (ESI) m/z : 305 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 3.72 (s, 3H), 7.13 (s, 1H), 7.56 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 1.6$ Hz, 1H).

[00604] To a solution of Intermediate **D** (380 mg, 1.29 mmol) and Compound **35C** (395 mg, 1.29 mmol) in 1,4-dioxane (6 mL) was added *N,N*-diisopropylethylamine (333 mg, 2.58 mmol), $Pd_2(dba)_3$ (110 mg, 0.12 mmol), and Xantphos (133 mg, 0.23 mmol). The mixture was purged with nitrogen for 2 minutes and heated in a microwave oven at 120 °C for 70 minutes. After cooling down to room temperature, the mixture was filtered. The filtrate was concentrated

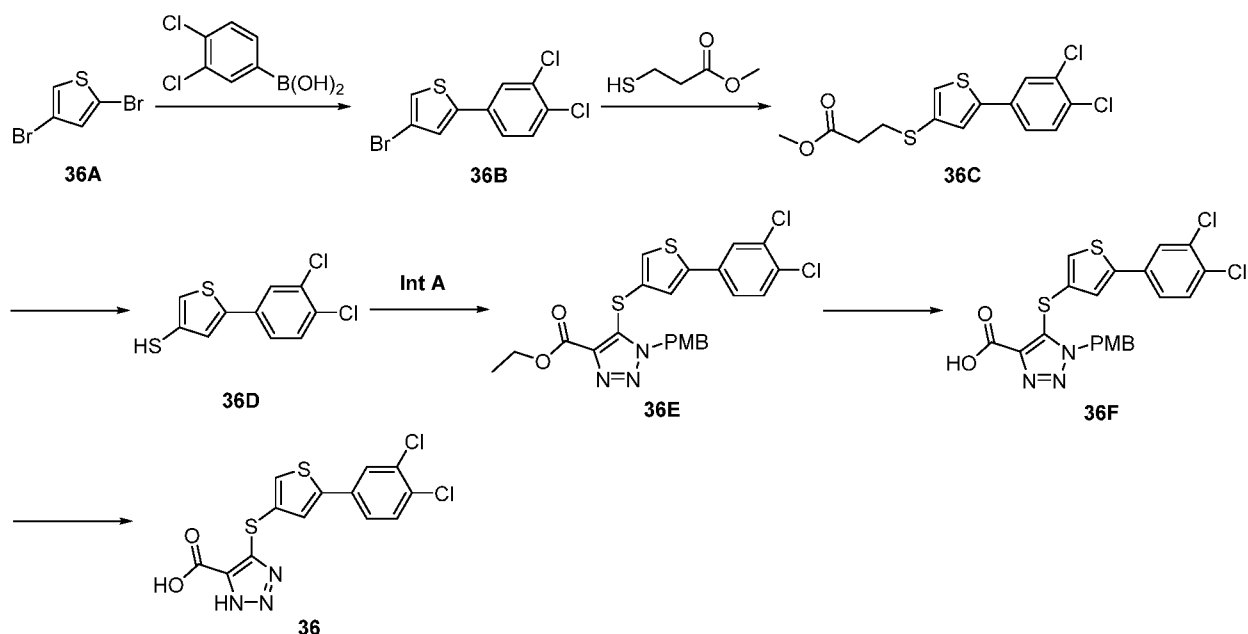
and purified with reverse phase chromatography using eluents (methanol in H₂O, from 20% to 100% v/v) to yield Compound **35D**. LC-MS (ESI) m/z: 518 [M+H]⁺.

[00605] Compounds **35E** and **35** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **35D** and **35E** in lieu of Compounds **8E** and **1E**.

Compound **35E**: LC-MS (ESI) m/z: 490 [M+H]⁺. Compound **35**: LC-MS (ESI) m/z: 370 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.70 (s, 3H), 7.77-7.79 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H).

[00606] **Example 36**

[00607] **Synthesis of 4-((5-(3,4-dichlorophenyl)thiophen-3-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (36)**

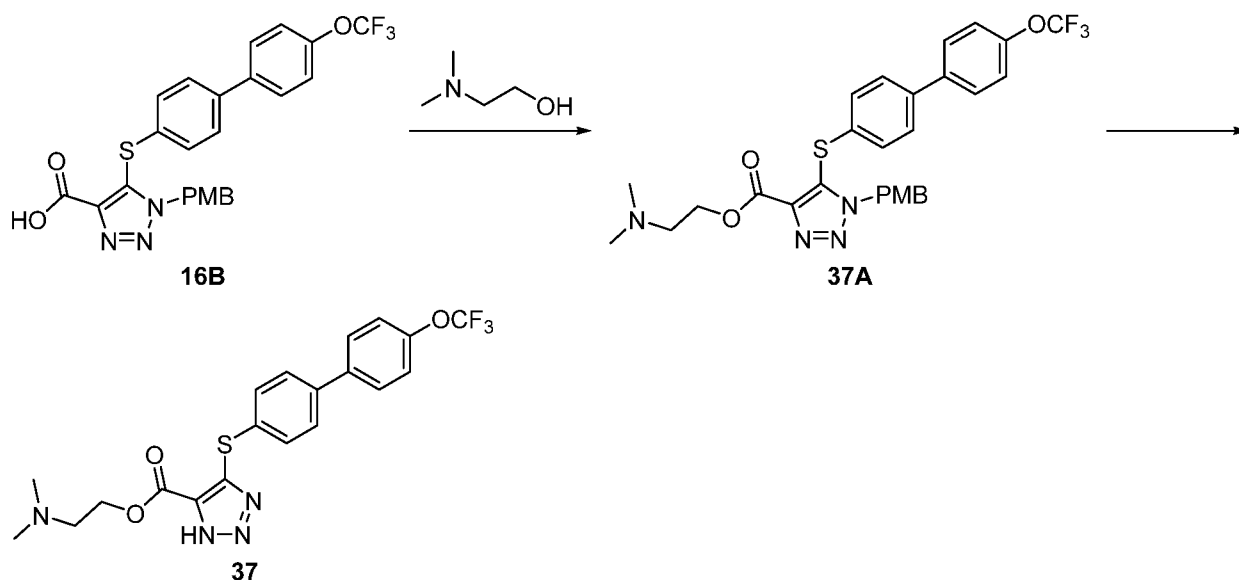


[00608] Compounds **36B**, **36C**, **36D**, **36E**, **36F**, and **36** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **2**, and **1** using Compounds **36A**, **36B**, **36C**, Intermediate **A**, **36D**, **36E**, and **36F** in lieu of Compounds **8A**, Intermediates **A**, **D-1**, **B**, **1D**, **1**, and **1E**. Compound **36B**: LC-MS (ESI) m/z: no ionizable compound under routine conditions used. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.21-7.23 (m, 2H), 7.36-7.39 (m, 1H), 7.45-7.47 (m, 1H), 7.62-7.64 (m, 1H). Compound **36C**: LC-MS (ESI) m/z: 347 [M+H]⁺. Compound **36D**: LC-MS (ESI) m/z: no ionizable compound under routine conditions used. Compound **36E**: LC-MS (ESI) m/z: 520 [M+H]⁺. Compound **36F**: LC-MS

(ESI) m/z : 492 $[M+H]^+$. Compound **36**: LC-MS (ESI) m/z : 372 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 7.55-7.60 (m, 3H), 7.74 (s, 1H), 7.82 (d, $J = 1.6$ Hz, 1H).

[00609] Example 37

[00610] Synthesis of 2-(dimethylamino)ethyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (37**)**

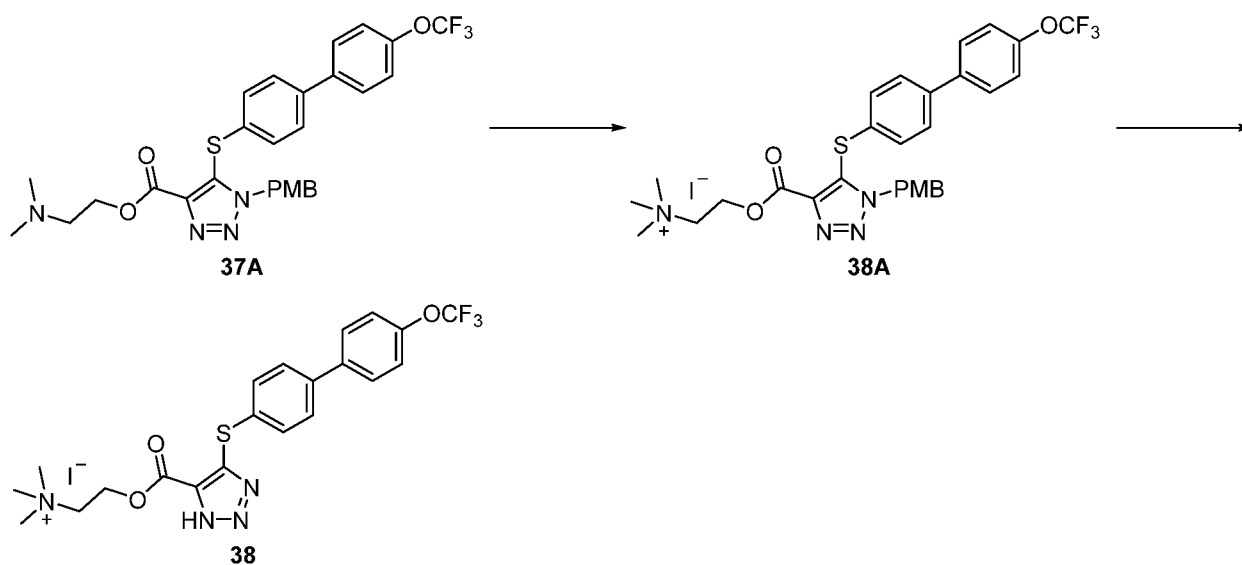


[00611] Compounds **37A** and **37** were synthesized by employing the procedures described for Compounds **19A** and **1** using 2-(dimethylamino)ethanol, Compounds **16B** using TEA as base and dichloromethane as solvent, and **37A** in lieu of cyclopropanol, Compounds **9A** using DIPEA as base and DMF as solvent, and **1E**. Compound **37A**: LC-MS (ESI) m/z : 573 $[M+H]^+$.

Compound **37**: LC-MS (ESI) m/z : 453 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 2.87 (s, 6H), 3.50 (t, $J = 4.8$ Hz, 2H), 4.62 (t, $J = 4.8$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 8.8$ Hz, 2H).

[00612] Example 38

[00613] Synthesis of N,N,N-trimethyl-2-((4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carbonyl)oxy)ethan-1-aminium iodide (38**)**

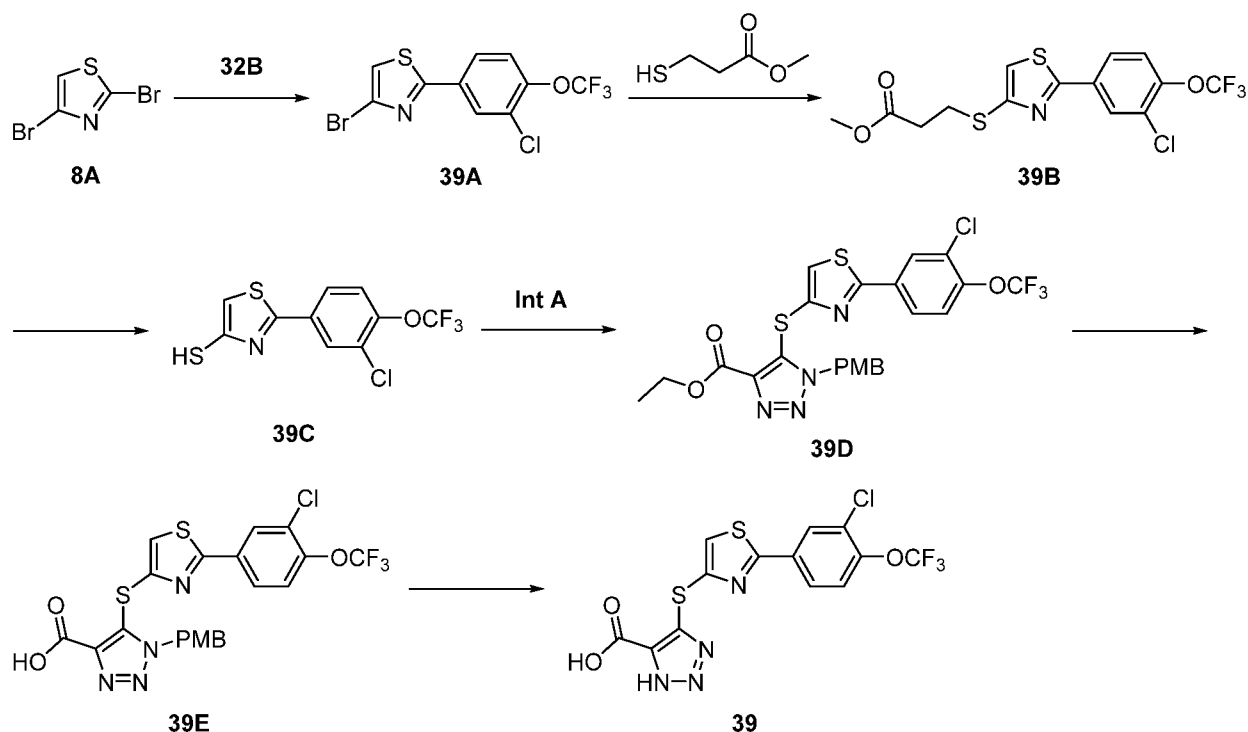


[00614] A mixture of Compound **37A** (200 mg, 0.349 mmol) and iodomethane (495 mg, 3.49 mmol) in acetonitrile (5 mL) was stirred at 50 °C for 4 hours. The mixture was concentrated under reduced pressure to furnish Compound **38A**. LC-MS (ESI) m/z : 587 $[M]^+$.

[00615] Compound **38** was synthesized by employing the procedure described for Compound **1** using Compound **38A** in lieu of Compound **1E**, LC-MS (ESI) m/z : 467 $[M]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.14 (s, 9H), 3.67-3.69 (m, 2H), 4.56-4.57 (m, 2H), 7.24 (d, $J = 8.8$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.8$ Hz, 2H).

[00616] Example 39

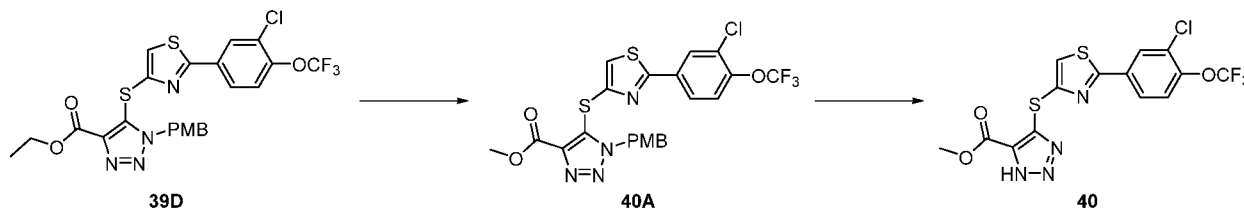
[00617] Synthesis of 4-((2-(3-chloro-4-(trifluoromethoxy)phenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (39)



[00618] Compounds **39A**, **39B**, **39C**, **39D**, **39E**, and **39** were synthesized by employing the procedures described for Compounds **8B**, Intermediates **D-1**, **D**, **1E**, **8F**, and **1** using Compounds **32B**, **39A**, **39B**, Intermediate **A**, **39C**, **39D**, and **39E** in lieu of (3,4-dichlorophenyl)boronic acid, Intermediates **A**, **D-1**, **B**, Compounds **1D**, **8E**, and **1E**. Compound **39A**: LC-MS (ESI) m/z : 358 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28 (s, 1H), 7.38-7.42 (m, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 8.10 (d, $J = 2.0$ Hz, 1H). Compound **39B**: LC-MS (ESI) m/z : 398 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.78 (t, $J = 6.8$ Hz, 2H), 3.35 (t, $J = 6.8$ Hz, 2H), 3.71 (s, 3H), 7.15 (s, 1H), 7.37-7.40 (m, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 8.09 (d, $J = 2.4$ Hz, 1H). Compound **39C**: LC-MS (ESI) m/z : 312 $[M+H]^+$. Compound **39D**: LC-MS (ESI) m/z : 571 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.36 (t, $J = 7.2$ Hz, 3H), 3.70 (s, 3H), 4.36-4.42 (m, 2H), 5.75 (s, 2H), 6.74 (d, $J = 9.2$ Hz, 2H), 7.10 (s, 1H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.35 (d, $J = 10.4$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 2.4$ Hz, 1H). Compound **39E**: LC-MS (ESI) m/z : 543 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.55 (s, 3H), 5.53 (s, 2H), 6.59 (brs, 2H), 7.16 (brs, 2H), 7.19 (s, 1H), 7.34 (brs, 1H), 7.70 (brs, 2H). Compound **39**: LC-MS (ESI) m/z : 423 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.70 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 8.07 (s, 1H), 8.19 (d, $J = 2.0$ Hz, 1H).

[00619] **Example 40**

[00620] Synthesis of methyl 4-((2-(3-chloro-4-(trifluoromethoxy)phenyl)thiazol-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (40)

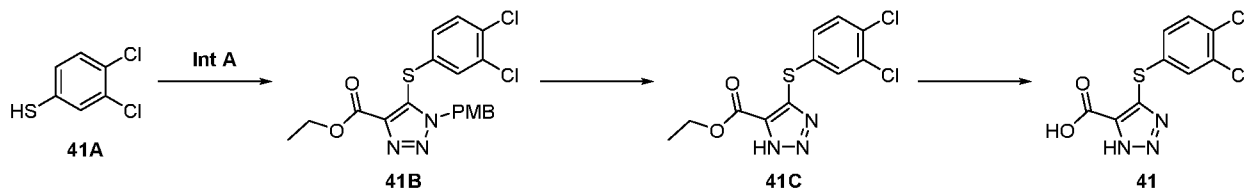


[00621] A solution of Compound **39D** (110 mg, 0.19 mmol) and concentrated H₂SO₄ (0.1 mL) in MeOH (5 mL) was stirred at 60 °C for 16 hours. The mixture was cooled down to room temperature, concentrated, and purified with reverse phase chromatography using eluents (acetonitrile in water, from 0% to 100% v/v) to afford Compound **40A**. LC-MS (ESI) m/z: 557 [M+H]⁺.

[00622] Compound **40** was synthesized by employing the procedure described for Compound **1** using Compound **40A** in lieu of Compound **1E**, LC-MS (ESI) m/z: 437 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.86 (s, 3H), 7.70 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 8.19 (d, *J* = 2.4 Hz, 1H).

[00623] Example 41

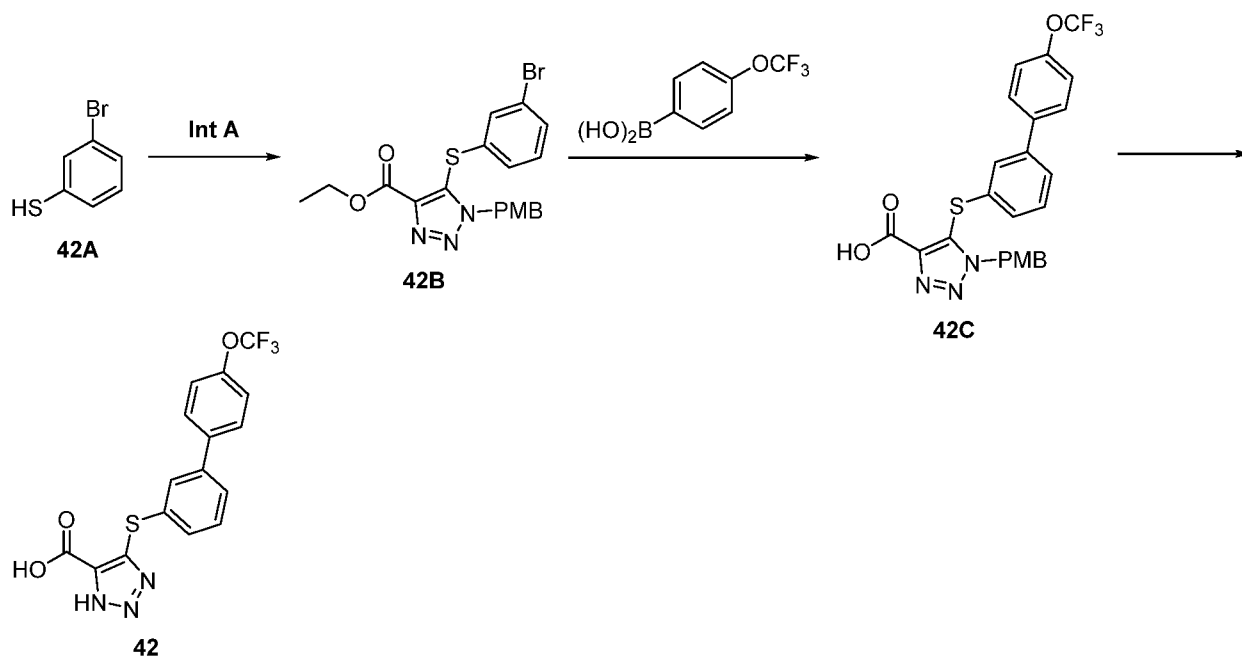
[00624] Synthesis of 4-((3,4-dichlorophenyl)thio)-1H-1,2,3-triazole-5-carboxylic acid (41)



[00625] Compounds **41B**, **41C**, and **41** were synthesized by employing the procedures described for Compounds **1E**, **1**, and **8F** using Intermediate **A**, Compounds **41A** using NMP as solvent at 100 °C, **41B**, and **41C** in lieu of Intermediates **B**, Compounds **1D** using DMF as solvent at 50 °C, **1E**, and **8E**. Compound **41B**: LC-MS (ESI) m/z: 438 [M+H]⁺. Compound **41C**: LC-MS (ESI) m/z: 318 [M+H]⁺. Compound **41**: LC-MS (ESI) m/z: 290 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 7.40 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H).

[00626] Example 42

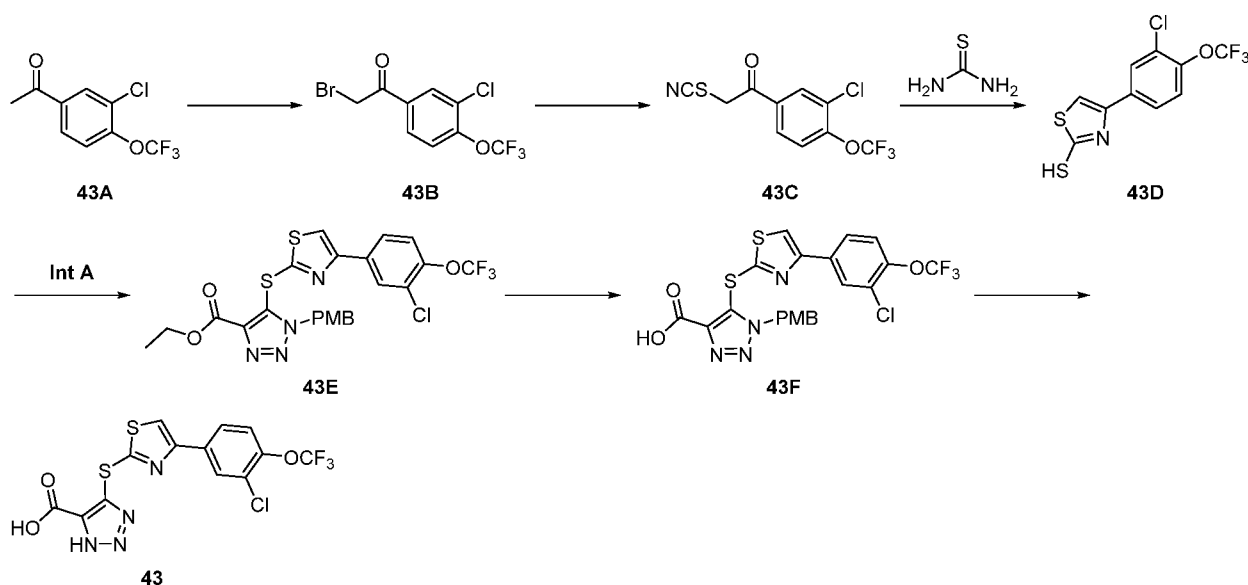
[00627] Synthesis of 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (42)



[00628] Compounds **42B**, **42C**, and **42** were synthesized by employing the procedures described for Compounds **1E**, **8B**, and **1** using Intermediate **A**, Compounds **42A** using NMP as solvent at 100 °C, **42B**, 4-(trifluoromethoxy)phenylboronic acid, and **42C** in lieu of Intermediates **B**, Compounds **1D** using DMF as solvent at 50 °C, **8A**, (3,4-dichlorophenyl)boronic acid, and **8E**. Compound **42B**: LC-MS (ESI) m/z : 448 $[\text{M}+\text{H}]^+$. Compound **42C**: LC-MS (ESI) m/z : 502 $[\text{M}+\text{H}]^+$. Compound **42**: LC-MS (ESI) m/z : 382 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 7.37 (d, $J = 8.4$ Hz, 2H), 7.51-7.80 (m, 6H).

[00629] Example 43

[00630] Synthesis of 4-((4-(3-chloro-4-(trifluoromethoxy)phenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (43)



[00631] To a solution of Compound **43A** (2.38 g, 10.0 mmol) in Et₂O (15 mL) was dropped Br₂ (1.60 g, 10.0 mmol) and stirred at room temperature for 2 hours. The mixture was washed with saturated NaHSO₃ solution (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **43B**. LC-MS (ESI) m/z: 317 [M+H]⁺.

[00632] To a solution of Compound **43B** (3.17 g, 10.0 mmol) in EtOH (50 mL) was added KSCN (970 mg, 10.0 mmol). After the mixture was stirred at room temperature for 1 hour, it was concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with H₂O (30 mL), dried over anhydrous sodium sulfate, filtered, and evaporated to give Compound **43C**. LC-MS (ESI) m/z: 296 [M+H]⁺.

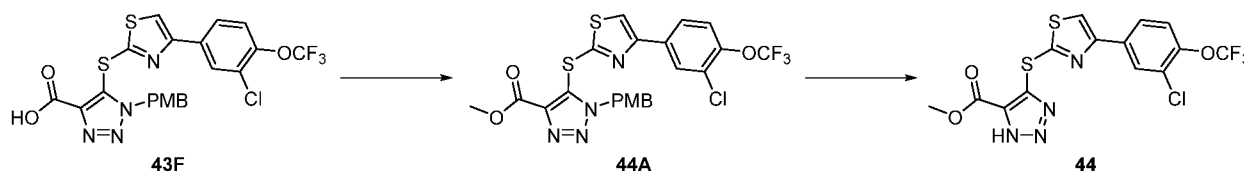
[00633] To a solution of Compound **43C** (1.9 g, 6.4 mmol) in EtOH (30%, 60 mL) was added thiourea (975 mg, 12.8 mmol) and concentrated HCl solution (10 mL). The mixture was stirred at 90 °C under nitrogen overnight. After cooling down to room temperature, the reaction mixture was concentrated and purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 12% v/v) to furnish Compound **43D**. LC-MS (ESI) m/z: 312 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 6.77 (s, 1H), 7.45-7.48 (m, 2H), 7.68 (d, *J* = 2.4 Hz, 1H), 11.6 (br, 1H).

[00634] Compounds **43E**, **43F**, and **43** were synthesized by employing the procedures described for Compounds **1E**, **8F**, and **1** using Intermediate **A**, Compound **43D** using NMP as solvent at 90 °C, **43E**, and **43F** in lieu of Intermediates **B**, Compound **1D** using DMF as solvent

at 50 °C, **8E**, and **1E**. Compound **43E**: LC-MS (ESI) m/z : 571 $[M+H]^+$. Compound **43F**: LC-MS (ESI) m/z : 543 $[M+H]^+$. Compound **43**: LC-MS (ESI) m/z : 423 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.64 (dd, $J_1 = 8.8$ Hz, $J_2 = 1.2$ Hz, 1H), 8.01 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 8.21 (d, $J = 2.0$ Hz, 1H), 8.37 (s, 1H).

[00635] Example 44

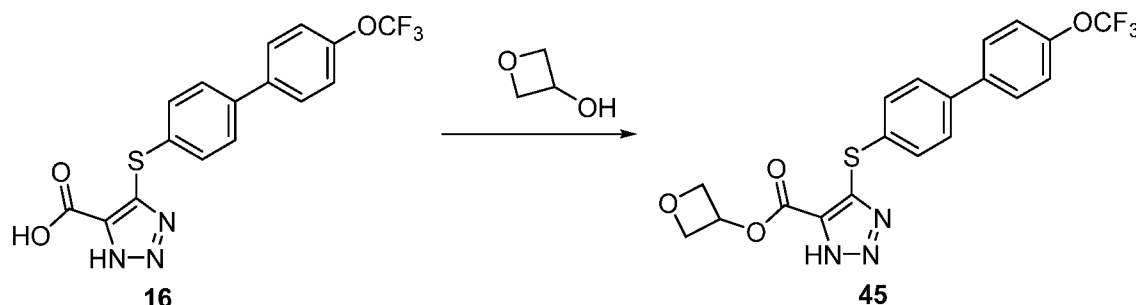
[00636] Synthesis of methyl 4-((4-(3-chloro-4-(trifluoromethoxy)phenyl)thiazol-2-yl)thio)-1H-1,2,3-triazole-5-carboxylate (44**)**



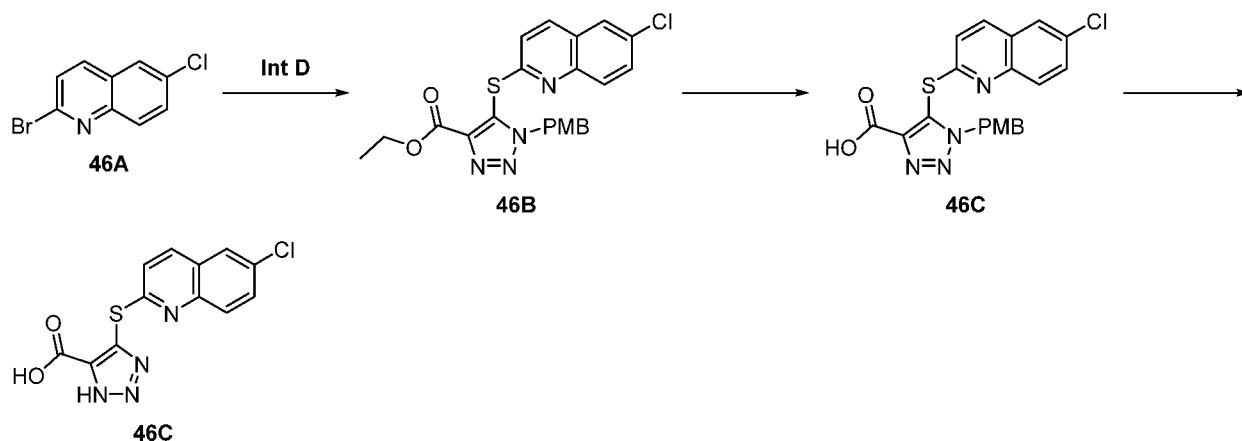
[00637] Compounds **44A** and **44** were synthesized by employing the procedures described for Compounds **11A** and **1** using methanol, Compounds **43F**, and **44A** in lieu of propan-2-ol, Compounds **9A**, and **1E**. Compound **44A**: LC-MS (ESI) m/z : 557 $[M+H]^+$. Compound **44**: LC-MS (ESI) m/z : 437 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 3.85 (s, 3H), 7.65 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.2$ Hz, 1H), 8.00 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 8.20 (d, $J = 2.4$ Hz, 1H), 8.40 (s, 1H).

[00638] Example 45

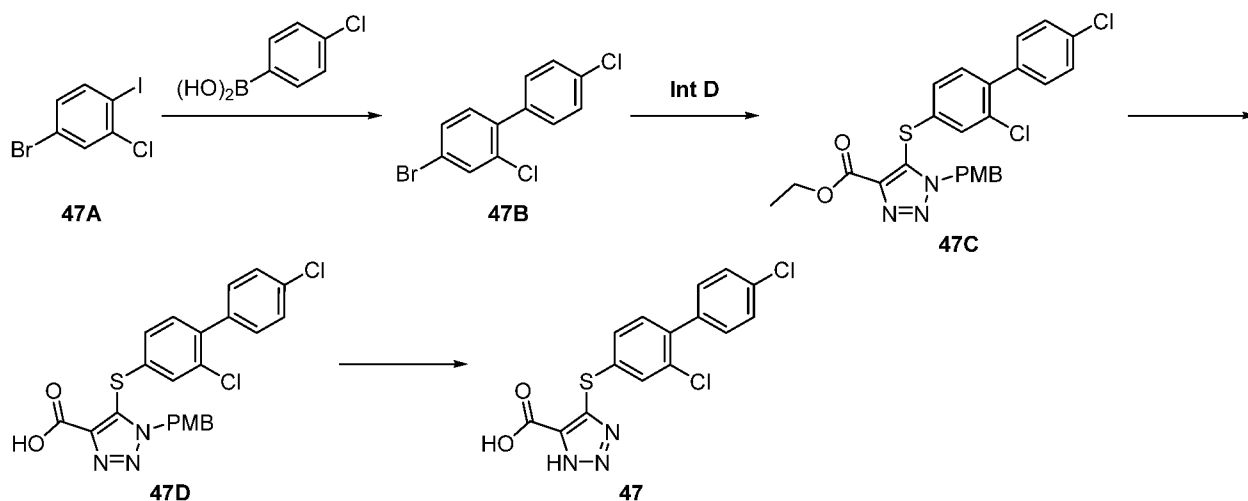
[00639] Synthesis of oxetan-3-yl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (45**)**



[00640] Compound **45** was synthesized by employing the procedure described for Compound **19A** using oxetan-3-ol and Compound **16** using TEA as base and dichloromethane as solvent in lieu of cyclopropanol and Compound **9A** using DIPEA as base and DMF as solvent, LC-MS (ESI) m/z : 438 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 4.52-4.55 (m, 2H), 4.81-4.85 (m, 2H), 5.53-5.59 (m, 1H), 7.45-7.48 (m, 4H), 7.68 (d, $J = 8.0$ Hz, 2H), 7.80 (d, $J = 8.8$ Hz, 2H).

[00641] Example 46**[00642] Synthesis of 4-((6-chloroquinolin-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (46)**

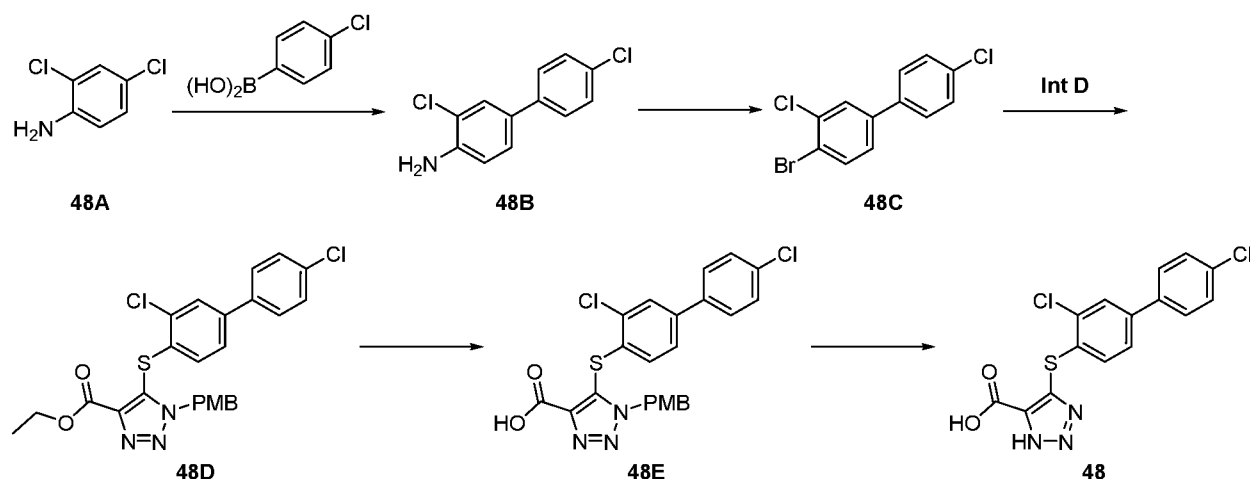
[00643] Compounds **46B**, **46C**, and **46** were synthesized by employing the procedures described for Compounds **35D**, **8F**, and **1** using Compounds **46A**, **46B**, and **46** in lieu of Compounds **35C**, **8E**, and **1E**. Compound **46B**: LC-MS (ESI) m/z : 455 $[M+H]^+$. Compound **46C**: LC-MS (ESI) m/z : 427 $[M+H]^+$. Compound **46**: LC-MS (ESI) m/z : 307 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.36 (d, $J = 8.8$ Hz, 1H), 7.72-7.81 (m, 2H), 8.08 (s, 1H), 8.23 (d, $J = 8.8$ Hz, 1H), 13.56 (brs, 1H), 16.08 (brs, 1H).

[00644] Example 47**[00645] Synthesis of 4-((2,4'-dichloro-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (47)**

[00646] Compounds **47B**, **47C**, **47D**, and **47** were synthesized by employing the procedures described for Compounds **8B**, **35D**, **8F**, and **1** using 4-chlorophenylboronic acid, Compounds **47A**, **47B**, **47C**, and **47D** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A**, **35C**, **8E**, and **1E**. Compound **47B**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 7.18 (d, $J = 8.0$ Hz, 1H), 7.33-7.35 (m, 2H), 7.40-7.42 (m, 2H), 7.45 (dd, $J = 2.0$ Hz, 8.4 Hz, 1H), 7.65 (d, $J = 2.0$ Hz, 1H). Compound **47C**: LC-MS (ESI) m/z : 514 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.36 (t, $J = 6.8$ Hz, 3H), 3.72 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 5.63 (s, 2H), 6.73-6.75 (m, 2H), 6.86-6.90 (m, 2H), 7.06-7.08 (m, 1H), 7.14-7.16 (m, 2H), 7.27-7.29 (m, 2H), 7.38-7.40 (m, 2H). Compound **47D**: LC-MS (ESI) m/z : 486 $[\text{M}+\text{H}]^+$. Compound **47**: LC-MS (ESI) m/z : 366 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.46-7.50 (m, 4H), 7.55-7.57 (m, 2H), 7.69 (s, 1H).

[00647] **Example 48**

[00648] **Synthesis of 4-((3,4'-dichloro-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (**48**)**

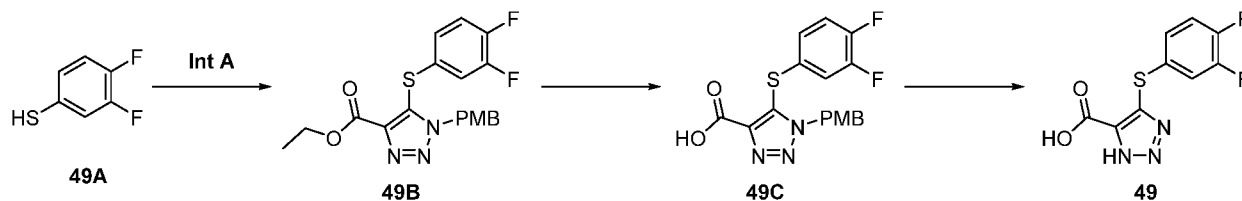


[00649] Compounds **48B**, **48C**, **48D**, **48E**, and **48** were synthesized by employing the procedures described for Compounds **8B**, **30B**, **35D**, **8F**, and **1** using 4-chlorophenylboronic acid, Compounds **48A** using Na_2CO_3 as base and 1,4-dioxane as solvent, **48B** using *t*-butyl nitrite and CuBr , **48C**, **48D**, and **48E** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** using Cs_2CO_3 as base and DME as solvent, **30A** using isoamyl nitrite and CuCl_2 , **35C**, **8E**, and **1E**. Compound **48B**: LC-MS (ESI) m/z : 238 $[\text{M}+\text{H}]^+$. Compound **48C**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **48D**: LC-MS (ESI) m/z : 514 $[\text{M}+\text{H}]^+$. Compound **48E**: LC-MS (ESI) m/z : 486 $[\text{M}+\text{H}]^+$. Compound **48**: LC-MS (ESI) m/z :

366 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.40 (d, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.63-7.66 (m, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 2.0 Hz, 1H), 13.55 (br, 1H), 14.75 (br, 1H).

[00650] Example 49

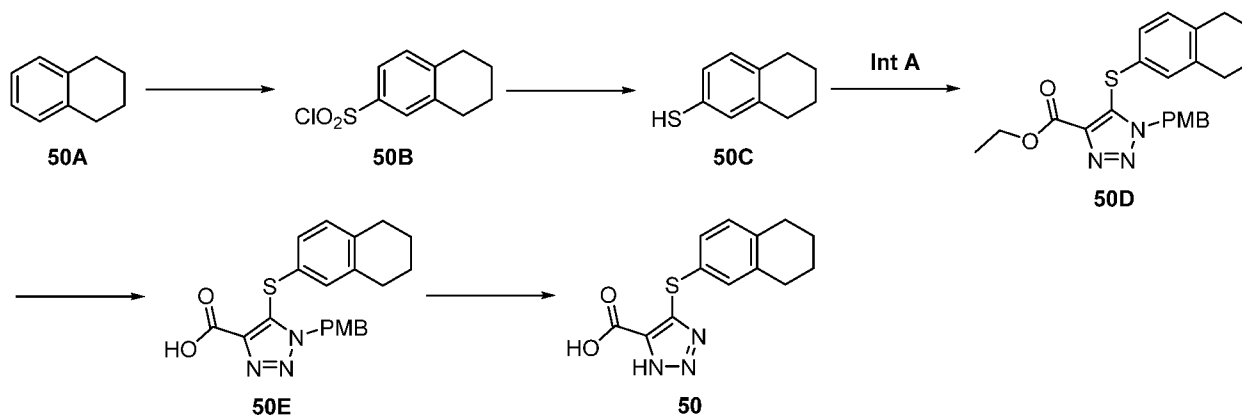
[00651] Synthesis of 4-((3,4-difluorophenyl)thio)-1H-1,2,3-triazole-5-carboxylic acid (49)



[00652] Compounds **49B**, **49C**, and **49** were synthesized by employing the procedures described for Compounds **1E**, **8F**, and **1** using Intermediate **A**, Compounds **49A**, **49B**, and **49C** in lieu of Intermediates **B**, Compounds **1D**, **8E**, and **1E**. Compound **49B**: LC-MS (ESI) *m/z*: 406 [M+H]⁺. Compound **49C**: LC-MS (ESI) *m/z*: 400 [M+Na]⁺. Compound **49**: LC-MS (ESI) *m/z*: 258 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.36 (s, 1H), 7.45-7.52 (m, 1H), 7.66 (t, *J* = 8.4 Hz, 1H).

[00653] Example 50

[00654] Synthesis of 4-((5,6,7,8-tetrahydronaphthalen-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (50)



[00655] To a solution of Compound **50A** (9.66 g, 73 mmol) in CHCl₃ (22 mL) was dropped ClSO₃H (26 g, 0.223 mol) at -10 °C. The mixture was stirred at room temperature for 1 hour, poured into ice-water (100 mL), and extracted with dichloromethane (100 mL x 2). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The

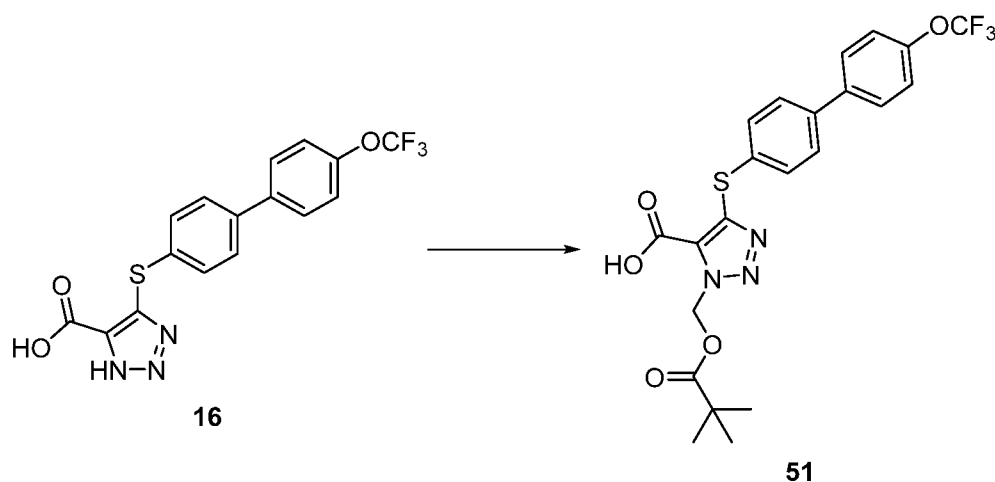
residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to yield Compound **50B**. LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.83-1.86 (m, 4H), 2.85-2.88 (m, 4H), 7.27-7.29 (m, 1H), 7.71-7.73 (m, 2H).

[00656] To a mixture of Compound **50B** (1.5 g, 6.5 mmol) and Zn powder (2.5 g, 38.2 mmol) in ethanol (10 mL) was dropped concentrated HCl (10 mL) over a period of 30 minutes. After the mixture was stirred at 80 °C for 1 hour and cooled down to room temperature, it was filtered. The filtration was diluted with ethyl acetate (200 mL). The organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to yield Compound **50C**. LC-MS (ESI) m/z: 163 [M-H]⁻; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.75-1.78 (m, 4H), 2.68-2.72 (m, 4H), 3.34 (s, 1H), 6.92-6.94 (m, 1H), 7.00-7.02 (m, 2H).

[00657] Compounds **50D**, **50E**, and **50** were synthesized by employing the procedures described for Compounds **1E**, **8F**, and **1** using Intermediate **A**, Compounds **50C**, **50D**, and **50E** in lieu of Intermediates **B**, Compounds **1D**, **8E**, and **1E**. Compound **50D**: LC-MS (ESI) m/z: 424 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ 1.34 (t, *J* = 6.8 Hz, 3H), 1.72-1.73 (m, 4H), 2.53-2.56 (m, 2H), 2.66-2.68 (m, 2H), 3.76 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.51 (s, 2H), 6.63 (s, 1H), 6.75-6.78 (m, 2H), 6.83-6.91 (m, 2H), 7.12-7.15 (m, 2H). Compound **50E**: LC-MS (ESI) m/z: 396 [M+H]⁺. Compound **50**: LC-MS (ESI) m/z: 276 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.71-1.74 (m, 4H), 2.69-2.71 (m, 4H), 7.07-7.09 (m, 1H), 7.16-7.20 (m, 2H).

[00658] **Example 51**

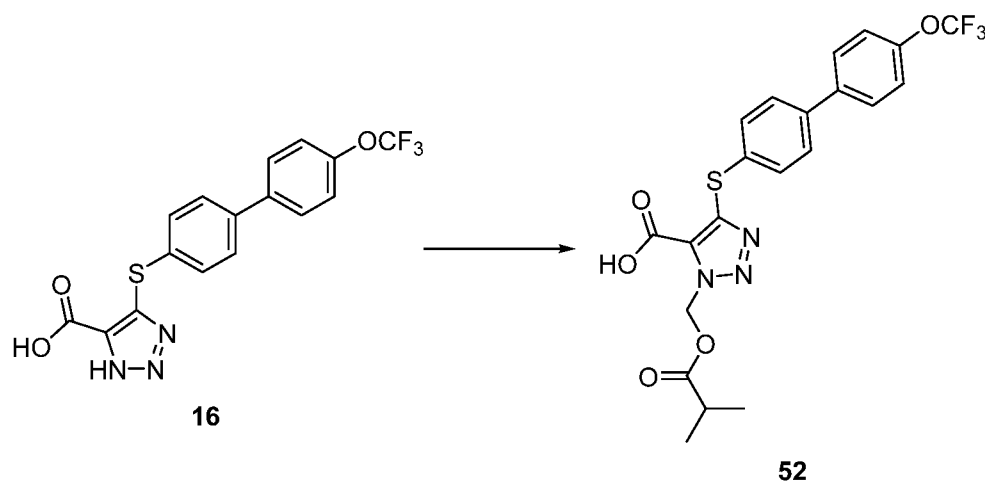
[00659] **Synthesis of 1-((pivaloyloxy)methyl)-4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (51)**



[00660] To a solution of Compound **16** (50 mg, 0.13 mmol) in 1,4-dioxane (2 mL) was added chloromethyl pivalate (21 mg, 0.143 mmol), triethylamine (59 mg, 0.26 mmol), and NaI (2 mg). The mixture was stirred at 50 °C for 1 hour and concentrated under vacuum. The residue was purified by preparative HPLC to furnish Compound **51**. LC-MS (ESI) *m/z*: 496 [M+H]⁺. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.11 (s, 9H), 6.15 (s, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.68 (d, *J* = 6.8 Hz, 2H), 7.82 (d, *J* = 6.8 Hz, 2H).

[00661] Example 52

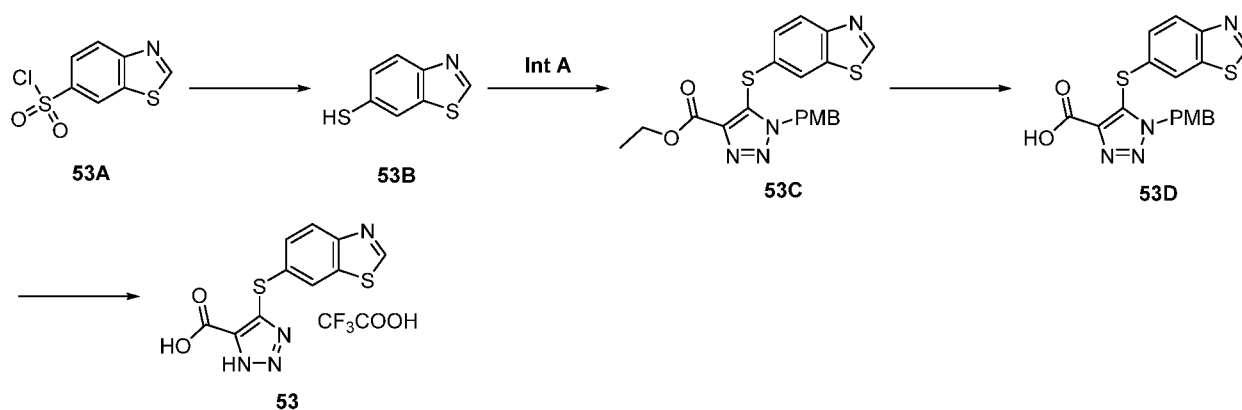
[00662] Synthesis of 1-((isobutyryloxy)methyl)-4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (52**)**



[00663] Compound **52** was synthesized by employing the procedure described for Compound **51** using chloromethyl isobutyrate in lieu of chloromethyl pivalate, LC-MS (ESI) *m/z*: 482 [M+H]⁺. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.03 (s, 3H), 1.05 (s, 3H), 2.55-2.57 (m, 1H), 6.15 (s, 2H), 7.46 (d, *J* = 6.8 Hz, 2H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.68 (d, *J* = 6.8 Hz, 2H), 7.82 (d, *J* = 6.8 Hz, 2H).

[00664] Example 53

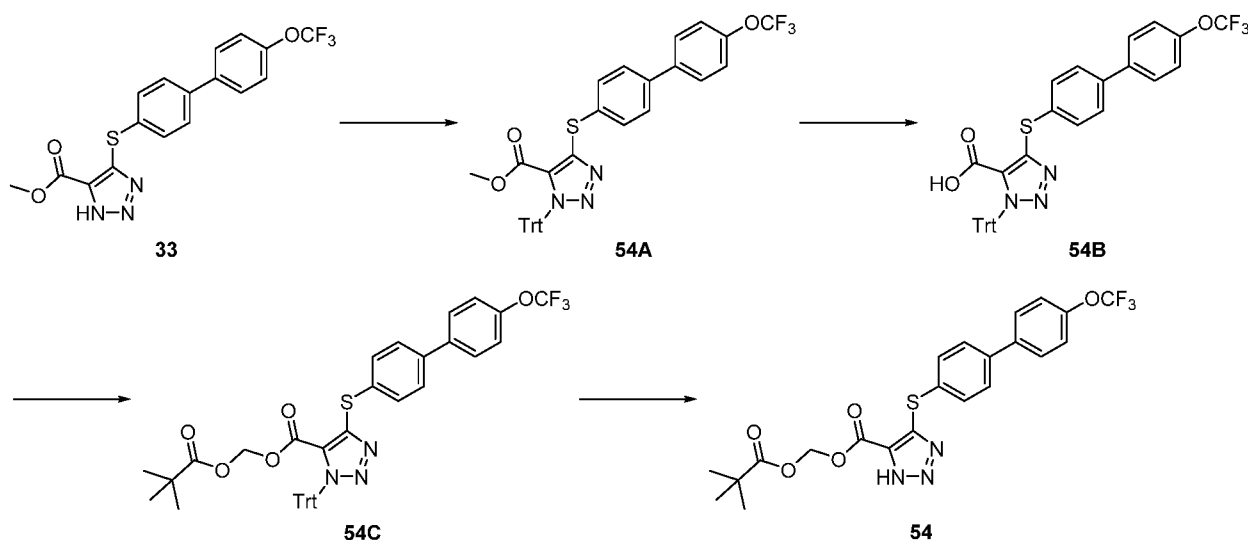
[00665] Synthesis of 4-(benzo[d]thiazol-6-ylthio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (53**)**



[00666] Compounds **53B**, **53C**, **53D**, and **53** were synthesized by employing the procedures described for Compounds **50C**, **1E**, **8F**, and **1** using Compounds **53A**, Intermediate **A**, **53B** using NMP as solvent at 100 °C, **53C**, and **53D** in lieu of Compounds **50B**, Intermediates **B**, Compounds **1D** using DMF as solvent at 50 °C, **8E**, and **1E**. Compound **53B**: LC-MS (ESI) *m/z*: 168 [M+H]⁺. Compound **53C**: LC-MS (ESI) *m/z*: 427 [M+H]⁺. Compound **53D**: LC-MS (ESI) *m/z*: 399 [M+H]⁺. Compound **53**: LC-MS (ESI) *m/z*: 279 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.60 (dd, *J*₁ = 8.8 Hz, *J*₂ = 2.0 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 1.2 Hz, 1H), 9.43 (s, 1H).

[00667] **Example 54**

[00668] **Synthesis of (pivaloyloxy)methyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (**54**)**



[00669] To a solution of Compound **33** (280 mg, 0.71 mmol) in CH₃CN (20 mL) was added (chloromethanetriyl)tribenzene (198 mg, 0.71 mmol) and triethylamine (143 mg, 1.42

mmol) and stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **54A**. LC-MS (ESI) m/z : 638 $[M+H]^+$.

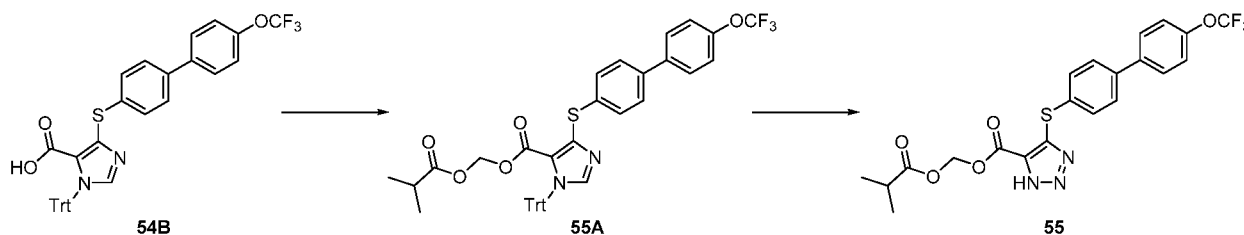
[00670] Compound **54B** was synthesized by employing the procedure described for Compound **8F** using Compound **54A** in lieu of Compound **8E**, LC-MS (ESI) m/z : 622. $[M-H]^-$.

[00671] To a solution of Compound **54B** (150 mg, 0.24 mmol) in DMF (10 mL) was added chloromethyl isobutyrate (36 mg, 0.24 mmol) and Na_2CO_3 (50 mg, 0.48 mmol). The reaction mixture was stirred at 50 °C for 3 hour. After cooling down to room temperature, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL x 3). The combined extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to furnish Compound **54C**. LC-MS (ESI) m/z : non-ionizable compound under routine conditions used.

[00672] To a solution of Compound **54C** (110 mg, 0.16 mmol) in dichloromethane (4 mL) was added 2,2,2-trifluoroacetic acid (1 mL) and stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC to afford Compound **54**. LC-MS (ESI) m/z : 496 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.19 (s, 9H), 5.99 (s, 2H), 7.35 (d, J = 6.8 Hz, 2H), 7.56 (d, J = 6.8 Hz, 2H), 7.65 (d, J = 6.8 Hz, 2H), 7.73 (d, J = 6.8 Hz, 2H).

[00673] Example 55

[00674] Synthesis of (isobutyryloxy)methyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylate (55**)**

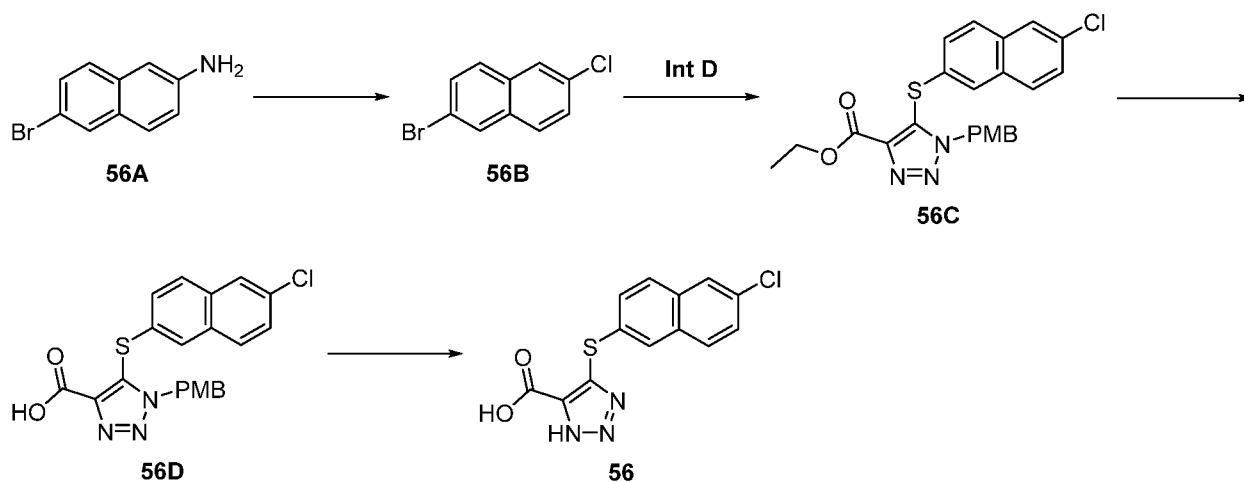


[00675] Compounds **55A** and **55** were synthesized by employing the procedures described for Compounds **54C** and **1** using chloromethyl isobutyrate and **55A** in lieu of chloromethyl pivalate and **1E**. Compound **55A**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **55**: LC-MS (ESI) m/z : 482 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz):

δ (ppm) 1.13 (s, 3H), 1.15 (s, 3H), 2.57-2.60 (m, 1H), 5.97 (s, 2H), 7.34 (d, J = 6.8 Hz, 2H), 7.51 (d, J = 6.8 Hz, 2H), 7.61 (d, J = 6.8 Hz, 2H), 7.71 (d, J = 6.8 Hz, 2H).

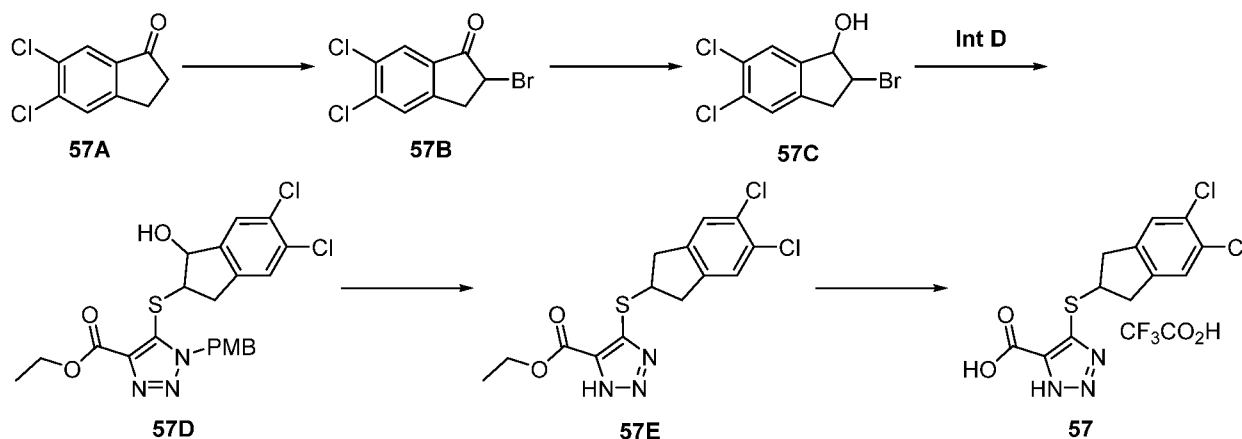
[00676] Example 56

[00677] Synthesis of 4-((6-chloronaphthalen-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (56**)**



[00678] To a solution of 6-bromonaphthalen-2-amine (Compound **56A**) (1 g, 4.52 mmol) in H₂O (5 mL) and HCl (6 N, 10 mL) was added NaNO₂ (350 mg, 4.97 mmol). After the mixture was stirred at room temperature for 1 hour, to it was added a solution of CuCl (2.27 g, 20.73 mmol) in HCl (6 N, 5 mL) and stirred at room temperature for 3 hours. The reaction mixture was poured into ice water (50 mL). A solid was precipitated, filtered, and dried under vacuum to give Compound **56B**. LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used.

[00679] Compounds **56C**, **56D**, and **56** were synthesized by employing the procedures described for Compounds **35D**, **8F**, and **1** using Compounds **56B**, **56C**, and **56D** in lieu of Compounds **35C**, **8E**, and **1E**. Compound **56C**: LC-MS (ESI) m/z : 454 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.08 (t, J = 6.8 Hz, 3H), 3.59 (s, 3H), 4.13-4.20 (m, 2H), 5.66 (s, 2H), 6.72 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 7.49-7.53 (m, 1H), 7.56-7.57 (m, 1H), 7.76-7.79 (m, 2H), 7.99 (d, J = 2.0 Hz, 1H). Compound **56D**: LC-MS (ESI) m/z : 426 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.55 (s, 3H), 5.50 (s, 2H), 6.63 (d, J = 9.2 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 1H), 7.43-7.49 (m, 2H), 7.69-7.75 (m, 2H), 7.96 (d, J = 1.6 Hz, 1H). Compound **56**: LC-MS (ESI) m/z : 306 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.56 (d, J = 8.8 Hz, 2H), 7.91-7.98 (m, 2H), 8.10 (d, J = 8.8 Hz, 2H).

[00680] Example 57**[00681] Synthesis of 4-((5,6-dichloro-2,3-dihydro-1H-inden-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic 2,2,2-trifluoroacetate (57)**

[00682] To a solution of 5,6-dichloro-2,3-dihydro-1H-inden-1-one (Compound **57A**) (6.03 g, 30 mmol) in dichloromethane (100 mL) was added pyridinium bromide perbromide (10.5 g, 33 mmol) at 0 °C and stirred at room temperature overnight. The mixture was diluted with EtOAc (50 mL) and washed with brine (15 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to afford Compound **57B**. LC-MS (ESI) *m/z*: 279 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.36-3.41 (m, 1H), 3.78-3.85 (m, 1H), 4.67 (dd, *J* = 7.2, 2.8 Hz, 1H), 7.60 (s, 1H), 7.92 (s, 1H).

[00683] To a solution of Compound **57B** (500 mg, 1.79 mmol) in methanol (15 mL) was added sodium borohydride (102 mg, 2.68 mmol) and stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with brine (15 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **57C**. LC-MS (ESI) *m/z*: 281 [M+H]⁺.

[00684] A mixture of Compound **57C** (200 mg, 0.71 mmol), Intermediate **D** (208 mg, 0.71 mmol), and sodium carbonate (159 mg, 1.5 mmol) in 1-methylpyrrolidin-2-one (8 mL) was stirred at 80 °C overnight. The mixture was diluted with EtOAc (50 mL) and washed with brine (15 mL x 3). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated,

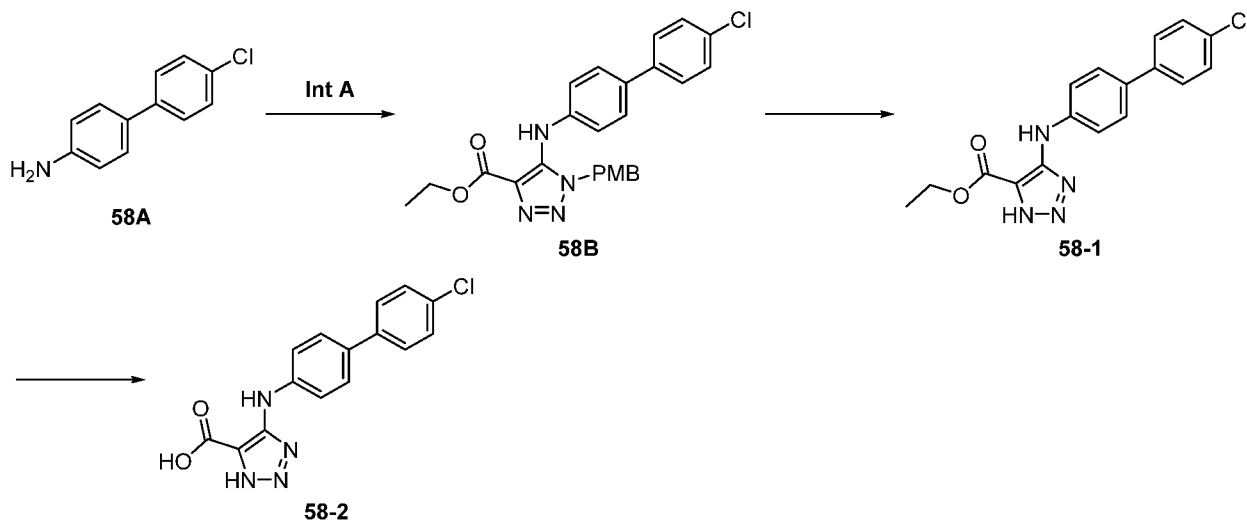
and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **57D**. LC-MS (ESI) m/z : 494 $[M+H]^+$.

[00685] A mixture of Compound **57D** (140 mg, 0.28 mmol) and triethylsilane (326 mg, 2.8 mmol) in TFA (2 mL) was stirred at 60 °C for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified with preparative TLC (ethyl acetate in dichloromethane, 20% v/v) to afford Compound **57E**. LC-MS (ESI) m/z : 358 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.42 (t, $J = 7.2$ Hz, 3H), 3.00 (dd, $J = 16.8, 5.2$ Hz, 2H), 3.52 (dd, $J = 16.8, 7.6$ Hz, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 4.46-4.50 (m, 1H), 7.30 (s, 2H).

[00686] Compound **57** was synthesized by employing the procedure described for Compound **8F** using Compound **57E** in lieu of Compound **8E**, LC-MS (ESI) m/z : 330 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 3.00 (dd, $J = 16.8, 5.2$ Hz, 2H), 3.52 (dd, $J = 16.8, 7.6$ Hz, 2H), 4.46-4.50 (m, 1H), 7.38 (s, 2H).

[00687] **Example 58**

[00688] **Synthesis of ethyl 4-((4'-chloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylate (**58-1**) and 4-((4'-chloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (**58-2**)**

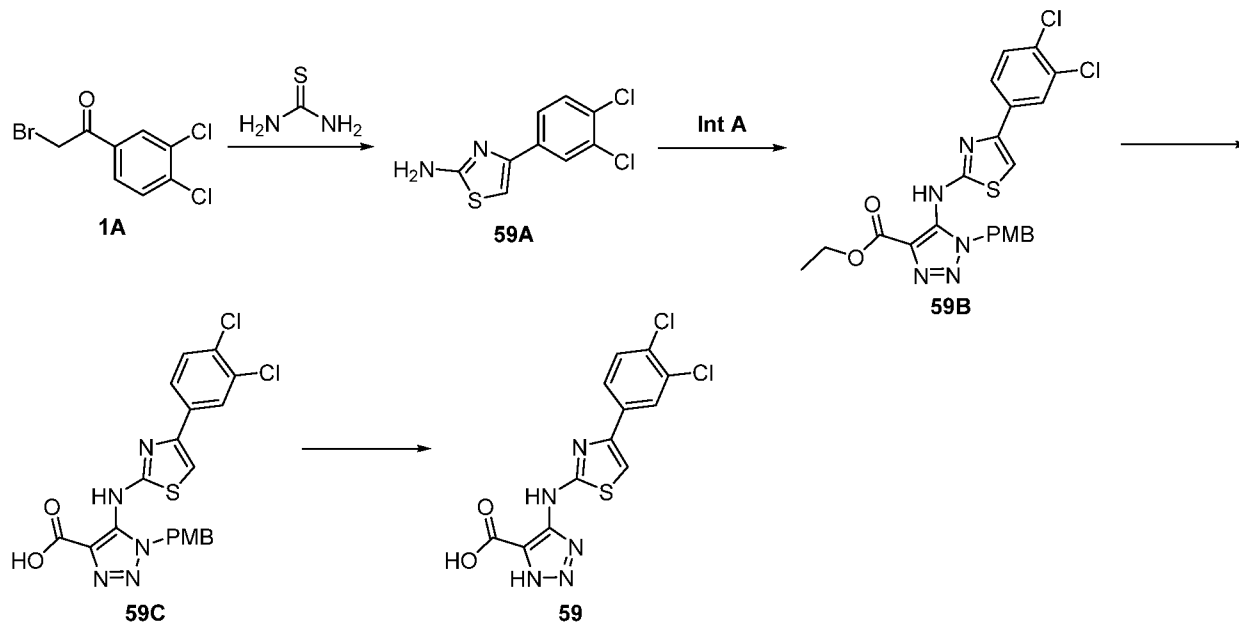


[00689] Compounds **58B**, **58-1**, and **58-2** were synthesized by employing the procedures described for Compounds **6B**, **1**, and **8F** using Intermediate A, Compound **58A** using K_3PO_4 as base, **58B**, and **58-1** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **1E**, and **8E**. Compound **58B**: LC-MS (ESI) m/z : 463 $[M+H]^+$. Compound **58-1**: LC-MS (ESI) m/z : 343. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.41 (t, $J = 7.2$ Hz, 3H), 4.44 (q, $J = 7.2$ Hz, 2H),

7.45-7.47 (m, 2H), 7.64-7.69(s, 4H), 7.77-7.79 (s, 2H), 8.19 (brs, 1H). Compound **58-2**: LC-MS (ESI) m/z : 315. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.45-7.47 (m, 2H), 7.54-7.63 (s, 4H), 7.65-7.67 (s, 2H), 9.13 (brs, 1H).

[00690] Example 59

[00691] Synthesis of 4-((4-(3,4-dichlorophenyl)thiazol-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (59**)**



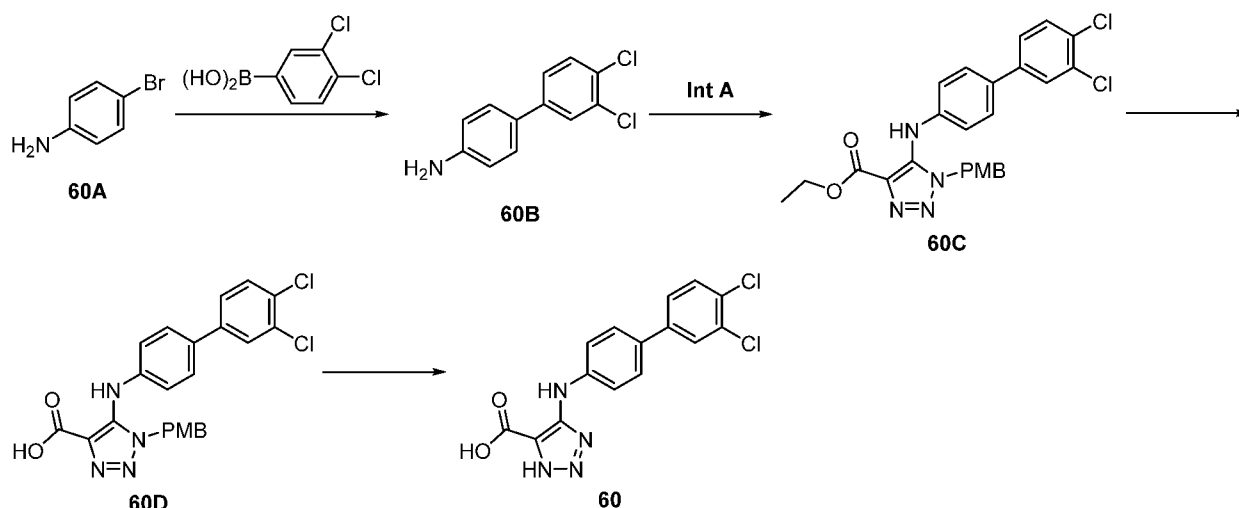
[00692] A suspension of 2-bromo-1-(3,4-dichlorophenyl)ethanone (**1A**) (2.68 g, 10 mmol) and thiourea (912 mg, 12.0 mmol) in EtOH (20 mL) was heated at reflux for 2 hours. The mixture was concentrated and the residue was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to yield Compound **59A**. LC-MS (ESI) m/z : 245 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 5.01 (br, 2H), 6.75 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.59 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 7.89 (d, $J = 2.0$ Hz, 1H)

[00693] Compounds **59B**, **59C**, and **59** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **59A** using K_3PO_4 as base, **59B**, and **59C** in lieu of Compounds **6A**, 1-methylpiperazine using t-BuONa as base, **8E**, and **1E**. Compound **59B**: LC-MS (ESI) m/z : 504 $[\text{M}+\text{H}]^+$. Compound **59C**: LC-MS (ESI) m/z : 476 $[\text{M}+\text{H}]^+$. Compound **59**: LC-MS (ESI) m/z : 356 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz,):

δ (ppm) 4.02 (br, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.93 (d, J = 6.8 Hz, 1H), 8.19 (s, 1H), 9.57 (br, 1H).

[00694] Example 60

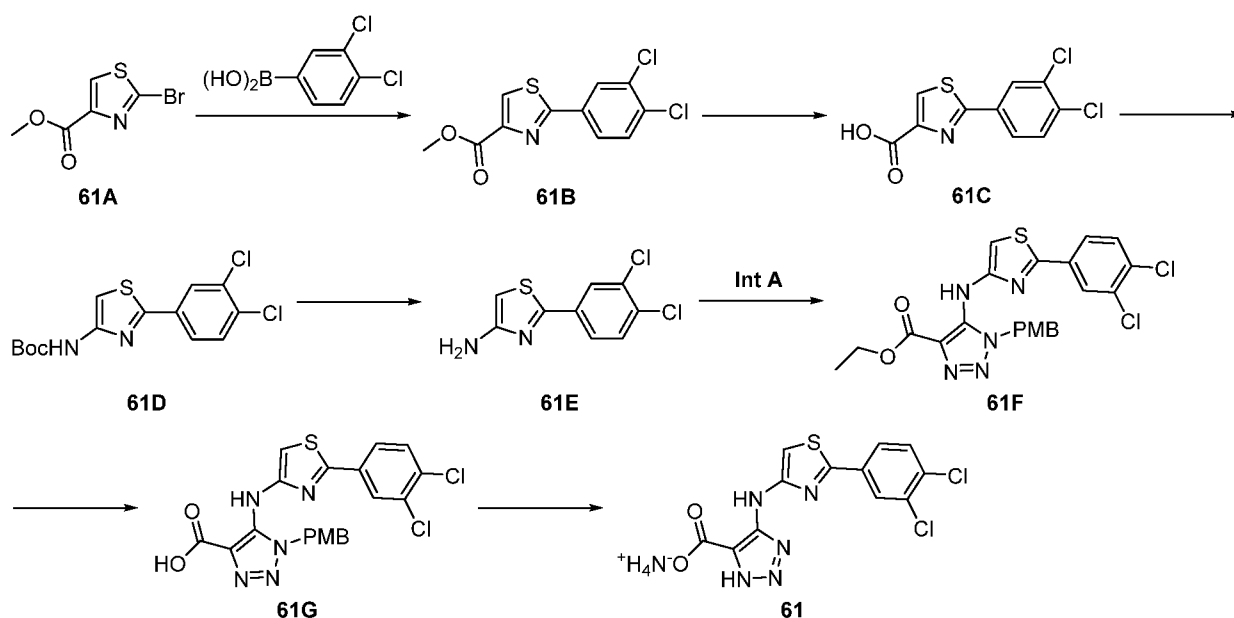
[00695] Synthesis of 4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (60)



[00696] Compounds **60B**, **60C**, **60D**, and **60** were synthesized by employing the procedures described for Compounds **8B**, **6B**, **8F**, and **1** using Compound **60A** using Na_2CO_3 as base, Intermediate **A**, **60B** using K_3PO_4 as base, **60C**, and **60D** in lieu of Compound **8A** using Cs_2CO_3 as base, **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **60B**: LC-MS (ESI) m/z : 238 $[\text{M}+\text{H}]^+$. Compound **60C**: LC-MS (ESI) m/z : 497 $[\text{M}+\text{H}]^+$. ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 1.40 (t, J = 6.8 Hz, 3H), 3.75 (s, 3H), 4.41 (q, J = 7.6 Hz, 2H), 5.22 (s, 2H), 6.73 (dd, J = 2.4, 6.8 Hz, 2H), 6.82-6.89 (m, 4H), 7.16 (s, 1H), 7.38 (dd, J = 2.4, 8.8 Hz, 1H), 7.46 (dd, J = 1.6, 6.8 Hz, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 2.0 Hz, 1H). Compound **60D**: LC-MS (ESI) m/z : 469 $[\text{M}+\text{H}]^+$. Compound **60**: LC-MS (ESI) m/z : 349 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.65-7.68 (m, 7H), 7.90 (s, 1H), 8.33 (s, 1H), 14.95 (s, 1H).

[00697] Example 61

[00698] Synthesis of ammonium 4-((2-(3,4-dichlorophenyl)thiazol-4-yl)amino)-1H-1,2,3-triazole-5-carboxylate (61)



[00699] Compounds **61B** and **61C** were synthesized by employing the procedures described for Compounds **8B** and **8F** using Compound **61A** using KF as base and THF as solvent, and **61B** in lieu of Compound **8A** using Cs₂CO₃ as base and DME as solvent, and **8E**. Compound **61B**: LC-MS (ESI) m/z: 288 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.00 (s, 3H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J*₁ = 8.8 Hz, *J*₂ = 2.0 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.22 (s, 1H). Compound **61C**: LC-MS (ESI) m/z: 274 [M+H]⁺.

[00700] To a solution of Compound **61C** (2.1 g, 7.66 mmol) in t-BuOH (100 mL) was added Et₃N (851 mg, 8.43 mmol) and DPPA (2.32 g, 8.43 mmol) at 0 °C. The mixture was heated at reflux overnight and evaporated under reduced pressure. The residue was diluted with CH₂Cl₂ (50 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to yield Compound **61D**. LC-MS (ESI) m/z: 367 [M+Na]⁺.

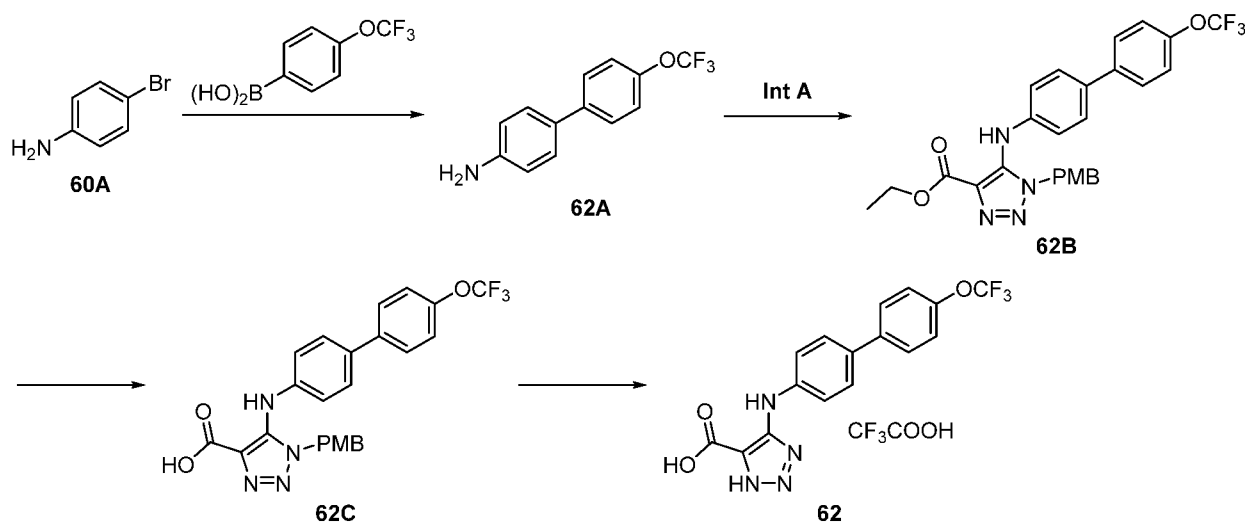
[00701] Compound **61D** (400 mg, 1.6 mmol) was dissolved in a solution of HCl/1,4-dioxane (4 N, 5 mL) and stirred at room temperature overnight. The mixture was concentrated to yield Compound **61E**. LC-MS (ESI) m/z: 245 [M+H]⁺.

[00702] Compounds **61F**, **61G**, and **61** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate A, Compound **61E** using K₃PO₄ as base, **61F**, and **61G** in lieu of Compound **6A**, 1-methylpiperazine using t-BuONa as base, **8E**, and **1E**. Compound **61F**: LC-MS (ESI) m/z: 504 [M+H]⁺. Compound **61G**: LC-MS (ESI) m/z: 476 [M+H]⁺. Compound **61**: LC-MS (ESI) m/z: 356 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz):

δ (ppm) 3.98 (br, 4H), 6.07 (s, 1H), 7.29 (s, 1H), 7.23 (d, $J = 8.8$ Hz, 1H), 7.88 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 8.12 (d, $J = 2.0$ Hz, 1H).

[00703] Example 62

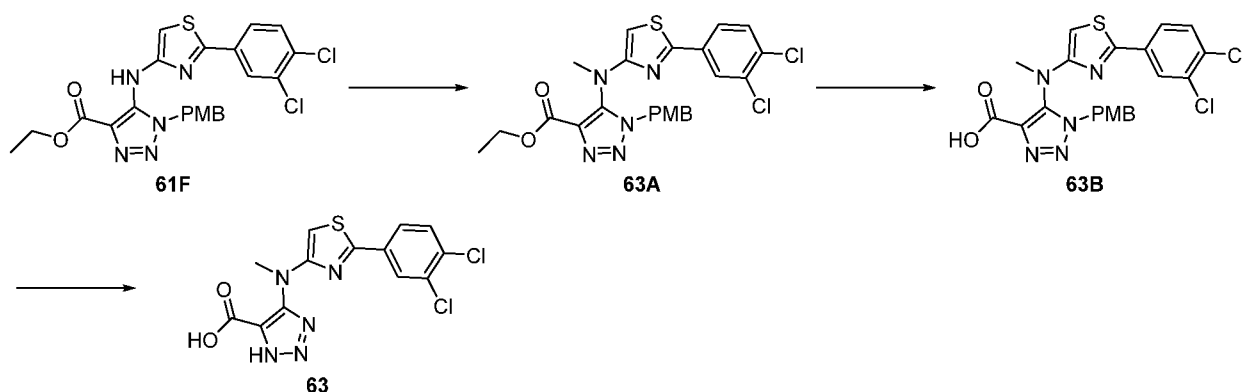
[00704] Synthesis of 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (62**)**



[00705] Compounds **62A**, **62B**, **62C**, and **62** were synthesized by employing the procedures described for Compounds **8B**, **6B**, **2**, and **1** using Compound **60A** using K_2CO_3 as base, Intermediate **A**, **62A** using K_3PO_4 as base, **62B**, and **62C** in lieu of Compound **8A** using CS_2CO_3 as base, **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **1**, and **1E**. Compound **62A**: LC-MS (ESI) m/z : 254 $[M+H]^+$. Compound **62B**: LC-MS (ESI) m/z : 513 $[M+H]^+$. Compound **62C**: LC-MS (ESI) m/z : 485 $[M+H]^+$. Compound **62**: LC-MS (ESI) m/z : 365 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 7.31 (d, $J = 8.4$ Hz, 2H), 7.59-7.70 (m, 6H).

[00706] Example 63

[00707] Synthesis of 4-((2-(3,4-dichlorophenyl)thiazol-4-yl)(methyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (63**)**

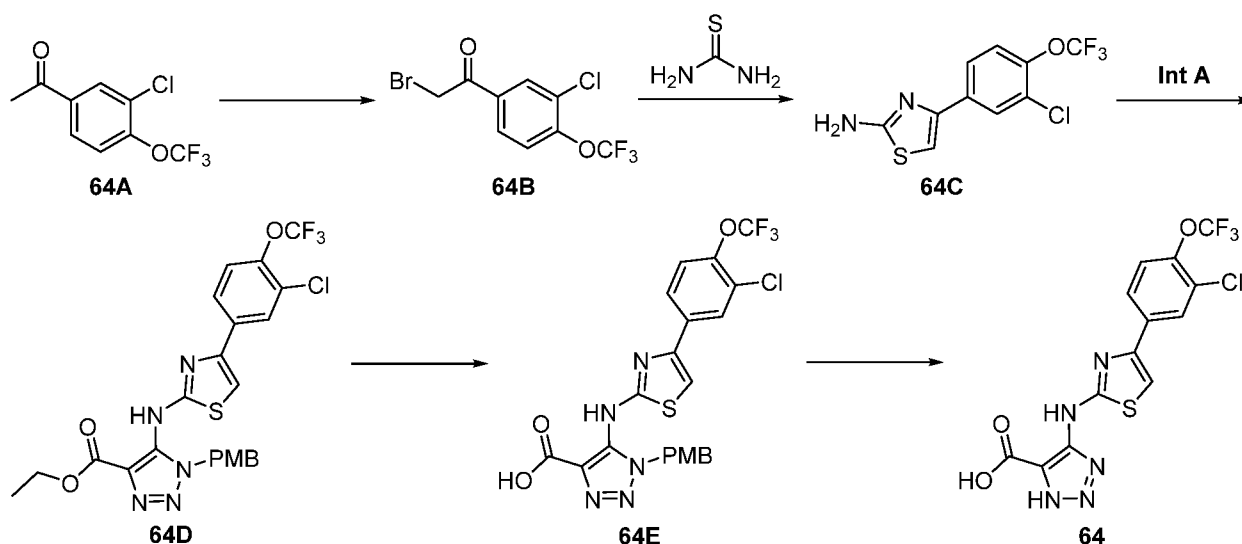


[00708] To a mixture of Compound **61F** (250 mg, 0.5 mmol) and Cs_2CO_3 (326 mg, 1 mmol) in DMF (20 mL) was added MeI (142 mg, 1 mmol) and stirred at 60 °C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **63A**. LC-MS (ESI) m/z : 518 $[\text{M}+\text{H}]^+$.

[00709] Compounds **63B** and **63** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **63A** and **63B** in lieu of Compounds **8E** and **1E**. Compound **63B**: LC-MS (ESI) m/z : 490 $[\text{M}+\text{H}]^+$. Compound **63**: LC-MS (ESI) m/z : 370 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 3.48 (s, 3H), 6.64 (s, 1H), 7.73-7.75(m, 2H), 7.98 (s, 1H).

[00710] Example 64

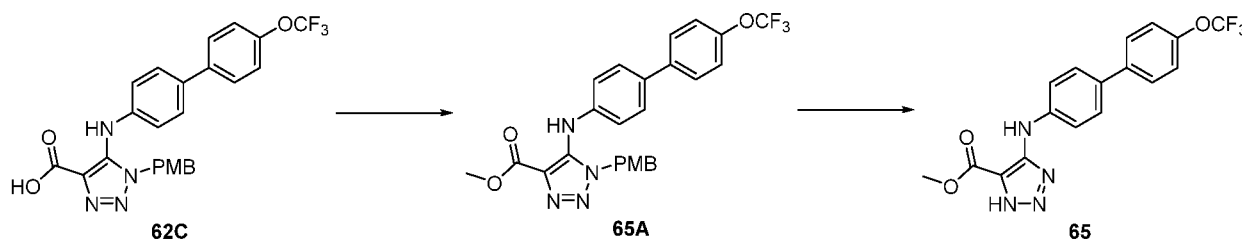
[00711] Synthesis of 4-((4-(3-chloro-4-(trifluoromethoxy)phenyl)thiazol-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (**64**)



[00712] Compounds **64B**, **64C**, **64D**, **64E**, and **64** were synthesized by employing the procedures described for Compounds **15B**, **58A**, **6B**, **8F**, and **1** using Compounds **64A**, **64B**, Intermediate **A**, **64C** using K_3PO_4 as base at 160 °C in a microwave oven, **64D**, and **64E** in lieu of Compounds **15A**, **1A**, **6A**, 1-methylpiperazine using *t*-BuONa as base at 120 °C, **8E**, and **1E**. Compound **64B**: LC-MS (ESI) *m/z*: 317 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.39 (s, 2H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 8.11 (d, $J = 2.4$ Hz, 1H). Compound **64C**: LC-MS (ESI) *m/z*: 295 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 6.70 (s, 1H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 2.4$ Hz, 1H), 8.86 (s, 2H). Compound **64D**: LC-MS (ESI) *m/z*: 554 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.42 (t, $J = 8.8$ Hz, 3H), 3.74 (s, 3H), 4.40-4.46 (m, 2H), 5.73 (s, 2H), 6.72 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.10 (s, 1H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.68-7.72 (m, 1H), 7.89 (d, $J = 2.0$ Hz, 1H), 8.23 (s, 1H). Compound **64E**: LC-MS (ESI) *m/z*: 526 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 3.68 (s, 3H), 5.55 (s, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 7.42 (s, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.82 (d, $J = 8.8$ Hz, 1H), 8.02 (d, $J = 2.4$ Hz, 1H). Compound **64**: LC-MS (ESI) *m/z*: 406 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.61 (d, $J = 8.0$ Hz, 1H), 7.79 (s, 1H), 8.01 (d, $J = 6.4$ Hz, 1H), 8.20 (s, 1H), 9.57 (s, 1H), 13.76 (brs, 1H), 15.32 (brs, 1H).

[00713] **Example 65**

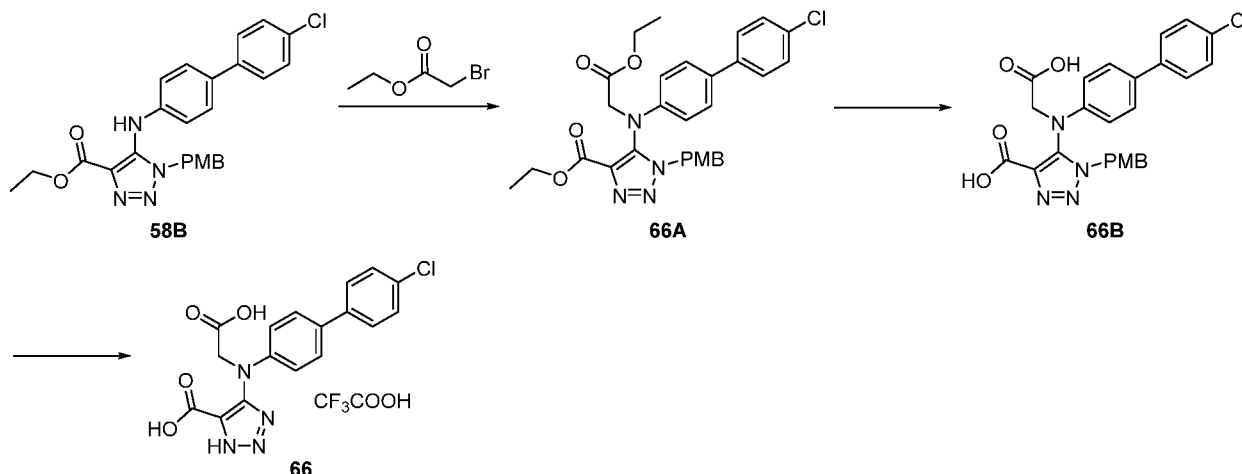
[00714] **Synthesis of methyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylate (**65**)**



[00715] Compounds **65A** and **65** were synthesized by employing the procedures described for Compounds **11A** and **1** using Compounds **62C** using methanol and **65A** in lieu of Compounds **9A** using propan-2-ol and **1E**. Compound **65A**: LC-MS (ESI) *m/z*: 499 $[M+H]^+$. Compound **65**: LC-MS (ESI) *m/z*: 379 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 3.98 (s, 3H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.69-7.71 (m, 4H).

[00716] **Example 66**

[00717] Synthesis of 4-((carboxymethyl)(4'-chloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (66)



[00718] A mixture of Compound **58B** (462 mg, 1 mmol), ethyl 2-bromoacetate (250 mg, 1.5 mmol) and Na₂CO₃ (160 mg, 1.5 mmol) in DMF (10 mL) was stirred at 70 °C overnight. The mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to afford Compound **66A**. LC-MS (ESI) m/z: 549 [M+H]⁺.

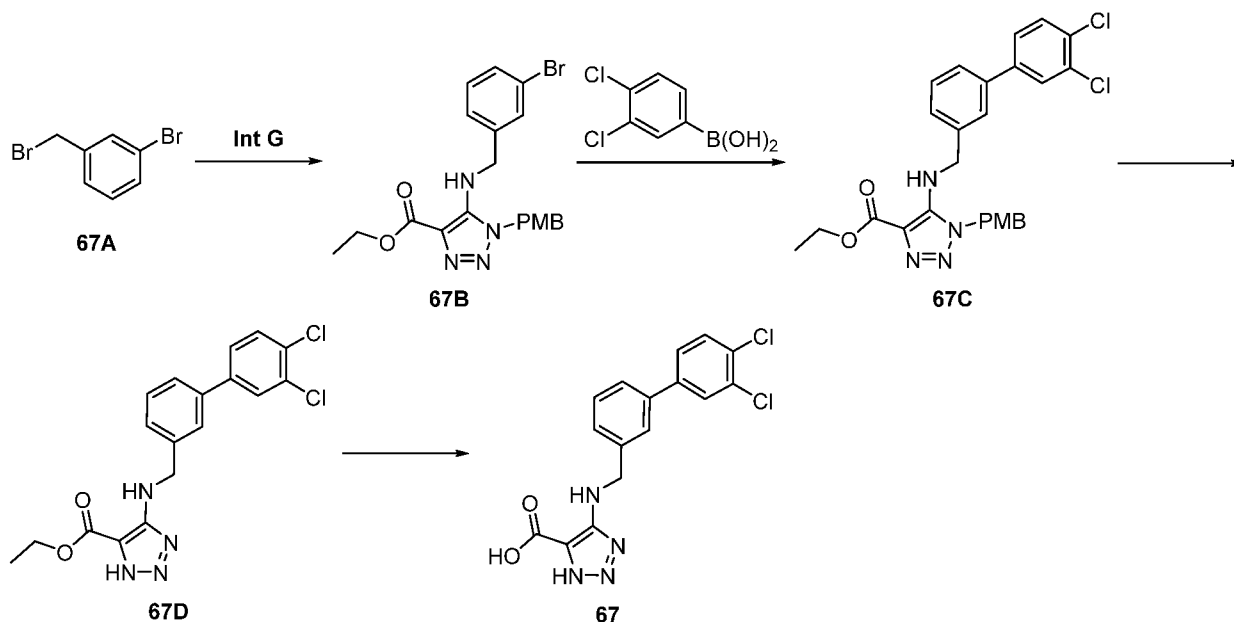
[00719] Compounds **66B** and **66** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **66A** and **66B** in lieu of Compounds **8E** and **1E**.

Compound **66B**: LC-MS (ESI) m/z: 493 [M+H]⁺. Compound **66**: LC-MS (ESI) m/z: 373

[M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 4.52 (s, 2H), 6.83 (s, 2H), 7.46-7.53 (m, 4H), 7.62-7.64 (m, 2H), 12.87 (s, 1H), 15.13 (s, 1H).

[00720] Example 67

[00721] Synthesis of 4-(((3',4'-dichloro-[1,1'-biphenyl]-3-yl)methyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (67)

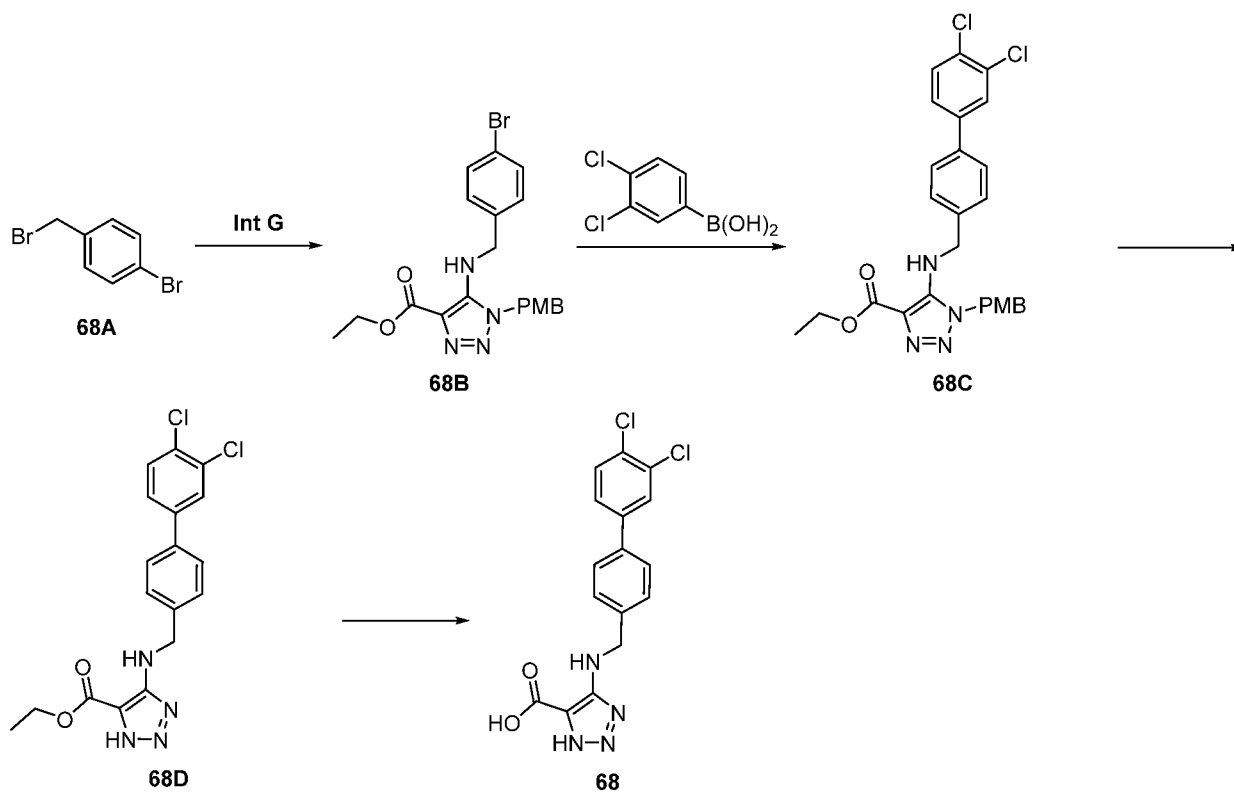


[00722] A mixture of Intermediate **G** (500 mg, 1.8 mmol) and NaH (60% suspension in oil, 216 mg, 5.4 mmol) in DMF (5 mL) was stirred at room temperature for 30 minutes. To the mixture was added 1-bromo-3-(bromomethyl)benzene (**67A**) (500 mg, 2.0 mmol) and was stirred at room temperature for 3 hours. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined extracts were concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 33% v/v) to afford Compound **67B**. LC-MS (ESI) m/z : 445 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.25 (t, $J = 6.8$ Hz, 3H), 3.74 (s, 3H), 4.20-4.26 (m, 2H), 4.59 (d, $J = 6.8$ Hz, 2H), 5.42 (s, 2H), 6.88-6.94 (m, 3H), 7.07-7.09 (m, 3H), 7.19 (t, $J = 8.0$ Hz, 1H), 7.29 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 1H).

[00723] Compounds **67C**, **67D**, and **67** were synthesized by employing the procedures described for Compounds **4B**, **1**, and **8F** using 3,4-dichlorophenylboronic acid, Compounds **67B** using 1,4-dioxane and H₂O as solvent, **67C**, and **67D** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using toluene/EtOH/H₂O as solvent, **1E**, and **8E**. Compound **67C**: LC-MS (ESI) m/z : 511 $[M+H]^+$. Compound **67D**: LC-MS (ESI) m/z : 391 $[M+H]^+$. Compound **67**: LC-MS (ESI) m/z : 363 $[M+H]^+$; ^1H -NMR (CD₃OD, 400 MHz): δ (ppm) 4.57 (s, 2H), 7.40-7.65 (m, 6H), 7.78 (s, 1H).

[00724] **Example 68**

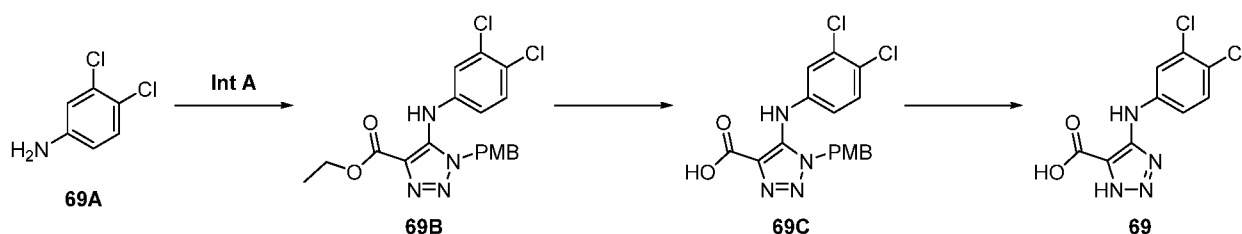
[00725] Synthesis of 4-(((3',4'-dichloro-[1,1'-biphenyl]-4-yl)methyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (68)



[00726] Compounds **68B**, **68C**, **68D**, and **68** were synthesized by employing the procedures described for Compounds **67B**, **4B**, **1**, and **8F** using Compounds **68A**, 3,4-dichlorophenylboronic acid, **68B** using 1,4-dioxane and H₂O as solvent, **68C**, and **68D** in lieu of Compounds **67A**, (4-bromophenyl)boronic acid, **4A** using toluene/EtOH/H₂O as solvent, **1E**, and **8E**. Compound **68B**: LC-MS (ESI) m/z: 445 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.25 (t, *J* = 7.2 Hz, 3H), 3.74 (s, 3H), 4.21-4.24 (m, 2H), 4.56 (d, *J* = 6.8 Hz, 2H), 5.40 (s, 2H), 6.88-6.91 (m, 3H), 7.02-7.07 (m, 4H), 7.40-7.42 (m, 2H). Compound **68C**: LC-MS (ESI) m/z: 511 [M+H]⁺. Compound **68D**: LC-MS (ESI) m/z: 391 [M+H]⁺. Compound **68**: LC-MS (ESI) m/z: 363 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 4.54 (s, 2H), 7.48-7.56 (m, 6H), 7.77 (s, 1H).

[00727] Example 69

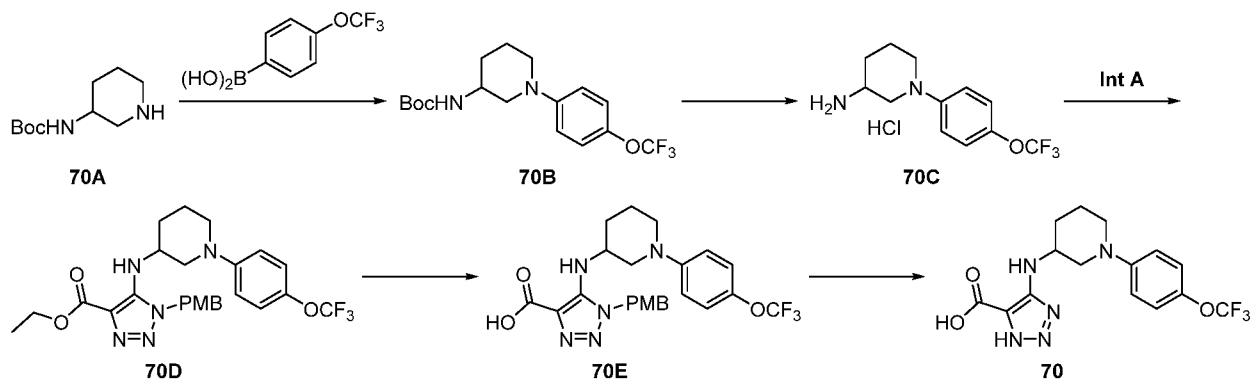
[00728] Synthesis of 4-((3,4-dichlorophenyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (69)



[00729] Compounds **69B**, **69C**, and **69** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **69A** using K_3PO_4 as base, **69B**, and **69C** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **69B**: LC-MS (ESI) m/z : 421 $[M+H]^+$; $^1\text{H-NMR}$ ($CDCl_3$, 400 MHz): δ (ppm) 1.40 (t, $J = 7.2$ Hz, 3H), 3.77 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 5.21 (s, 2H), 6.64 (dd, $J = 8.8$, 2.2 Hz, 1H), 6.74-6.77 (m, 2H), 6.79 (d, $J = 2.4$ Hz, 1H), 6.83-6.86 (m, 2H), 6.94 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 1H). Compound **69C**: LC-MS: (ESI) m/z : 393 $[M+H]^+$; $^1\text{H-NMR}$ ($DMSO-d_6$, 400 MHz): δ (ppm) 3.69 (s, 3H), 5.31 (s, 2H), 6.56 (dd, $J = 8.8$, 2.4 Hz, 1H), 6.66 (d, $J = 2.4$ Hz, 1H), 6.80-6.84 (m, 2H), 7.05-7.07 (m, 2H), 7.33 (d, $J = 8.8$ Hz, 1H), 8.73 (brs, 1H). Compound **69**: LC-MS (ESI) m/z : 273 $[M+H]^+$; $^1\text{H-NMR}$ ($DMSO-d_6$, 400 MHz): δ (ppm) 7.50 (d, $J = 8.8$ Hz, 1H), 7.59 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.98 (d, $J = 2.4$ Hz, 1H), 8.50 (s, 1H), 13.47 (brs, 1H), 15.06 (brs, 1H).

[00730] Example 70

[00731] Synthesis of 4-((1-(4-(trifluoromethoxy)phenyl)piperidin-3-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (**70**)



[00732] A mixture of tert-butyl piperidin-3-ylcarbamate (**70A**) (1.5 g, 7.29 mmol), 4-(trifluoromethoxy)phenylboronic acid (1.5 g, 7.29 mmol), $Cu(OAc)_2$ (1.57 g, 8.75 mmol), and K_3PO_4 (3.09 g, 14.58 mmol) in DMSO (30 mL) was stirred at 80 °C overnight. The mixture was cooled down to room temperature, diluted with water (100 mL), and extracted with EtOAc (50

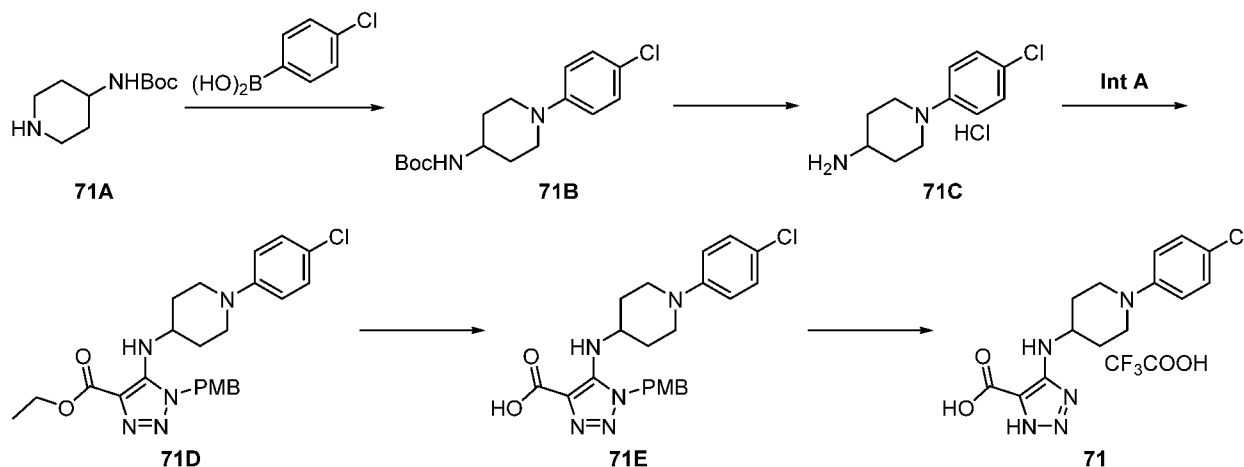
mL x 3). The combined extracts were concentrated under reduced pressure. The residue was purified with column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to furnish Compound **70B**. LC-MS (ESI) m/z : 361 $[M+H]^+$.

[00733] A mixture of Compound **70B** (432 mg, 1.2 mmol) and a solution of HCl in 1,4-dioxane (4 M, 10 mL) was stirred at room temperature for 2 hours. The mixture was concentrated to give Compound **70C**. LC-MS (ESI) m/z : 261 $[M+H]^+$.

[00734] Compounds **70D**, **70E**, and **70** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **70C** using K_3PO_4 as base, **70D**, and **70E** in lieu of Compounds **6A**, 1-methylpiperazine using t-BuONa as base, **8E**, and **1E**. Compound **70D**: LC-MS (ESI) m/z : 520 $[M+H]^+$. Compound **70E**: LC-MS (ESI) m/z : 492 $[M+H]^+$. Compound **70**: LC-MS (ESI) m/z : 372 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.58-1.60 (m, 2H), 1.71-1.73 (m, 1H), 2.31-2.33 (m, 1H), 2.89-2.94 (m, 2H), 3.33-3.51 (m, 3H), 7.99 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H).

[00735] Example 71

[00736] Synthesis of 4-((1-(4-chlorophenyl)piperidin-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**71**)

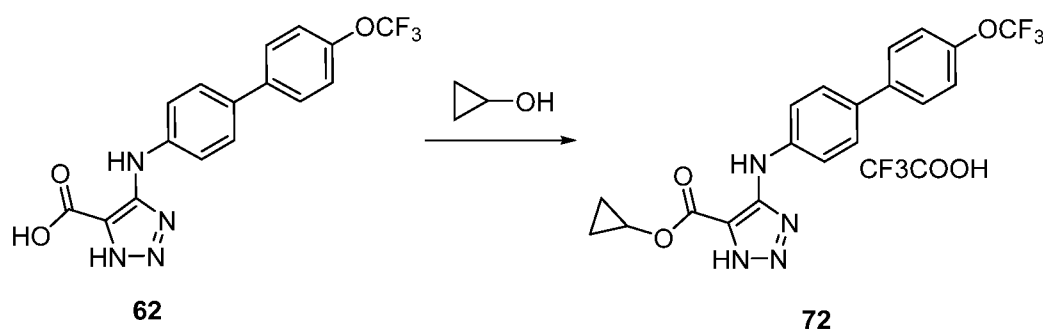


[00737] Compounds **71B**, **71C**, **71D**, **71E**, and **71** were synthesized by employing the procedures described for Compounds **70B**, **70C**, **6B**, **8F**, and **1** using 4-chlorophenylboronic acid, Compounds **71A** using dichloromethane as solvent, **71B** using EtOAc as solvent, Intermediate **A**, **71C** using K_3PO_4 as base, **71D**, and **71E** in lieu of 4-(trifluoromethoxy)phenylboronic acid, Compounds **70A** using DMSO as solvent, **70B** using 1,4-dioxane as solvent, **6A**, 1-methylpiperazine using t-BuONa as base, **8E**, and **1E**. Compound **71B**:

LC-MS (ESI) m/z : 311 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.46 (s, 9H), 1.51-1.59 (m, 2H), 2.03-2.06 (m, 2H), 2.79-2.86 (m, 2H), 3.54-3.61 (m, 3H), 4.47 (br, 1H), 6.82-6.86 (m, 2H), 7.17-7.21 (m, 2H). Compound **71C**: LC-MS (ESI) m/z : 211 $[M+H]^+$. Compound **71D**: LC-MS (ESI) m/z : 470 $[M+H]^+$. Compound **71E**: LC-MS (ESI) m/z : 442 $[M+H]^+$. Compound **71**: LC-MS (ESI) m/z : 322 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.59-1.62 (m, 2H), 1.97-2.00 (m, 2H), 2.80-2.86 (m, 2H), 3.51 (br, 1H), 3.62-3.66 (m, 2H), 6.96-6.99 (m, 2H), 7.20-7.23 (m, 2H).

[00738] Example 72

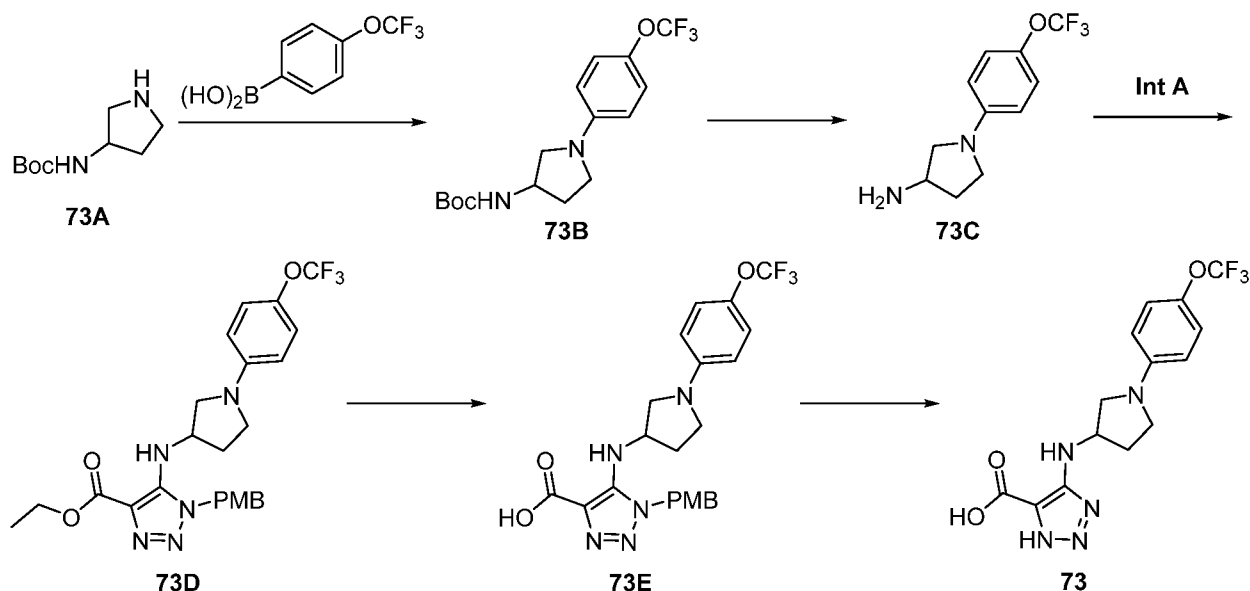
[00739] Synthesis of cyclopropyl 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylate 2,2,2-trifluoroacetate (72**)**



[00740] Compound **72** was synthesized by employing the procedure described for Compound **19A** using Compound **62** in lieu of Compound **9A**, LC-MS (ESI) m/z : 405 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 0.82-0.89 (m, 4H), 4.42-4.44 (m, 1H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.60-7.71 (m, 6H).

[00741] Example 73

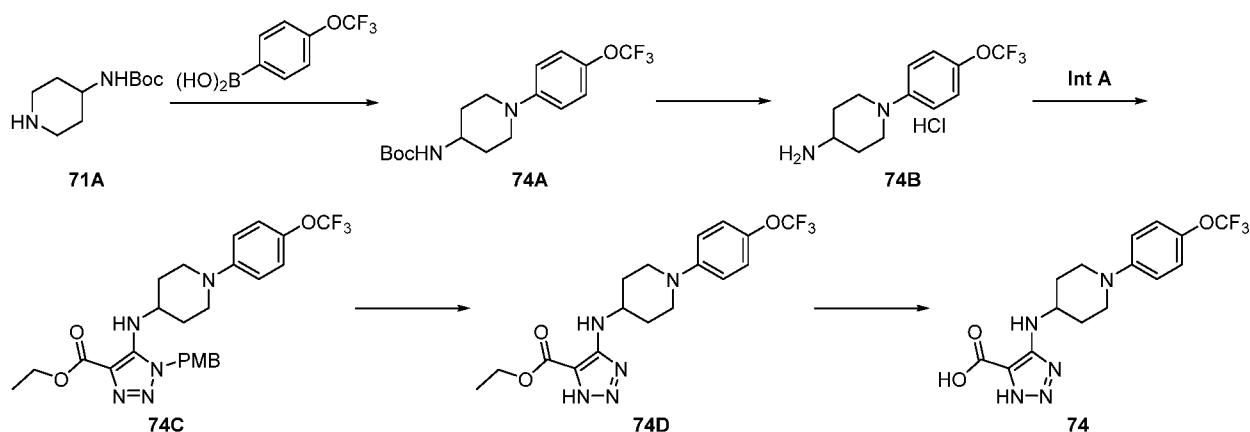
[00742] Synthesis of 4-((1-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (73**)**



[00743] Compounds **73B**, **73C**, **73D**, **73E**, and **73** were synthesized by employing the procedures described for Compounds **70B**, **70C**, **6B**, **8F**, and **1** using Compounds **73A**, **73B**, Intermediate A, **73C** using K_3PO_4 as base, **73D**, and **73E** in lieu of Compounds **70A**, **70B**, **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **73B**: LC-MS (ESI) m/z : 347 $[M+H]^+$. Compound **73C**: LC-MS (ESI) m/z : 247 $[M+H]^+$. ^1H -NMR (CD_3OD , 400 MHz): δ 2.14-2.22 (m, 1H), 2.44-2.53 (m, 1H), 3.34-3.45 (m, 2H), 3.56-3.62 (m, 2H), 4.00-4.05 (m, 1H), 6.64 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H). Compound **73D**: LC-MS (ESI) m/z : 506 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.38 (t, $J = 6.8$ Hz, 3H), 1.82-1.89 (m, 1H), 2.01-2.09 (m, 1H), 3.04-3.07 (m, 1H), 3.18-3.39 (m, 3H), 3.77 (s, 3H), 4.23-4.28 (m, 1H), 4.36 (q, $J = 7.2$ Hz, 2H), 5.48 (d, $J = 3.2$ Hz, 2H), 6.41 (d, $J = 9.2$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.06-7.11 (m, 4H). Compound **73E**: LC-MS (ESI) m/z : 478 $[M+H]^+$. Compound **73**: LC-MS (ESI) m/z : 358 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 2.05-2.13 (m, 1H), 2.28-2.36 (m, 1H), 3.21-3.42 (m, 3H), 3.58-3.62 (m, 1H), 4.26 (s, 1H), 6.58 (d, $J = 9.2$ Hz, 2H), 7.15 (d, $J = 8.8$ Hz, 2H).

[00744] Example 74

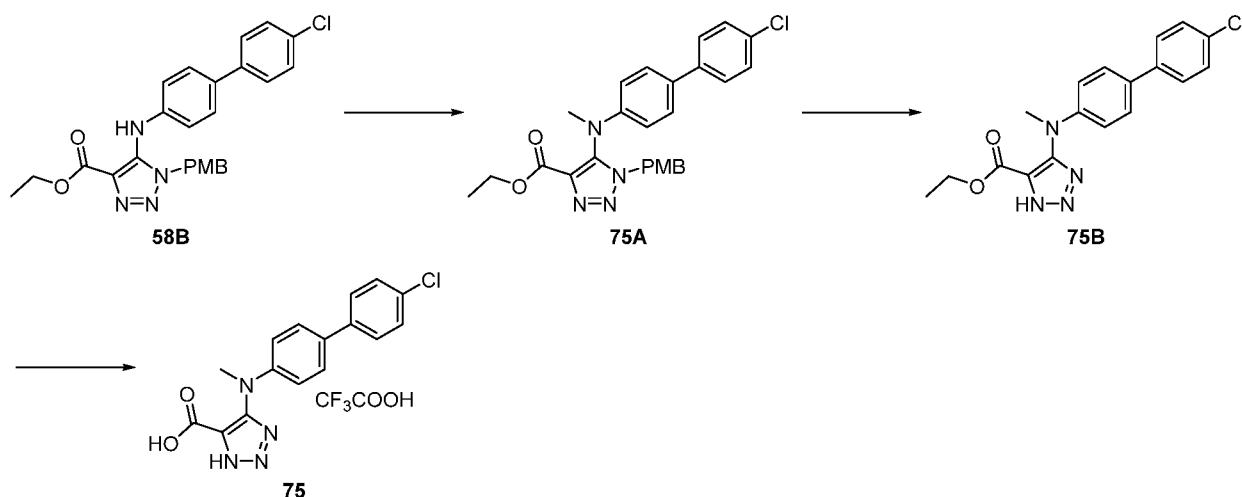
[00745] Synthesis of 4-((1-(4-(trifluoromethoxy)phenyl)piperidin-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (**74**)



[00746] Compounds **74A**, **74B**, **74C**, **74D**, and **74** were synthesized by employing the procedures described for Compounds **70B**, **70C**, **6B**, **1**, and **8F** using Compounds **71A**, **74A** using dichloromethane as solvent, Intermediate **A**, **74B** using K_3PO_4 as base, **74C**, and **74D** in lieu of Compounds **70A**, **70B** using 1,4-dioxane as solvent, **6A**, 1-methylpiperazine using t -BuONa as base, **1E**, and **8E**. Compound **74A**: LC-MS (ESI) m/z : 361 $[M+H]^+$. Compound **74B**: LC-MS (ESI) m/z : 261 $[M+H]^+$. Compound **74C**: LC-MS (ESI) m/z : 520 $[M+H]^+$. Compound **74D**: LC-MS (ESI) m/z : 400 $[M+H]^+$. Compound **74**: LC-MS (ESI) m/z : 372 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.53-1.56 (m, 2H), 1.99-2.02 (m, 2H), 2.82-2.88 (m, 2H), 3.51-3.53 (m, 1H), 3.63-3.66 (m, 2H), 7.01-7.03 (m, 2H), 7.16-7.18 (m, 2H).

[00747] Example 75

[00748] Synthesis of 4-((4'-chloro-[1,1'-biphenyl]-4-yl)(methyl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**75**)

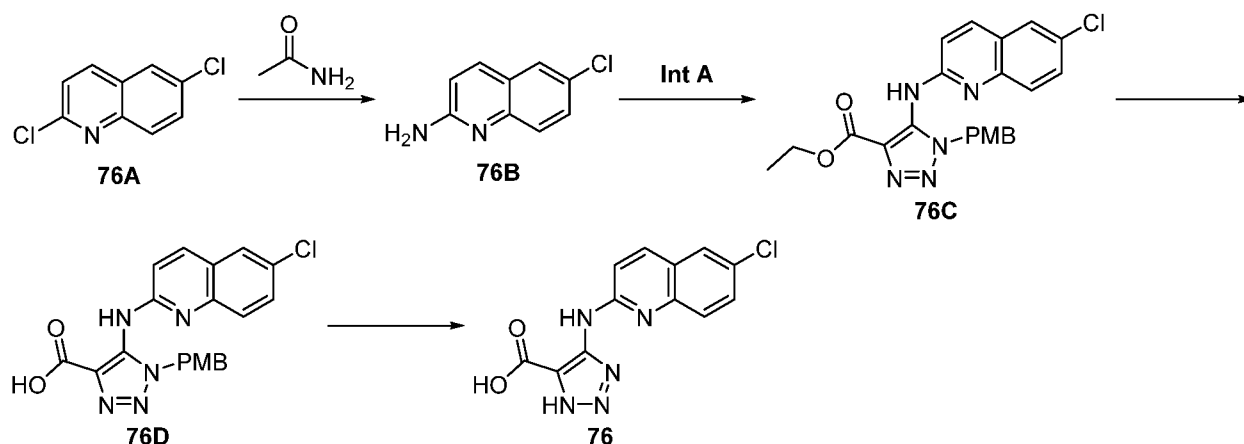


[00749] Compounds **75A**, **75B**, and **75** were synthesized by employing the procedures described for Compounds **63A**, **1**, and **8F** using Compounds **58B** using K_2CO_3 as base, **75A**, and

75B in lieu of Compounds **61F** using Cs_2CO_3 as base, **1E**, and **8E**. Compound **75A**: LC-MS (ESI) m/z : 477 $[\text{M}+\text{H}]^+$. Compound **75B**: LC-MS (ESI) m/z : 357 $[\text{M}+\text{H}]^+$. Compound **75**: LC-MS (ESI) m/z : 329 $[\text{M}+\text{H}]^+$. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 3.28 (s, 3H), 6.77-6.79 (m, 2H), 7.44-7.46 (m, 2H), 7.51-7.53 (m, 2H), 7.61-7.63 (m, 2H).

[00750] Example 76

[00751] Synthesis of 4-((6-chloroquinolin-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (76)

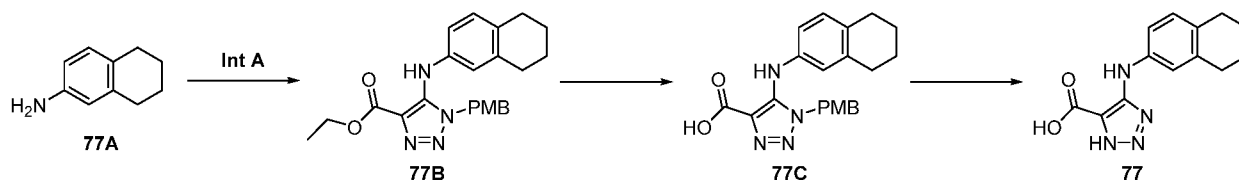


[00752] A mixture of 2,6-dichloroquinoline (Compound **76A**) (1.97 g, 10 mmol), acetamide (12 g, 200 mmol), and K_2CO_3 (7 g, 50 mmol) was heated at 200 °C under nitrogen for 4 hours. The reaction mixture was cooled down to room temperature, diluted with H_2O (200 mL), and extracted with ethyl acetate (50 mL x 2). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to afford Compound **76B**. LC-MS (ESI) m/z : 179 $[\text{M}+\text{H}]^+$.

[00753] Compounds **76C**, **76D**, and **76** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate A, Compounds **76B** using K_3PO_4 as base, **76C**, and **76D** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **76C**: LC-MS (ESI) m/z : 438 $[\text{M}+\text{H}]^+$. Compound **76D**: LC-MS (ESI) m/z : 410 $[\text{M}+\text{H}]^+$. Compound **76**: LC-MS (ESI) m/z : 290 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.61-7.64 (m, 1H), 7.85 (brs, 1H), 7.92 (d, $J = 2.4$ Hz, 1H), 8.18-8.25 (m, 2H), 10.13 (brs, 1H).

[00754] Example 77

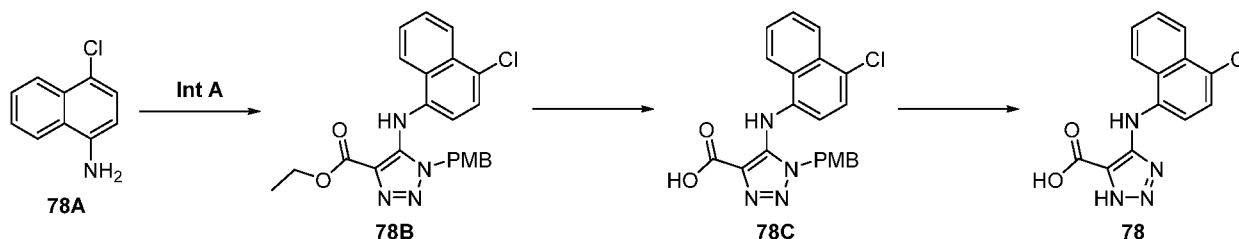
[00755] Synthesis of 4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (77)



[00756] Compounds **77B**, **77C**, and **77** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **77A** using K_3PO_4 as base, **77B**, and **77C** in lieu of Compounds **6A**, 1-methylpiperazine using $t-BuONa$ as base, **8E**, and **1E**. Compound **77B**: LC-MS (ESI) m/z : 407 $[M+H]^+$. Compound **77C**: LC-MS (ESI) m/z : 379 $[M+H]^+$. Compound **77**: LC-MS (ESI) m/z : 259 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.71-1.69 (m, 4H), 2.68-2.62 (m, 4H), 6.90 (d, $J = 8.4$ Hz, 1H), 7.15 (d, $J = 10.4$ Hz, 1H), 7.21 (s, 1H), 8.79 (s, 1H).

[00757] Example 78

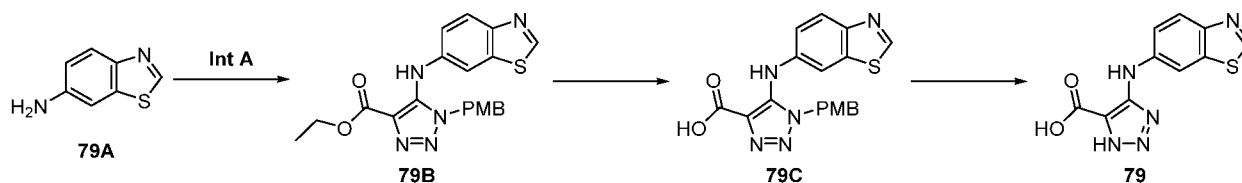
[00758] Synthesis of 4-((4-chloronaphthalen-1-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (78)



[00759] Compounds **78B**, **78C**, and **78** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **78A** using K_3PO_4 as base, **78B**, and **78C** in lieu of Compounds **6A**, 1-methylpiperazine using $t-BuONa$ as base, **8E**, and **1E**. Compound **78B**: LC-MS (ESI) m/z : 437 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.44 (t, $J = 7.2$ Hz, 3H), 3.67 (s, 3H), 4.45 (q, $J = 7.2$ Hz, 2H), 5.03 (s, 2H), 6.38-6.47 (m, 4H), 6.80 (d, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.50-7.53 (m, 1H), 7.61-7.68 (m, 2H), 7.81 (d, $J = 8.0$ Hz, 1H), 8.30 (d, $J = 8.8$ Hz, 1H). Compound **78C**: LC-MS (ESI) m/z : 409 $[M+H]^+$. Compound **78**: LC-MS (ESI) m/z : 289 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.71 (d, $J = 8.4$ Hz, 1H), 7.74-7.79 (m, 2H), 8.04-8.07 (m, 1H), 8.13-8.14 (m, 1H), 8.22-8.25 (m, 1H), 9.05 (s, 1H), 13.68 (s, 1H), 15.06 (s, 1H).

[00760] Example 79

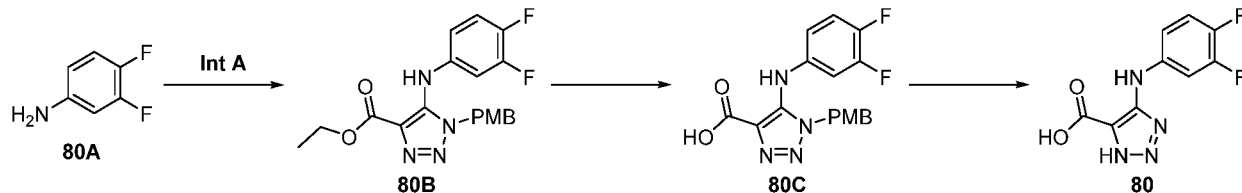
[00761] Synthesis of 4-(benzo[d]thiazol-6-ylamino)-1H-1,2,3-triazole-5-carboxylic acid (79)



[00762] Compounds **79B**, **79C**, and **79** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **79A** using K_3PO_4 as base, **79B**, and **79C** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **79B**: LC-MS: (ESI) m/z : 410 $[M+H]^+$. Compound **79C**: LC-MS (ESI) m/z : 382 $[M+H]^+$. Compound **79**: LC-MS (ESI) m/z : 262 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.67 (d, $J = 10.7$ Hz, 1H), 7.97 (d, $J = 8.8$ Hz, 1H), 8.43 (d, $J = 11.3$ Hz, 2H), 9.16 (s, 1H), 13.52 (s, 1H), 14.96 (s, 1H).

[00763] Example 80

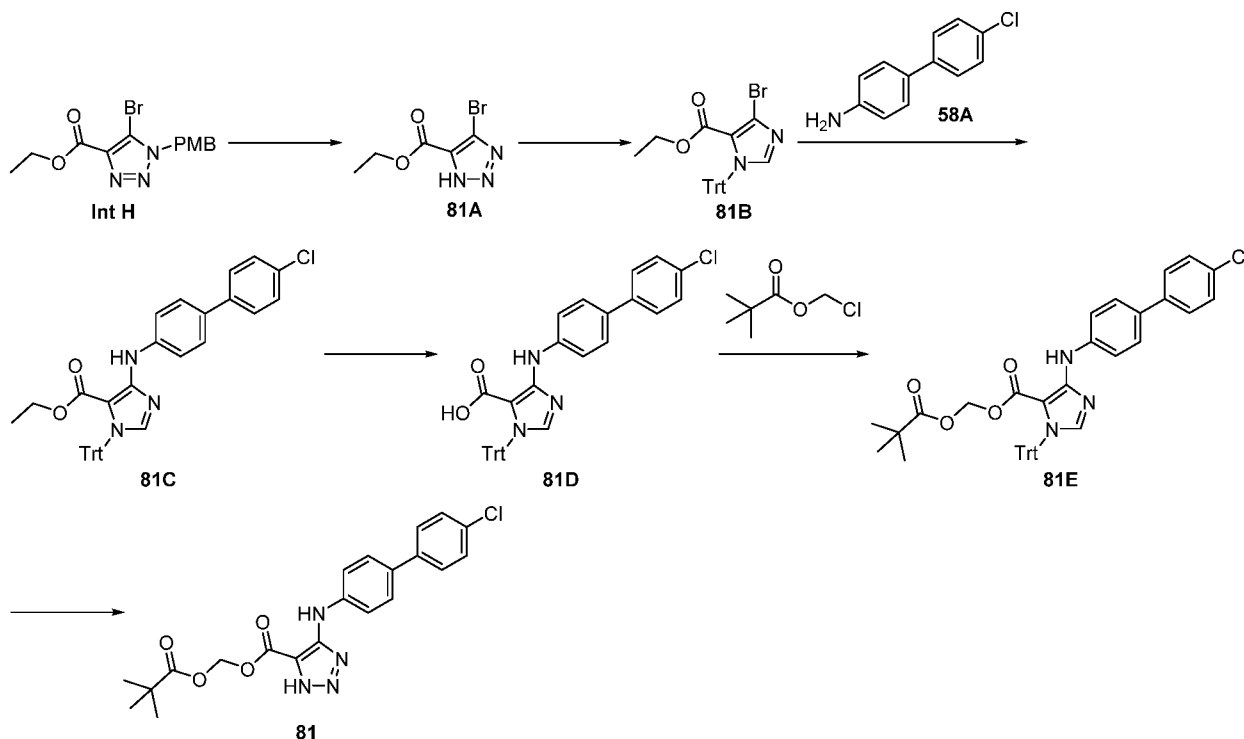
[00764] Synthesis of 4-((3,4-difluorophenyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (80)



[00765] Compounds **80B**, **80C**, and **80** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **80A** using K_3PO_4 as base, **80B**, and **80C** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **80B**: LC-MS: (ESI) m/z : 389 $[M+H]^+$. Compound **80C**: LC-MS (ESI) m/z : 361 $[M+H]^+$. Compound **80**: LC-MS (ESI) m/z : 241 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.28-7.41 (m, 2H), 7.71-7.76 (m, 1H), 8.34 (s, 1H), 13.37 (s, 1H), 14.96 (s, 1H).

[00766] Example 81

[00767] Synthesis of (pivaloyloxy)methyl 4-((4'-chloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylate (81)



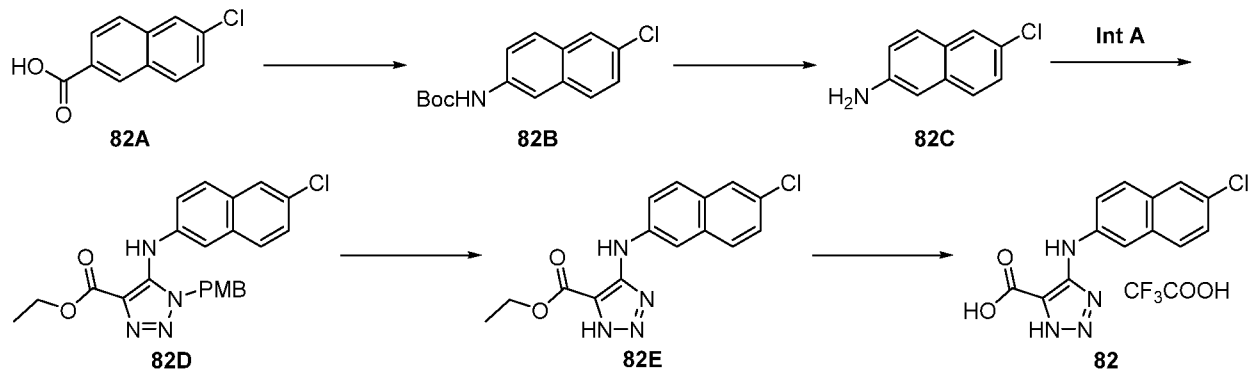
[00768] Compound **81A** was synthesized by employing the procedure described for Compound **1** using Intermediate **A** in lieu of Compound **1E**, LC-MS (ESI) m/z : 220 $[M+H]^+$.

[00769] To a solution of Compound **81A** (2.3 g, 10.4 mmol) in CH_3CN (8 mL) was added $TrtCl$ (2.9 g, 10.4 mmol) and Et_3N (2.17 g, 15.7 mmol). The mixture was stirred at room temperature for 18 hours and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **81B**. LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used.

[00770] Compounds **81C**, **81D**, **81E**, and **81** were synthesized by employing the procedures described for Compounds **6B**, **8F**, **54C**, and **1** using Compounds **81B**, **58A** using K_3PO_4 as base, **81C**, **81D**, and **81E** in lieu of Compounds **6A**, 1-methylpiperazine using t -BuONa as base, **8E**, **54B**, and **1E**. Compound **81C**: LC-MS (ESI) m/z : 607 $[M+Na]^+$. Compound **81D**: LC-MS (ESI) m/z : 555. $[M-H]^-$. Compound **81E**: LC-MS (ESI) m/z : 669 $[M-H]^-$. Compound **81**: LC-MS (ESI) m/z : 429 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.16 (s, 9H), 5.97 (s, 2H), 7.47 (d, $J = 6.8$ Hz, 2H), 7.62 (d, $J = 6.8$ Hz, 2H), 7.67 (d, $J = 6.8$ Hz, 2H), 7.71 (d, $J = 6.8$ Hz, 2H), 8.18 (s, 1H).

[00771] **Example 82**

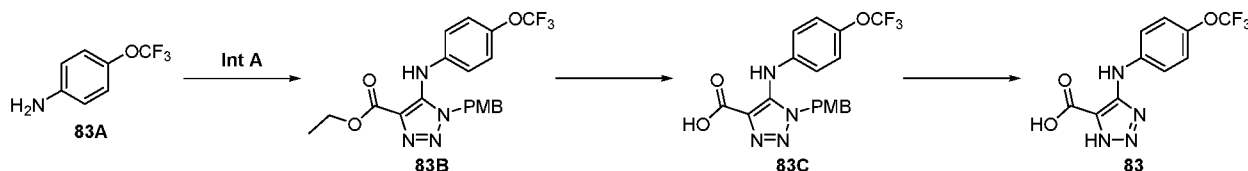
[00772] Synthesis of 4-((6-chloronaphthalen-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (82)



[00773] Compounds **82B**, **82C**, **82D**, **82E**, and **82** were synthesized by employing the procedures described for Compounds **61D**, **61E**, **6B**, **1**, and **8F** using Compounds **82A**, **82B**, Intermediate **A**, **82C** using K₃PO₄ as base, **82D**, and **82E** in lieu of Compounds **61C**, **61E**, **6A**, 1-methylpiperazine using t-BuONa as base, **1E**, and **8E**. Compound **82B**: LC-MS (ESI) m/z: 276 [M-H]⁻; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.51 (s, 9H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.81 (t, *J* = 8.4 Hz, 2H), 7.91 (s, 1H), 8.13 (s, 1H), 9.64 (s, 1H). Compound **82C**: LC-MS (ESI) m/z: 178 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 5.49 (s, 2H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 7.23 (s, *J* = 8.8 Hz, 1H), 7.51-7.59 (m, 2H), 7.71 (d, *J* = 2.0 Hz, 1H). Compound **82D**: LC-MS (ESI) m/z: 437 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.40 (t, *J* = 8.8 Hz, 3H), 3.72 (s, 3H), 4.38-4.43 (m, 2H), 5.18 (s, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.99 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.23 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.80 (s, 1H). Compound **82E**: LC-MS (ESI) m/z: 317 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.35 (t, *J* = 7.2 Hz, 3H), 4.34-4.42 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.80-7.85 (m, 2H), 7.92 (s, 1H), 8.22 (s, 1H), 8.40 (s, 1H), 15.12 (s, 1H). Compound **82**: LC-MS (ESI) m/z: 289 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.42 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.82 (t, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 2.0 Hz, 1H), 8.21 (s, 1H), 8.47 (s, 1H).

[00774] Example 83

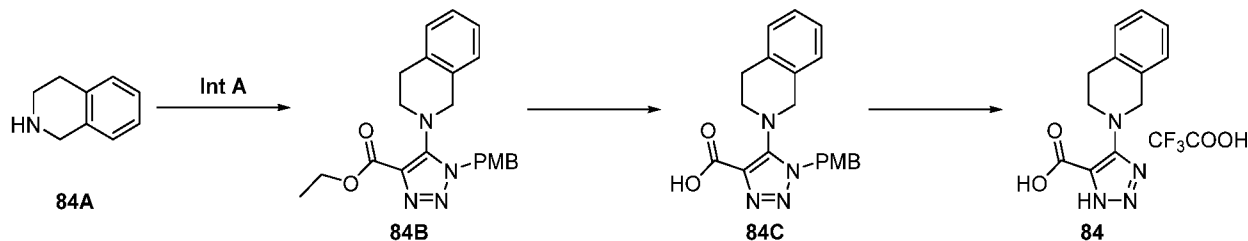
[00775] Synthesis of 4-((4-(trifluoromethoxy)phenyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (83)



[00776] Compounds **83B**, **83C**, and **83** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate A, Compounds **83A** using K_3PO_4 as base, **83B**, and **83C** in lieu of Compounds **6A**, 1-methylpiperazine using $t-BuONa$ as base, **8E**, and **1E**. Compound **83B**: LC-MS (ESI) m/z : 437 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.96 (t, $J = 7.2$ Hz, 3H), 3.69 (s, 3H), 4.02-4.07 (m, 2H), 5.40 (s, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.09-7.16 (m, 4H), 8.67 (s, 1H). Compound **83C**: LC-MS (ESI) m/z : 409 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.67 (s, 3H), 5.18 (s, 2H), 6.70 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H). Compound **83**: LC-MS (ESI) m/z : 289 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.28 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 8.8$ Hz, 2H), 8.34 (s, 1H), 13.42 (s, 1H), 15.01 (s, 1H).

[00777] Example 84

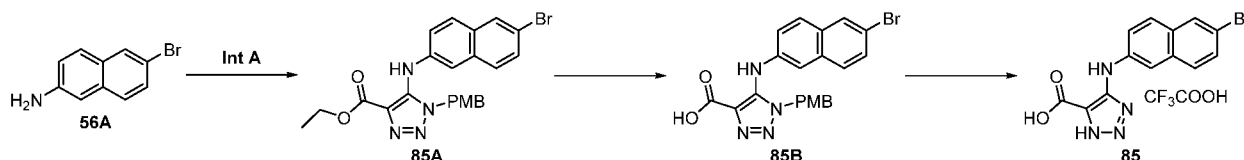
[00778] Synthesis of 4-(3,4-dihydroisoquinolin-2(1H)-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**84**)



[00779] Compounds **84B**, **84C**, and **84** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate A, Compounds **84A** using Cs_2CO_2 as base and 1,4-dioxane as solvent, **84B**, and **84C** in lieu of Compounds **6A**, 1-methylpiperazine using $t-BuONa$ as base and toluene as solvent, **8E**, and **1E**. Compound **84B**: LC-MS (ESI) m/z : 393 $[M+H]^+$. Compound **84C**: LC-MS (ESI) m/z : 365 $[M+H]^+$. Compound **84**: LC-MS (ESI) m/z : 245 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 2.86-2.91 (m, 2H), 3.53-3.71 (m, 2H), 4.38-4.59 (m, 2H), 7.09-7.30 (m, 4H), 12.83 (brs, 1H), 14.78 (brs, 1H).

[00780] Example 85

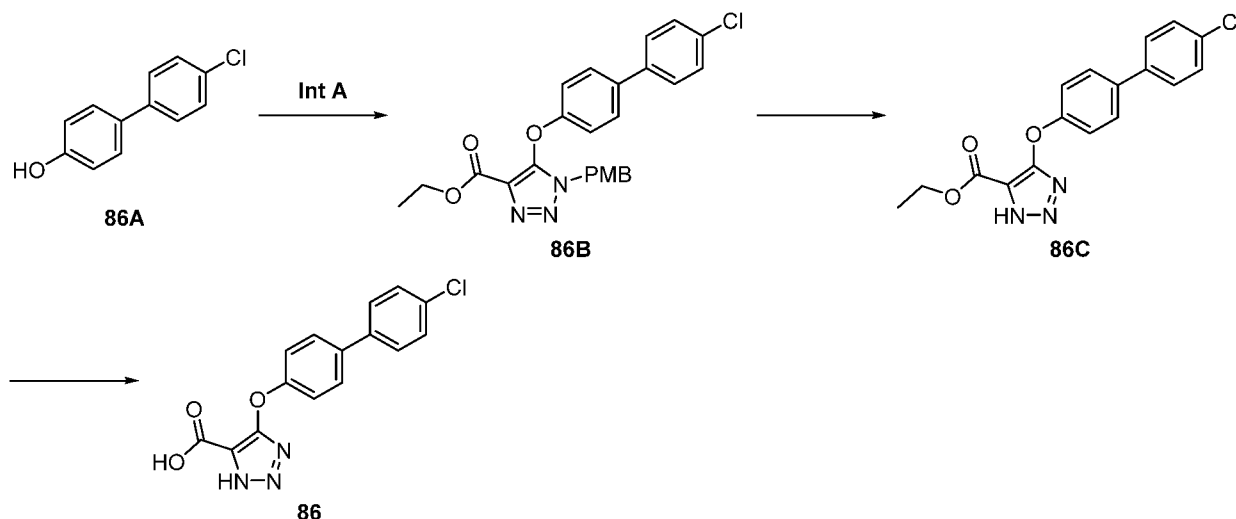
[00781] Synthesis of 4-((6-bromonaphthalen-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (85)



[00782] Compounds **85A**, **85B**, and **85** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **56A** using K_3PO_4 as base and DMF as solvent, **85A**, and **85B** in lieu of Compounds **6A**, 1-methylpiperazine using t -BuONa as base and toluene as solvent, **8E**, and **1E**. Compound **85A**: LC-MS (ESI) m/z : 481 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.40 (t, $J = 7.6$ Hz, 3H), 3.72 (s, 3H), 4.38-4.43 (m, 2H), 5.19 (s, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 6.98 (s, 1H), 7.07-7.10 (m, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.97 (d, $J = 1.6$ Hz, 1H). Compound **85B**: LC-MS (ESI) m/z : 453 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.30 (s, 3H), 5.20 (s, 2H), 6.77 (d, $J = 8.4$ Hz, 2H), 6.83 (s, 1H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 1H), 7.46 (d, $J = 6.8$ Hz, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 1H), 8.05 (d, $J = 1.6$ Hz, 1H). Compound **85**: LC-MS (ESI) m/z : 333 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.53 (d, $J = 8.8$ Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 8.07 (s, 1H), 8.20 (s, 1H), 8.46 (s, 1H), 13.39 (s, 1H), 15.01 (s, 1H).

[00783] Example 86

[00784] Synthesis of 4-((4'-chloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (86)

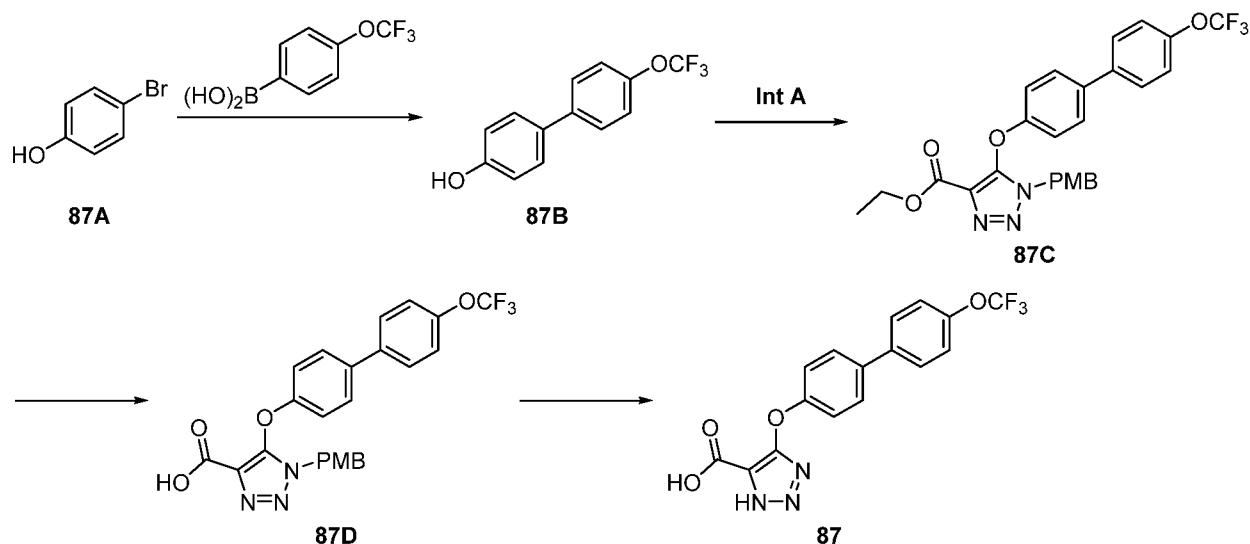


[00785] To a solution of 4'-chlorobiphenyl-4-ol (**86A**) (200 mg, 1 mmol) in DMF (100 mL) was added sodium hydride (60% in mineral oil, 40 mg, 1 mmol) under N₂ at 0 °C and stirred for 30 minutes. To the mixture was added Intermediate A (340 mg, 1 mmol) and stirred at 90 °C for 16 hours. The mixture was cooled down to room temperature, diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 27% v/v) to give Compound **86B**. LC-MS (ESI) *m/z*: 464 [M+H]⁺.

[00786] Compounds **86C** and **86** were synthesized by employing the procedures described for Compounds **1** and **8F** using Compounds **86B** and **86C** in lieu of Compounds **1E** and **8E**. Compound **86C**: LC-MS (ESI) *m/z*: 344 [M+H]⁺. Compound **86**: LC-MS (ESI) *m/z*: 316 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.15 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.66 (dd, *J* = 8.8, 2.4 Hz, 4H).

[00787] **Example 87**

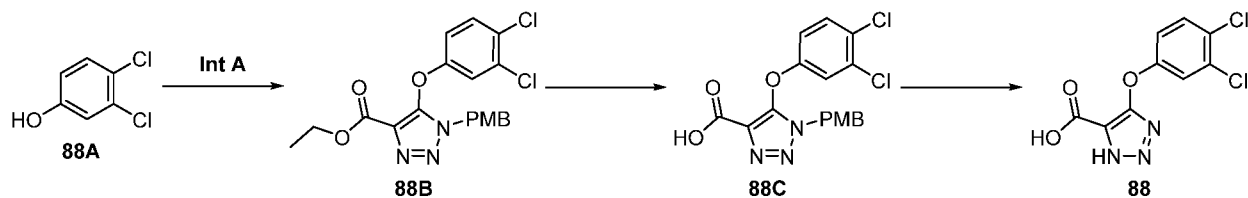
[00788] **Synthesis of 4-((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (**87**)**



[00789] Compounds **87B**, **87C**, **87D**, and **87** were synthesized by employing the procedures described for Compounds **4B**, **86B**, **8F**, and **1** using (4-(trifluoromethoxy)phenyl)boronic acid, Compounds **87A** using DME and H₂O as solvent, **87B**, **87C**, and **87D** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using toluene/EtOH/H₂O as solvent, **86A**, **8E**, and **1E**. Compound **87B**: LC-MS (ESI) m/z: 255 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.82 (s, 1H), 6.90-6.92 (m, 2H), 7.25-7.27 (m, 2H), 7.43-7.46 (m, 2H), 7.52-7.55 (m, 2H). Compound **87C**: LC-MS (ESI) m/z: 514 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.12 (t, $J = 7.2$ Hz, 3H), 3.73 (s, 3H), 4.21 (q, $J = 7.2$ Hz, 2H), 5.38 (s, 2H), 6.76-6.79 (m, 2H), 6.81-6.84 (m, 2H), 7.20-7.23 (m, 2H), 7.26-7.30 (m, 2H), 7.41-7.45 (m, 2H), 7.51-7.54 (m, 2H). Compound **87D**: LC-MS: (ESI) m/z: 486 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.68 (s, 3H), 5.40 (s, 2H), 6.83-6.85 (m, 2H), 6.95-6.97 (m, 2H), 7.16-7.18 (m, 2H), 7.43-7.47 (m, 2H), 7.60-7.63 (m, 2H), 7.73-7.75 (m, 2H). Compound **87**: LC-MS (ESI) m/z: 366 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.14-7.18 (m, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.66-7.70 (m, 2H), 7.75-7.79 (m, 2H).

[00790] **Example 88**

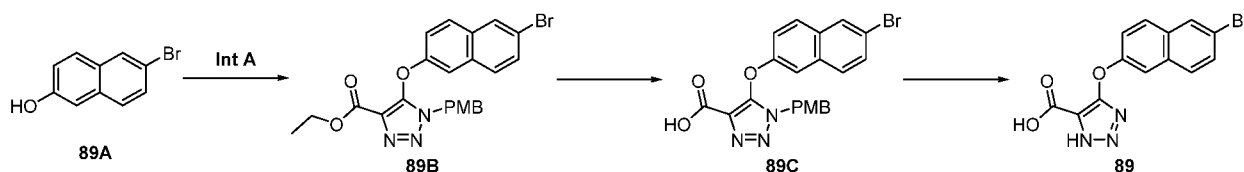
[00791] **Synthesis of 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (88)**



[00792] Compounds **88B**, **88C**, and **88** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **88A**, **88B**, and **88C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **88B**: LC-MS (ESI) m/z : 422 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.17 (t, $J = 7.2$ Hz, 3H), 3.76 (s, 3H), 4.23 (q, $J = 7.2$ Hz, 2H), 5.38 (s, 2H), 6.58 (dd, $J = 8.8$, 2.8 Hz, 1H), 6.70 (d, $J = 2.8$ Hz, 1H), 6.75-6.77 (m, 2H), 7.15-7.17 (m, 2H), 7.28 (d, $J = 8.8$ Hz, 1H). Compound **88C**: LC-MS: (ESI) m/z : 394 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 3.70 (s, 3H), 5.43 (s, 2H), 6.81-6.83 (m, 2H), 7.10-7.12 (m, 1H), 7.15-7.17 (m, 2H), 7.37 (d, $J = 2.8$ Hz, 1H), 7.64 (d, $J = 8.8$ Hz, 1H), 13.24 (brs, 1H). Compound **88**: LC-MS (ESI) m/z : 274 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.11 (dd, $J = 8.8$, 2.8 Hz, 1H), 7.46 (d, $J = 2.8$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H).

[00793] **Example 89**

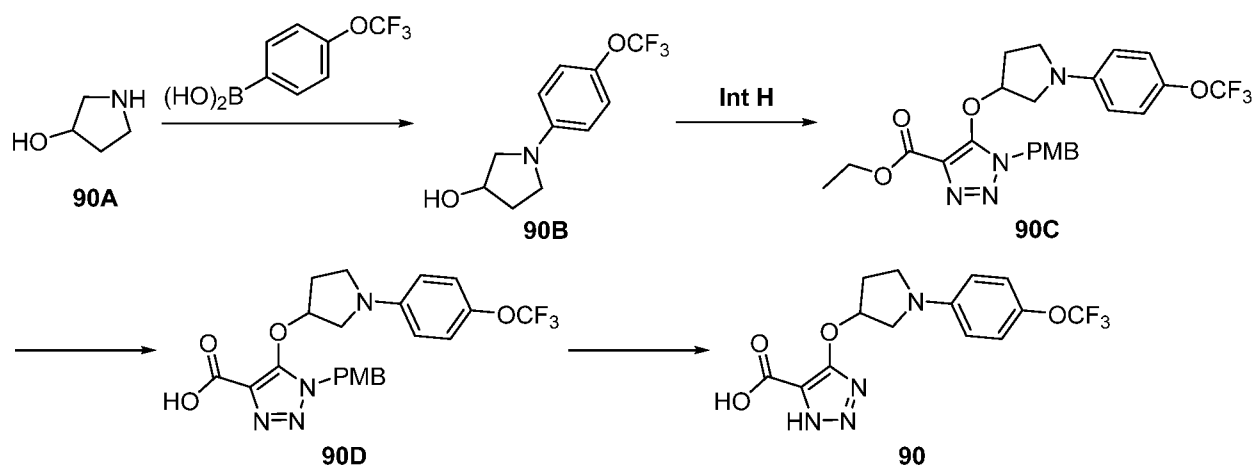
[00794] **Synthesis of 4-((6-bromonaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (89)**



[00795] Compounds **89B**, **89C**, and **89** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **89A**, **89B**, and **89C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **89B**: LC-MS (ESI) m/z : 482 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.03 (t, $J = 7.2$ Hz, 3H), 3.65 (s, 3H), 4.14 (q, $J = 7.2$ Hz, 2H), 5.39 (s, 2H), 6.67-6.69 (m, 2H), 6.76 (d, $J = 2.8$ Hz, 1H), 7.14-7.26 (m, 3H), 7.40 (d, $J = 8.8$ Hz, 1H), 7.52 (dd, $J = 8.8$ Hz, 2.0 Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.96 (d, $J = 2.0$ Hz, 1H). Compound **89C**: LC-MS: (ESI) m/z : 454 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 3.62 (s, 3H), 5.43 (s, 2H), 6.76-6.78 (m, 2H), 7.14-7.17 (m, 3H), 7.34 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.60 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 8.20 (d, $J = 2.0$ Hz, 1H). Compound **89**: LC-MS (ESI) m/z : 334 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.43 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.49 (d, $J = 2.0$ Hz, 1H), 7.62 (dd, $J = 8.8$, 2.0 Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 8.21 (d, $J = 2.0$ Hz, 1H).

[00796] **Example 90**

[00797] **Synthesis of 4-((1-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (90)**



[00798] The mixture of 4-(trifluoromethoxy)phenylboronic acid (1.5 g, 7.28 mmol), pyrrolidin-3-ol (Compound **90A**) (0.63 g, 7.28 mmol), Cu(OAc)₂ (1.57 g, 8.75 mmol), and K₃PO₄ (3.09 g, 14.58 mmol) in DMSO (20 mL) was stirred at 90 °C overnight. The reaction mixture was cooled down to room temperature, diluted with water (50 mL), and extracted with EtOAc (50 mL x 3). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 40% v/v) to furnish Compound **90B**. LC-MS (ESI) m/z: 248 [M+H]⁺.

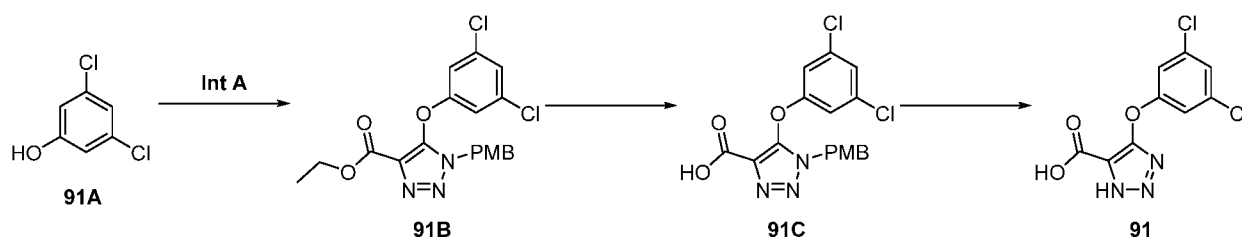
[00799] A mixture of Compound **90B** (100 mg, 0.40 mmol), Intermediate **H** (93 mg, 0.34 mmol), and PPh₃ (132 mg, 0.51 mmol) in dry THF (5 mL) was dropped DIAD (103 mg, 0.51 mmol) at 0 °C and stirred at room temperature overnight. The mixture was concentrated to give a product, which was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to furnish Compound **90C**. LC-MS (ESI) m/z: 507 [M+H]⁺.

[00800] Compounds **90D** and **90** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **90C** and **90D** in lieu of Compounds **8E** and **1E**.

Compound **90D**: LC-MS (ESI) m/z: 479 [M+H]⁺. Compound **90**: LC-MS (ESI) m/z: 359 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 2.27-2.35 (m, 2H), 3.38-3.45 (m, 3H), 3.64-3.68 (m, 1H), 5.35 (s, 1H), 6.59 (d, *J* = 6.8 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 12.82 (s, 1H), 14.81 (s, 1H).

[00801] **Example 91**

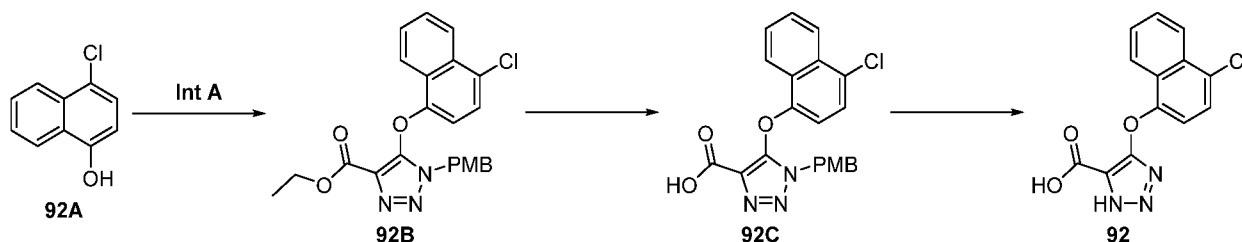
[00802] **Synthesis of 4-(3,5-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (91)**



[00803] Compounds **91B**, **91C**, and **91** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **91A**, **91B**, and **91C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **91B**: LC-MS (ESI) m/z : 422 $[M+H]^+$. Compound **91C**: LC-MS (ESI) m/z : 392 $[M-H]^-$. Compound **91**: LC-MS (ESI) m/z : 272 $[M-H]^-$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.23 (d, $J = 1.6$ Hz, 2H), 7.42 (d, $J = 1.6$ Hz, 1H).

[00804] **Example 92**

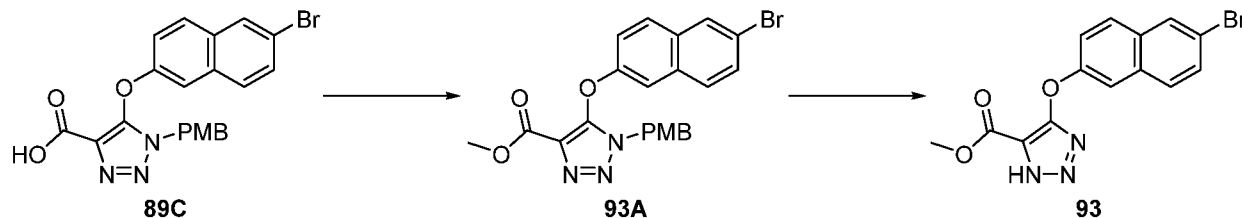
[00805] **Synthesis of 4-((4-chloronaphthalen-1-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (92)**



[00806] Compounds **92B**, **92C**, and **92** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **92A**, **92B**, and **92C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **92B**: LC-MS (ESI) m/z : 438 $[M+H]^+$. Compound **92C**: LC-MS (ESI) m/z : 410 $[M+H]^+$. Compound **92**: LC-MS (ESI) m/z : 290 $[M+H]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ (ppm) 7.11 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.79 (t, $J = 8.0$ Hz, 1H), 8.21 (d, $J = 8.0$ Hz, 1H), 8.29 (d, $J = 8.4$ Hz, 1H).

[00807] **Example 93**

[00808] **Synthesis of methyl 4-((6-bromonaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylate (93)**

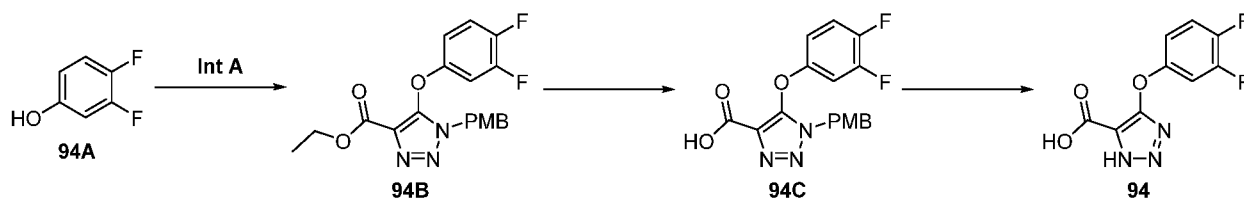


[00809] To a solution of Compound **89C** (60 mg, 0.132 mmol) in CH₃CN (10 mL) and MeOH (10 mL) was added a solution of TMSCHN₂ in hexane (2 M, 0.2 mL, 0.41 mmol) at 0 °C and stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was used directly for next step without further purification. LC-MS (ESI) m/z: 468 [M+H]⁺.

[00810] Compound **93** was synthesized by employing the procedure described for Compound **1** using Compound **93A** in lieu of Compound **1E**, LC-MS (ESI) m/z: 348 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.76 (s, 3H), 7.44 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.55 (d, *J* = 2.8 Hz, 1H), 7.63 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 1.6 Hz, 1H).

[00811] Example 94

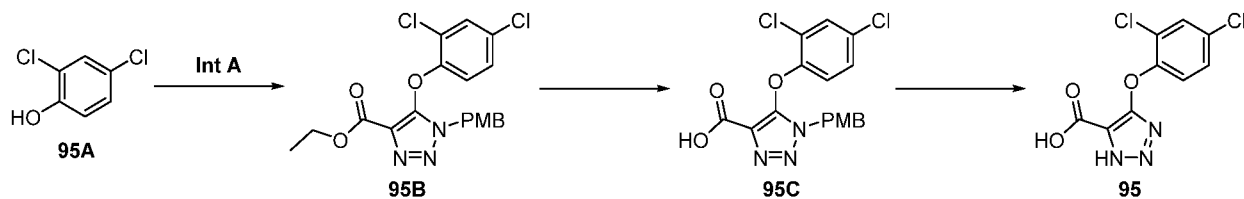
[00812] Synthesis of 4-(3,4-difluorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (**94**)



[00813] Compounds **94B**, **94C**, and **94** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **94A**, **94B**, and **94C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **94B**: LC-MS: (ESI) m/z: 801 [2M+Na]⁺. Compound **94C**: LC-MS (ESI) m/z: 745 [2M+Na]⁺. Compound **94**: LC-MS (ESI) m/z: 242 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 6.92-6.97 (m, 1H), 7.30-7.36 (m, 1H), 7.40-7.47 (m, 1H).

[00814] Example 95

[00815] Synthesis of 4-(2,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (**95**)

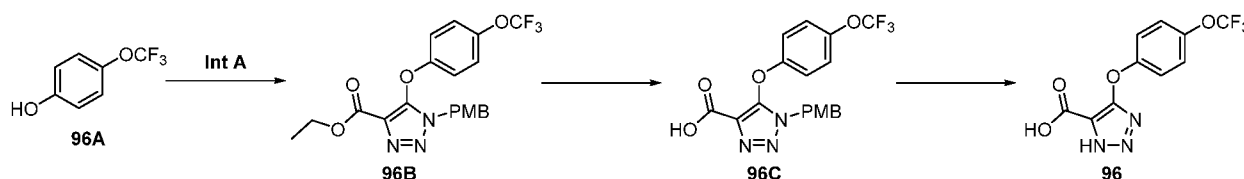


[00816] Compounds **95B**, **95C**, and **95** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **95A**, **95B**, and **95C** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **95B**: LC-MS (ESI) m/z: 422 [M+H]⁺. Compound **95C**: LC-MS (ESI) m/z: 392 [M-H]⁻. Compound **95**: LC-MS (ESI) m/z: 272 [M-H]⁻;

¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.20 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 9.2, 2.4 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H).

[00817] Example 96

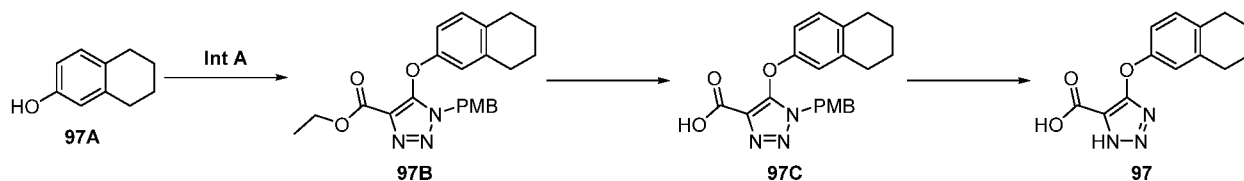
[00818] Synthesis of 4-(4-(trifluoromethoxy)phenoxy)-1H-1,2,3-triazole-5-carboxylic acid (96)



[00819] Compounds **96B**, **96C**, and **96** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **96A**, **96B**, and **96C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **96B**: LC-MS: (ESI) m/z : 438 $[M+H]^+$. Compound **96C**: LC-MS (ESI) m/z : 432 $[M+Na]^+$. Compound **96**: LC-MS (ESI) m/z : 290 $[M+H]^+$; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.17-7.19 (m, 2H), 7.38 (d, J = 8.4 Hz, 2H).

[00820] Example 97

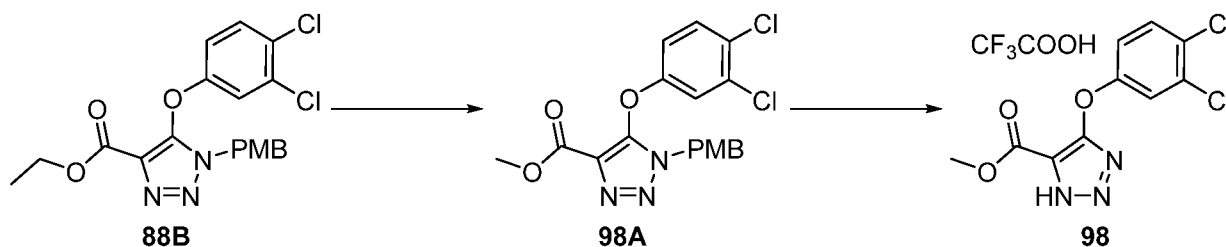
[00821] Synthesis of 4-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (97)



[00822] Compounds **97B**, **97C**, and **97** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **97A**, **97B**, and **97C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **97B**: LC-MS (ESI) m/z : 408 $[M+H]^+$. Compound **97C**: LC-MS (ESI) m/z : 380 $[M+H]^+$. Compound **97**: LC-MS (ESI) m/z : 260 $[M+H]^+$. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.69-1.70 (m, 4H), 2.64 (s, 4H), 6.62 (s, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H).

[00823] Example 98

[00824] Synthesis of methyl 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylate 2,2,2-trifluoroacetate (98)

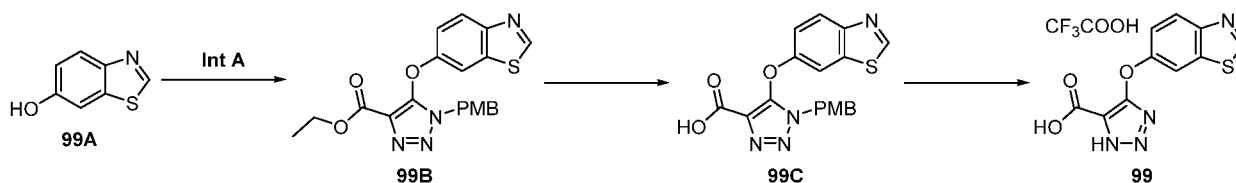


[00825] A solution of Compound **88B** (200 mg, 0.5 mmol) and concentrated H_2SO_4 (0.1 mL) in MeOH (5 mL) was stirred at 60 °C for 16 hours. After cooling down to room temperature, the mixture was concentrated and purified with reverse phase chromatography using eluents (acetonitrile in water, from 0% to 100% v/v) to afford Compound **98A**. LC-MS (ESI) m/z: 408 $[\text{M}+\text{H}]^+$.

[00826] Compound **98** was synthesized by employing the procedure described for Compound **1** using Compound **98A** in lieu of Compound **1E**, LC-MS (ESI) m/z: 288 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 3.87 (s, 3H), 7.10 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.37 (d, $J = 2.8$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H).

[00827] **Example 99**

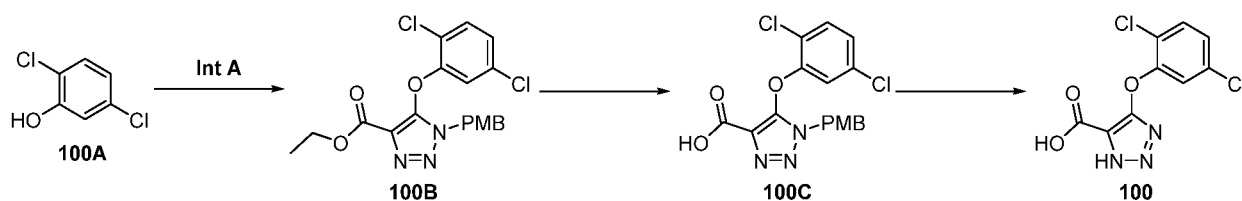
[00828] **Synthesis of 4-(benzo[d]thiazol-6-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**99**)**



[00829] Compounds **99B**, **99C**, and **99** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **99A** using NMP as solvent, **99B**, and **99C** in lieu of 4-bromophenol using DMF as solvent, Compounds **8E**, and **1E**. Compound **99B**: LC-MS (ESI) m/z: 411 $[\text{M}+\text{H}]^+$. Compound **99C**: LC-MS (ESI) m/z: 383 $[\text{M}+\text{H}]^+$. Compound **99**: LC-MS (ESI) m/z: 263 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.31 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.0$ Hz, 1H), 7.86 (d, $J = 2.0$ Hz, 1H), 8.05 (d, $J = 8.8$ Hz, 1H), 9.30 (s, 1H).

[00830] **Example 100**

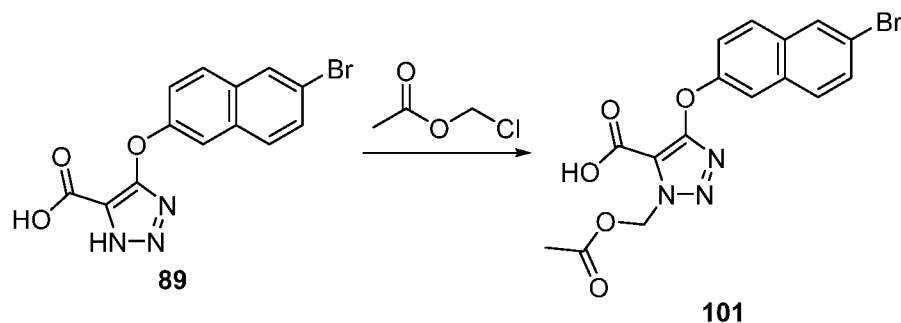
[00831] **Synthesis of 4-(2,5-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (**100**)**



[00832] Compounds **100B**, **100C**, and **100** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **100A**, **100B**, and **100C** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **100B**: LC-MS (ESI) m/z : 422 $[M+H]^+$. Compound **100C**: LC-MS (ESI) m/z : 392 $[M-H]^-$. Compound **100**: LC-MS (ESI) m/z : 274 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.31 (d, $J = 8.8$ Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 1H).

[00833] **Example 101**

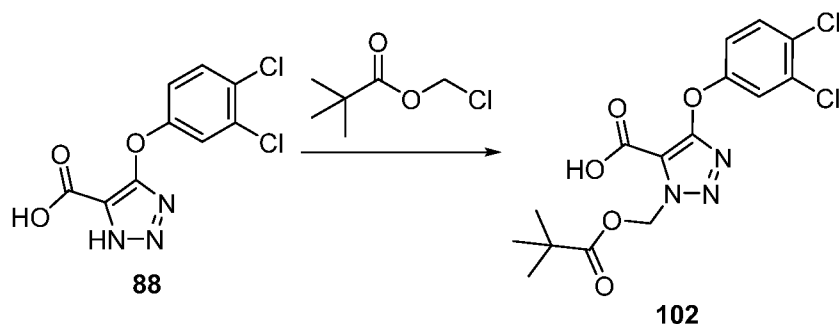
[00834] **Synthesis of 1-(acetoxymethyl)-4-((6-bromonaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (101)**



[00835] Compound **101** was synthesized by employing the procedure described for Compound **51** using chloromethyl acetate and Compound **89** in lieu of chloromethyl pivalate and Compound **16**, LC-MS (ESI) m/z : 406 $[M+H]^+$. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 2.09 (s, 3H), 6.15 (s, 2H), 7.37 (dd, $J = 2.4, 8.8$ Hz, 1H), 7.41 (d, $J = 5.2$ Hz, 1H), 7.60 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 9.2$ Hz, 1H), 8.20 (d, $J = 2$ Hz, 1H).

[00836] **Example 102**

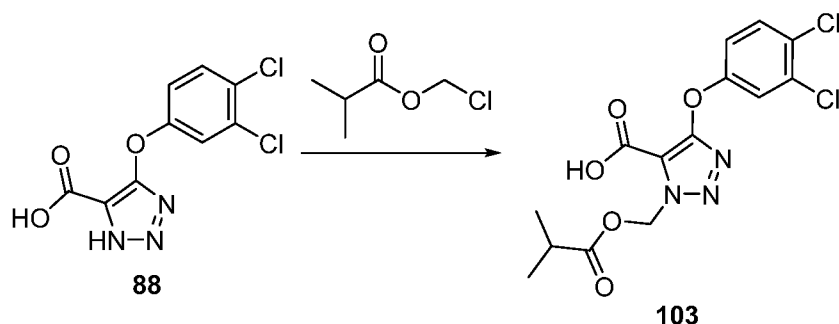
[00837] **Synthesis of 4-(3,4-dichlorophenoxy)-1-((pivaloyloxy)methyl)-1H-1,2,3-triazole-5-carboxylic acid (102)**



[00838] Compound **102** was synthesized by employing the procedure described for Compound **51** using Compound **88** in lieu of Compound **16**, LC-MS (ESI) m/z : 405 $[M+18]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.04 (s, 9H), 5.72 (s, 2H), 6.88 (dd, $J = 9.2, 2.8$ Hz, 1H), 7.06 (d, $J = 2.4$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 1H).

[00839] **Example 103**

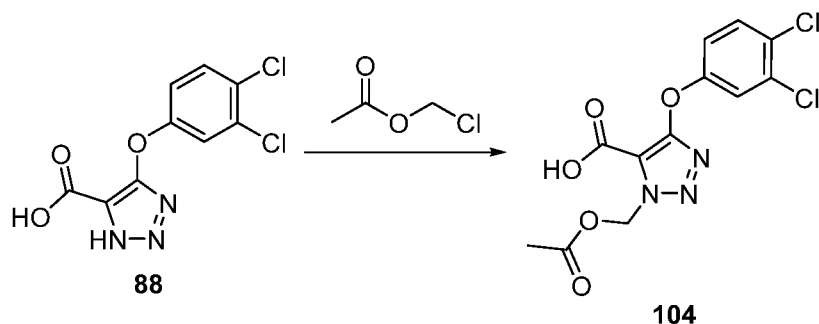
[00840] **Synthesis of 4-(3,4-dichlorophenoxy)-1-((isobutyryloxy)methyl)-1H-1,2,3-triazole-5-carboxylic acid (103)**



[00841] Compound **103** was synthesized by employing the procedure described for Compound **51** using chloromethyl isobutyrate and Compound **88** in lieu of chloromethyl pivalate and Compound **16**, LC-MS (ESI) m/z : 391 $[M+18]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.07 (d, $J = 6.8$ Hz, 6H), 2.58-2.59 (m, 1H), 6.18 (s, 2H), 7.03 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.28 (d, $J = 2.8$ Hz, 1H), 7.60 (d, $J = 8.8$ Hz, 1H).

[00842] **Example 104**

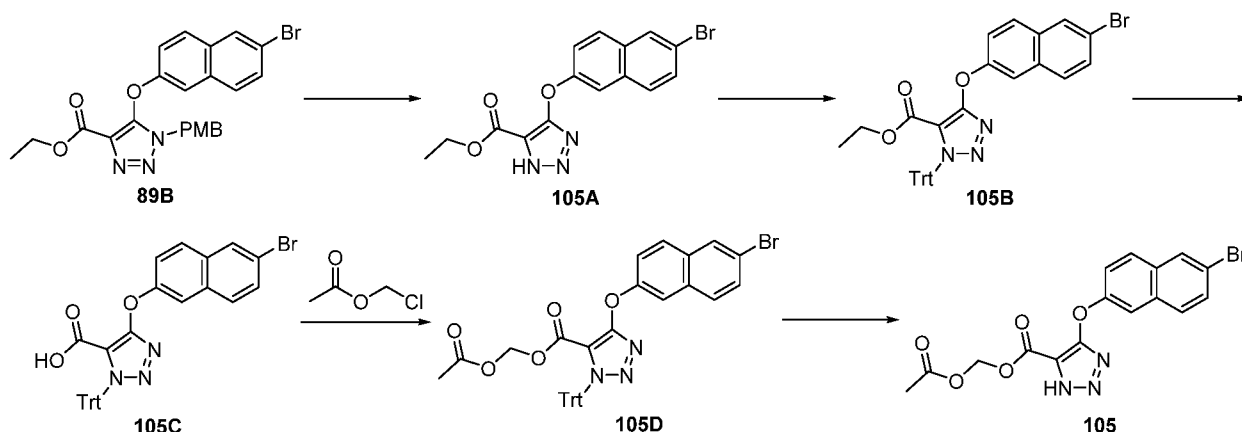
[00843] **Synthesis of 1-(acetoxymethyl)-4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylic acid (104)**



[00844] Compound **104** was synthesized by employing the procedure described for Compound **51** using chloromethyl acetate and Compound **88** in lieu of chloromethyl pivalate and Compound **16**, LC-MS (ESI) m/z : 363 $[M+18]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 2.08 (s, 3H), 6.15 (s, 2H), 7.05 (dd, $J = 8.4, 2.8$ Hz, 1H), 7.35 (d, $J = 3.2$ Hz, 1H), 7.60 (d, $J = 9.2$ Hz, 1H).

[00845] Example 105

[00846] Synthesis of acetoxyethyl 4-((6-bromonaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylate (**105**)

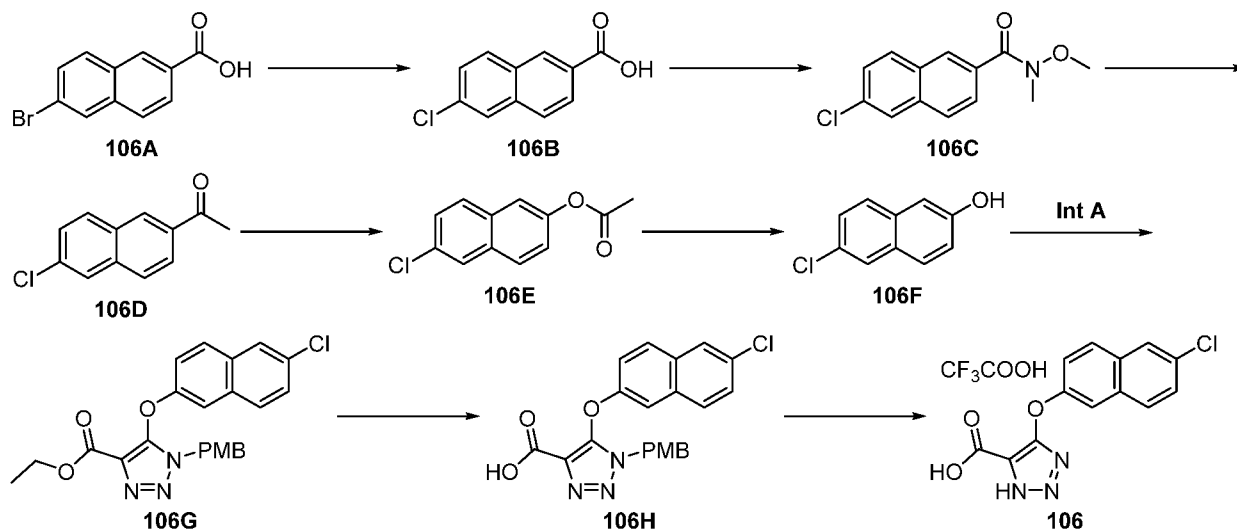


[00847] Compounds **105A**, **105B**, **105C**, **105D**, and **105** were synthesized by employing the procedures described for Compounds **1**, **54A**, **8F**, **54C**, and **54** using Compounds **89B**, **105A**, **105B**, **105C**, chloromethyl acetate, and **105D** in lieu of Compounds **1E**, **33**, **8E**, **54B**, chloromethyl pivalate, and **54C**. Compound **105A**: LC-MS (ESI) m/z : 362 $[M+H]^+$. Compound **105B**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.21 (t, $J = 6.8$ Hz, 3H), 4.27 (q, $J = 6.8$ Hz, 2H), 7.17-7.20 (m, 6H), 7.29-7.35 (m, 11H), 7.45-7.53 (m, 2H), 7.66-7.63 (m, 1H), 7.94-7.95 (m, 1H). Compound **105C**: LC-MS (ESI) m/z : 243 $[M-\text{Trt}]^+$. Compound **105D**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **105**: LC-MS (ESI) m/z : 406 $[M+H]^+$; $^1\text{H-NMR}$

(DMSO-*d*₆, 400 MHz): δ (ppm) 1.96 (s, 3H), 5.83 (s, 2H), 7.45 (dd, $J = 2.4$ Hz, 8.8 Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.64 (dd, $J = 2.0$ Hz, 8.8 Hz, 1H), 7.84 (d, $J = 9.2$ Hz, 1H), 7.98 (d, $J = 9.2$ Hz, 1H), 8.23 (d, $J = 1.6$ Hz, 1H).

[00848] Example 106

[00849] Synthesis of 4-((6-chloronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (106)



[00850] A mixture of 6-bromo-2-naphthoic acid (Compound **106A**) (3.00 g, 11.47 mmol), CuI (2.19 g, 11.50 mmol), and CuCl (11.70 g, 114.64 mmol) in DMF (20 mL) was stirred at 150 °C under nitrogen for 3 hours. The mixture was cooled down to room temperature and diluted with an aqueous HCl solution (3 M, 100 mL). A solid was formed, filtered, and washed with water (100 mL). It was suspended in THF (100 mL), filtered, and washed with THF (100 mL). The combined filtrates were concentrated under reduced pressure. The residue was suspended in an aqueous HCl solution (3 M, 100 mL), stirred at room temperature for 10 minutes, and filtered. The cake was washed with water (50 mL) and CH₃CN (50 mL) and dried under vacuum to yield Compound **106B**. LC-MS (ESI) m/z : 205 [M-H]⁻; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.61-7.64 (m, 1H), 7.99-8.05 (m, 2H), 8.15-8.19 (m, 2H), 8.65 (s, 1H), 13.18 (s, 1H).

[00851] A mixture of Compound **106B** (3.00 g, 14.56 mmol), *N,O*-dimethylhydroxylamine hydrochloride (1.71 g, 17.47 mmol), Et₃N (4.41 g, 43.68 mmol), and HATU (8.30 g, 21.84 mmol) in dichloromethane (30 mL) was stirred at room temperature for 4 hours. The mixture was diluted with ethyl acetate (160 mL), washed with water (100 mL) and

brine (100 mL), and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0% to 80% v/v) to yield Compound **106C**.

LC-MS (ESI) m/z : 250 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.31 (s, 3H), 3.56 (s, 3H), 7.59-7.62 (m, 1H), 7.71-7.74 (m, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.08-8.12 (m, 2H), 8.24 (s, 1H).

[00852] To a solution of Compound **106C** (3.00 g, 12.05 mmol) in dry THF (20 mL) was added a solution of MeMgBr in Et₂O (3 *M*, 6.4 mL, 19.28 mmol) at 0 °C and stirred at room temperature under nitrogen for 16 hours. The reaction mixture was quenched with methanol (10 mL) and an aqueous HCl solution (3 *M*, 50 mL), and extracted with ethyl acetate (160 mL). The extract was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0% to 10% v/v) to yield Compound **106D**.

LC-MS (ESI) m/z : 205 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 2.70 (s, 3H), 7.65 (d, J = 8.8 Hz, 1H), 7.99-8.05 (m, 2H), 8.14-8.20 (m, 2H), 8.71 (s, 1H).

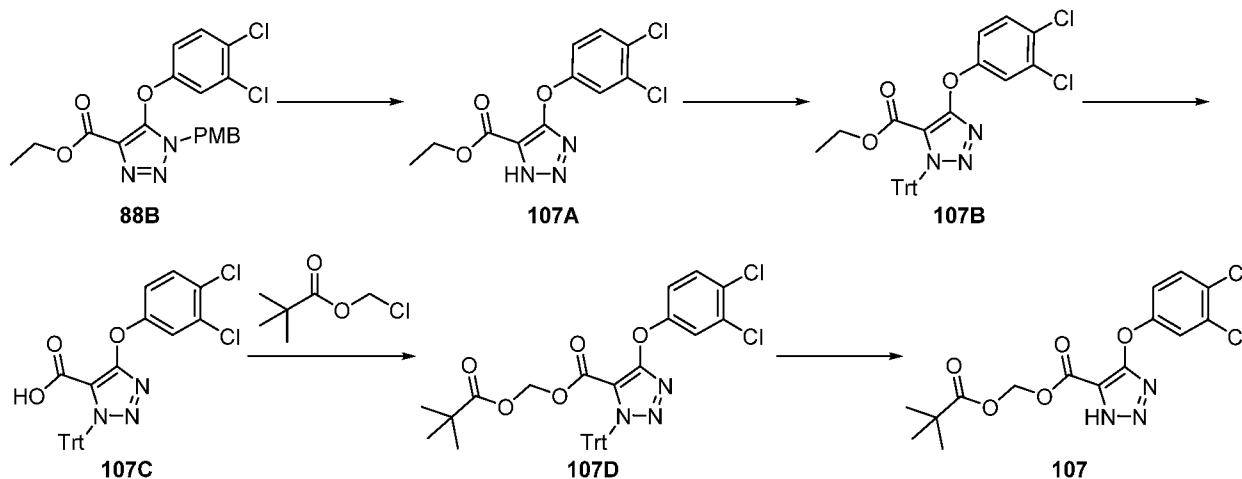
[00853] To a solution of Compound **106D** (2.38 g, 11.67 mmol) in 1,2-dichloroethane (30 mL) was added *m*-CPBA (3.00 g, 17.50 mmol) at room temperature and stirred at 80 °C for 4 hours. Another portion of *m*-CPBA (3.00 g, 17.50 mmol) was added and stirred at 80 °C for 16 hours. The mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether from 0% to 20% v/v) to yield Compound **106E**. LC-MS (ESI) m/z : 221 $[M+H]^+$.

[00854] Compounds **106F**, **106G**, **106H**, and **106I** were synthesized by employing the procedures described for Compounds **8F**, **86B**, **8F**, and **1** using Compounds **106E**, **106F**, **106G**, and **106H** in lieu of Compounds **8E**, **86A**, **8E**, and **1E**. Compound **106F**: LC-MS (ESI) m/z : 179 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.11-7.14 (m, 2H), 7.38 (d, J = 8.8 Hz, 1H), 7.71-7.77 (m, 2H), 7.88 (d, J = 2.0 Hz, 1H), 9.87 (s, 1H). Compound **106G**: LC-MS (ESI) m/z : 438 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 0.82 (t, J = 7.2 Hz, 3H), 3.63 (s, 3H), 3.97 (q, J = 7.2 Hz, 2H), 5.48 (s, 2H), 6.78 (d, J = 8.8 Hz, 2H), 7.18-7.25 (m, 2H), 7.30-7.35 (m, 1H), 7.37-7.40 (m, 1H), 7.48-7.52 (m, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.90-7.95 (m, 1H), 8.05 (d, J = 2.4 Hz, 1H). Compound **106H**: LC-MS (ESI) m/z : 410 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.61 (s, 3H), 5.30 (s, 2H), 6.74 (d, J = 8.8 Hz, 2H), 7.04 (s, 1H), 7.10 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.86 (d, J =

8.8 Hz, 1H), 8.01 (s, 1H). Compound **106**: LC-MS (ESI) m/z : 290 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.42 (d, J = 8.8 Hz, 1H), 7.19-7.52 (m, 2H), 7.90 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.06 (s, 1H).

[00855] Example 107

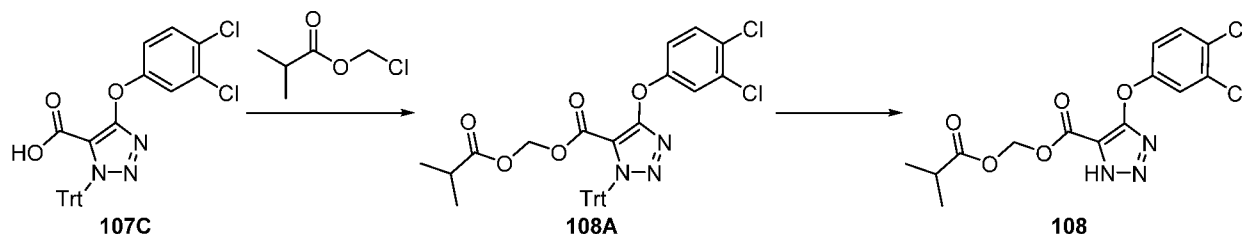
[00856] Synthesis of (pivaloyloxy)methyl 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylate (107)



[00857] Compounds **107A**, **107B**, **107C**, **107D**, and **107** were synthesized by employing the procedures described for Compounds **1**, **54A**, **8F**, **51**, and **1** using Compounds **88B**, **107A**, **107B**, **107C**, and **107D** in lieu of Compounds **1E**, **33**, **8E**, **16**, and **1E**. Compound **107A**: LC-MS (ESI) m/z : 302 $[M+H]^+$. Compound **107B**: LC-MS (ESI) m/z : 566 $[M+Na]^+$. Compound **107C**: LC-MS (ESI) m/z : 538 $[M+Na]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.08-7.12 (m, 7H), 7.37-7.43 (m, 10H), 7.58-7.60 (m, 1H), 13.50 (s, 1H). Compound **107D**: LC-MS (ESI) m/z : 652 $[M+Na]^+$. Compound **107**: LC-MS (ESI) m/z : 405 $[M+H_2O]^+$; $^1\text{H-NMR}$ (CD $_3$ OD, 400 MHz): δ (ppm) 1.17 (s, 9H), 5.93 (s, 2H), 7.07-7.10 (m, 1H), 7.33 (s, 1H), 7.50-7.52 (m, 1H).

[00858] Example 108

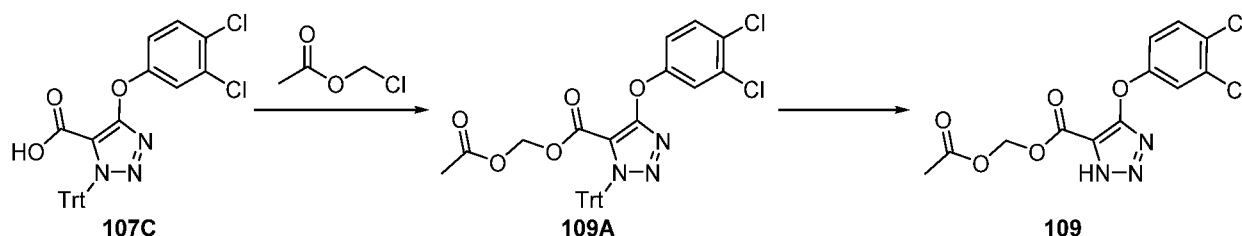
[00859] Synthesis of (isobutyryloxy)methyl 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylate (108)



[00860] Compounds **108A** and **108** were synthesized by employing the procedures described for Compounds **51** and **1** using chloromethyl isobutyrate, Compounds **107C**, and **108A** in lieu of chloromethyl pivalate, Compounds **16**, and **1E**. Compound **108A**: LC-MS (ESI) m/z : 633 $[M+H_2O]^+$. Compound **108**: LC-MS (ESI) m/z : 391 $[M+H_2O]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.10 (d, $J = 7.2$ Hz, 6H), 2.46-2.54 (m, 1H), 5.84 (s, 2H), 6.87-6.90 (m, 1H), 7.06-7.07 (m, 1H), 7.41-7.43 (m, 1H).

[00861] **Example 109**

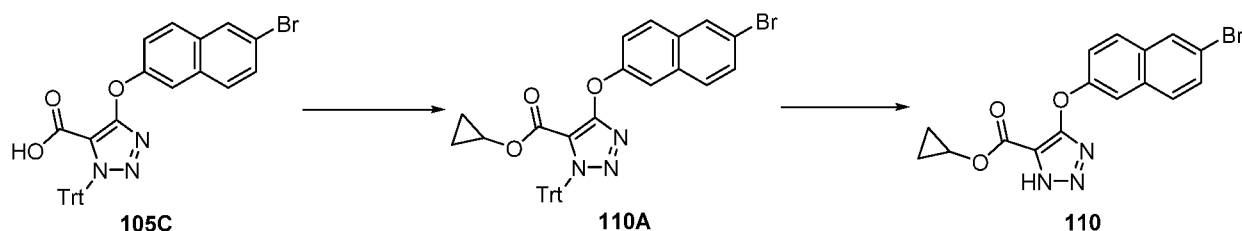
[00862] **Synthesis of acetoxymethyl 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylate (109)**



[00863] Compounds **109A** and **109** were synthesized by employing the procedures described for Compounds **51** and **1** using chloromethyl acetate, Compounds **107C**, and **109A** in lieu of chloromethyl pivalate, Compounds **16**, and **1E**. Compound **109A**: LC-MS (ESI) m/z : 605 $[M+H_2O]^+$. Compound **109**: LC-MS (ESI) m/z : 346 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.01 (s, 3H), 5.82 (s, 2H), 6.87-6.90 (m, 1H), 7.07-7.08 (m, 1H), 7.41-7.43 (m, 1H).

[00864] **Example 110**

[00865] **Synthesis of cyclopropyl 4-((6-bromonaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylate (110)**



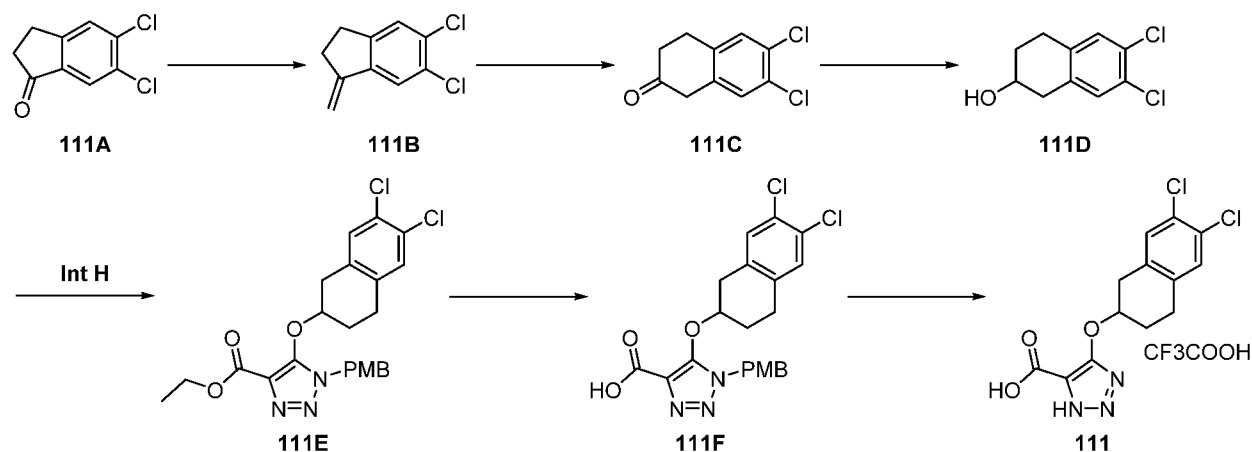
[00866] Compounds **110A** and **110** were synthesized by employing the procedures described for Compounds **19A** and **1** using Compounds **105C** using TEA as base and dichloromethane as solvent and **110A** in lieu of Compounds **9A** using DIPEA as base and DMF as solvent and **1E**. Compound **110A**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used; ^1H -NMR ($CDCl_3$, 400 MHz): δ 0.58-0.68 (m, 4H), 4.23-4.28 (m, 1H), 7.16-7.19

(m, 6H), 7.28-7.35 (m, 11H), 7.45-7.53 (m, 2H), 7.66-7.68 (m, 1H), 7.94-7.95 (m, 1H).

Compound **110**: LC-MS (ESI) m/z : 374 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 0.36-0.40 (m, 2H), 0.58-0.63 (m, 2H), 4.15-4.19 (m, 1H), 7.40 (dd, $J = 2.4$ Hz, 8.8 Hz, 1H), 7.45 (d, $J = 1.6$ Hz, 1H), 7.64 (dd, $J = 2.0$ Hz, 8.8 Hz, 1H), 7.81 (d, $J = 8.8$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 8.21 (d, $J = 1.6$ Hz, 1H).

[00867] Example 111

[00868] Synthesis of 4-((6,7-dichloro-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (111**)**



[00869] To a suspend of methyltriphenylphosphonium bromide (10.7 g, 30 mmol) in dry THF (150 mL) was added *t*-BuOK (3.37 g, 30 mmol) and stirred at 0 °C for 15 minutes. To the mixture was added a solution of 5,6-dichloro-2,3-dihydro-1H-inden-1-one (Compound **111A**) (3.0 g, 15.0 mmol) in dry THF (60 mL) in one portion at 0 °C. After stirring at 0 °C for 5 hours, to the mixture was added more methyltriphenylphosphonium bromide (10.7 g, 30 mmol) and *t*-BuOK (3.37 g, 30 mmol) at 0 °C and stirred at room temperature for 58 hours. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was diluted with *n*-hexane (100 mL) and passed through a short silica gel column. The eluent was concentrated to give Compound **111B**. LC-MS (ESI) m/z : Non-ionizable Compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.78-2.84 (m, 2H), 2.89-2.94 (m, 2H), 5.08 (t, $J = 2.0$ Hz, 1H), 5.42 (t, $J = 2.0$ Hz, 1H), 7.32 (s, 1H), 7.51 (s, 1H).

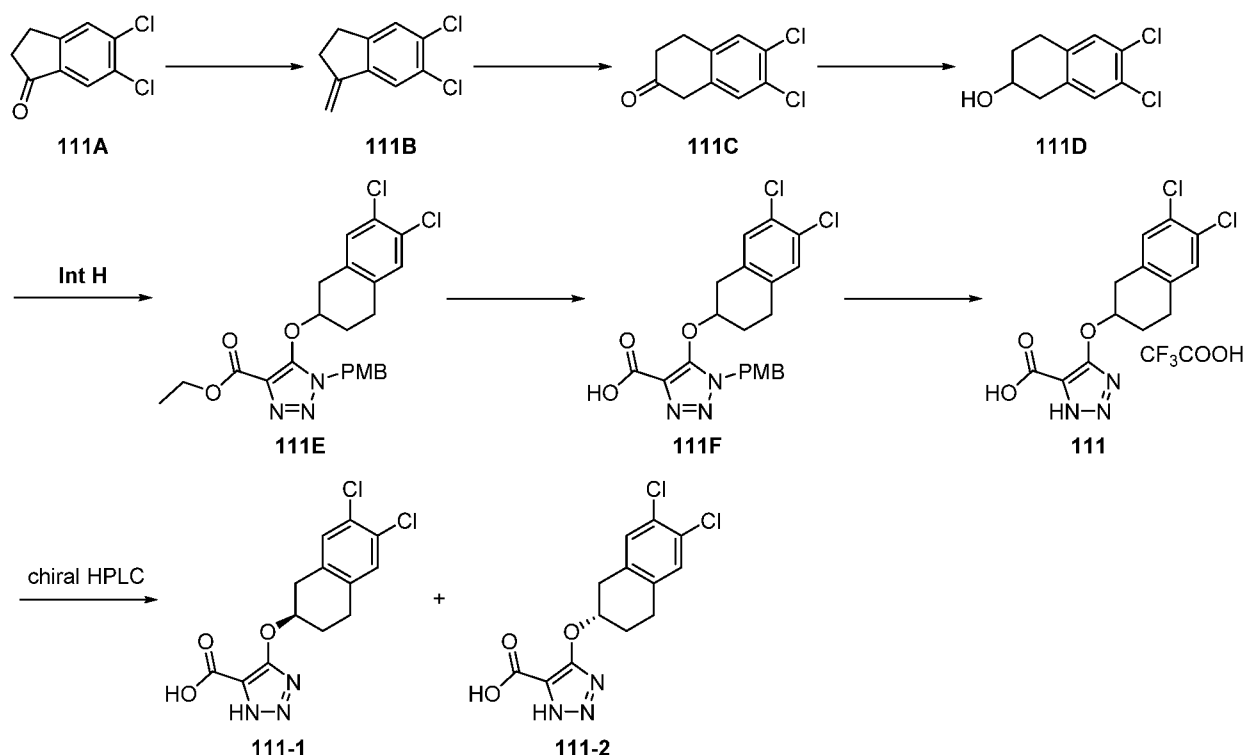
[00870] To a solution of Compound **111B** (907 mg, 4.56 mmol) in 95% MeOH (20 mL) at 0 °C was added hydroxy(tosyloxy)iodobenzene (1.8 g, 4.56 mmol) and stirred at 0 °C for 30 minutes. The mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (120 mL), washed with saturated aqueous NaHCO_3 solution (50 mL x 2) and

brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **111C**. The product was used directly in next step without further purification. LC-MS (ESI) m/z : 215 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.55 (t, $J = 6.4$ Hz, 2H), 3.03 (t, $J = 6.4$ Hz, 2H), 3.54 (s, 2H), 7.23 (s, 1H), 7.34 (s, 1H).

[00871] Compounds **111D**, **111E**, **111F**, and **111** were synthesized by employing the procedures described for Compounds **57C**, **90C**, **8F**, and **1** using Compounds **111C**, **111D**, **111E**, and **111F** in lieu of Compounds **57B**, **90B**, **8E**, and **1E**. Compound **111D**: LC-MS (ESI) m/z : 199 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.77-1.86 (m, 1H), 1.97-2.04 (m, 1H), 2.67-2.73 (m, 1H), 2.76-2.79 (m, 1H), 2.88-2.95 (m, 1H), 2.98-3.03 (m, 1H), 4.13-4.19 (m, 1H), 7.16 (s, 1H), 7.18 (s, 1H). Compound **111E**: LC-MS (ESI) m/z : 476 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.42 (t, $J = 7.2$ Hz, 3H), 1.94-2.13 (m, 2H), 2.69-2.84 (m, 3H), 2.94-2.99 (m, 1H), 3.77 (s, 3H), 4.41 (q, $J = 7.2$ Hz, 2H), 5.02-5.16 (m, 2H), 5.66-5.71 (m, 1H), 6.74-6.76 (m, 2H), 6.96-6.98 (m, 2H), 7.06 (s, 1H), 7.19 (s, 1H). Compound **111F**: LC-MS (ESI) m/z : 448 $[M+H]^+$. Compound **111**: LC-MS (ESI) m/z : 328 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.12-2.21 (m, 2H), 2.78-2.85 (m, 1H), 2.97-3.08 (m, 2H), 3.20-3.25 (m, 1H), 5.17 (t, $J = 4.0$ Hz, 1H), 7.25 (s, 1H), 7.27 (s, 1H).

[00872] **Example 111-1 and 111-2**

[00873] **Synthesis of (*R*)-4-((6,7-dichloro-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (111-1) and (*S*)-4-((6,7-dichloro-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (111-2)**



[00874] To a suspend of methyltriphenylphosphonium bromide (10.7 g, 30 mmol) in dry THF (150 mL) was added *t*-BuOK (3.37 g, 30 mmol) and stirred at 0 °C for 15 minutes. To the mixture was added a solution of 5,6-dichloro-2,3-dihydro-1H-inden-1-one (**111A**) (3.0 g, 15.0 mmol) in dry THF (60 mL) in one portion at 0 °C. After stirred at 0 °C for 5 hours, to the mixture was added more methyltriphenylphosphonium bromide (10.7 g, 30 mmol) and *t*-BuOK (3.37 g, 30 mmol) at 0 °C and stirred at room temperature for 58 hours. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was diluted with n-hexane (100 mL) and passed through a short silica gel column. The eluent was concentrated to give Compound **111B** as a colorless oil (2.3 g, yield 75%). LC-MS (ESI) m/z: Non-ionizable Compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.78-2.84 (m, 2H), 2.89-2.94 (m, 2H), 5.08 (t, *J* = 2.0 Hz, 1H), 5.42 (t, *J* = 2.0 Hz, 1H), 7.32 (s, 1H), 7.51 (s, 1H).

[00875] To a solution of Compound **111B** (907 mg, 4.56 mmol) in 95% MeOH (20 mL) at 0 °C was added hydroxy(tosyloxy)iodobenzene (1.8 g, 4.56 mmol) and stirred at 0 °C for 30 minutes. The mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (120 mL), washed with saturated aqueous NaHCO₃ solution (50 mL x 2) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude Compound **111C** as a yellow solid (980 mg, yield 100%). The crude product was used directly in

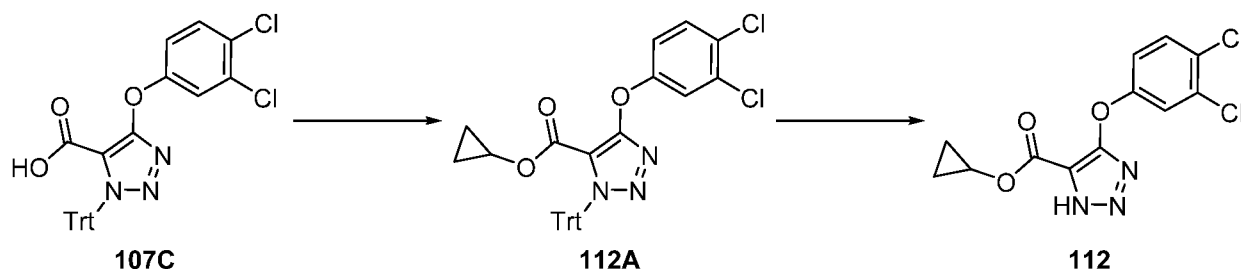
next step without further purification. LC-MS (ESI) m/z : 215 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.55 (t, $J = 6.4$ Hz, 2H), 3.03 (t, $J = 6.4$ Hz, 2H), 3.54 (s, 2H), 7.23 (s, 1H), 7.34 (s, 1H).

[00876] Compounds **111D**, **111E**, **111F**, and **111** were synthesized by employing the procedures described for Compounds **57C**, **90C**, **8F**, and **1** using Compounds **111C**, **111D**, **111E**, and **111F** in lieu of Compounds **57B**, **90B**, **8E**, and **1E**. Compound **111D**: LC-MS (ESI) m/z : 199 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.77-1.86 (m, 1H), 1.97-2.04 (m, 1H), 2.67-2.73 (m, 1H), 2.76-2.79 (m, 1H), 2.88-2.95 (m, 1H), 2.98-3.03 (m, 1H), 4.13-4.19 (m, 1H), 7.16 (s, 1H), 7.18 (s, 1H). Compound **111E**: LC-MS (ESI) m/z : 476 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.42 (t, $J = 7.2$ Hz, 3H), 1.94-2.13 (m, 2H), 2.69-2.84 (m, 3H), 2.94-2.99 (m, 1H), 3.77 (s, 3H), 4.41 (q, $J = 7.2$ Hz, 2H), 5.02-5.16 (m, 2H), 5.66-5.71 (m, 1H), 6.74-6.76 (m, 2H), 6.96-6.98 (m, 2H), 7.06 (s, 1H), 7.19 (s, 1H). Compound **111F**: LC-MS (ESI) m/z : 448 $[M+H]^+$. Compound **111**: LC-MS (ESI) m/z : 328 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.12-2.21 (m, 2H), 2.78-2.85 (m, 1H), 2.97-3.08 (m, 2H), 3.20-3.25 (m, 1H), 5.17 (t, $J = 4.0$ Hz, 1H), 7.25 (s, 1H), 7.27 (s, 1H).

[00877] Compound **111** (130 mg) was separated with preparative chiral-HPLC and HPLC to furnish Compound **111-1** as a white solid (29 mg, yield 22%) and Compound **111-2** as a white solid (29 mg, yield 22%). Compound **111-1**: LC-MS (ESI) m/z : 328 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.14-2.19 (m, 2H), 2.78-2.86 (m, 1H), 2.98-3.09 (m, 2H), 3.20-3.26 (m, 1H), 5.17 (brs, 1H), 7.26 (s, 1H), 7.28 (s, 1H). Chiral separation condition: n-hexane/EtOH contained 0.1% diethylamine (30/70); IE (4.6 x 250 mm, 5 μ m), retention time: 7.69 min. It is a mixture as mobile phase; Compound **111-2**: LC-MS (ESI) m/z : 328 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 2.16-2.21 (m, 2H), 2.80-2.88 (m, 1H), 3.00-3.11 (m, 2H), 3.23-3.28 (m, 1H), 5.19 (brs, 1H), 7.28 (s, 1H), 7.30 (s, 1H). Chiral separation condition: n-hexane/EtOH contained 0.1% diethylamine (30/70); IE (4.6 x 250 mm, 5 μ m), retention time: 12.62 min.

[00878] **Example 112**

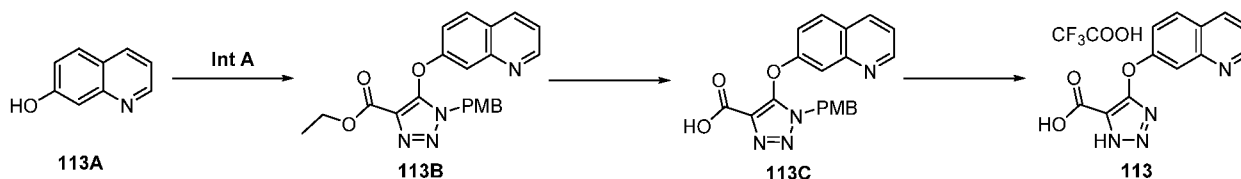
[00879] **Synthesis of cyclopropyl 4-(3,4-dichlorophenoxy)-1H-1,2,3-triazole-5-carboxylate (112)**



[00880] Compounds **112A** and **112** were synthesized by employing the procedures described for Compounds **19A** and **1** using Compounds **107C** using dichloromethane as solvent and **112A** in lieu of Compounds **9A** using DMF as solvent and **1E**. Compound **112A**: LC-MS (ESI) m/z : 578 $[M+Na]^+$. Compound **112**: LC-MS (ESI) m/z : 314 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.64-0.65 (m, 2H), 0.75-0.77 (m, 2H), 4.31-4.33 (m, 1H), 7.03-7.06 (m, 1H), 7.31-7.32 (m, 1H), 7.51-7.53 (m, 1H).

[00881] **Example 113**

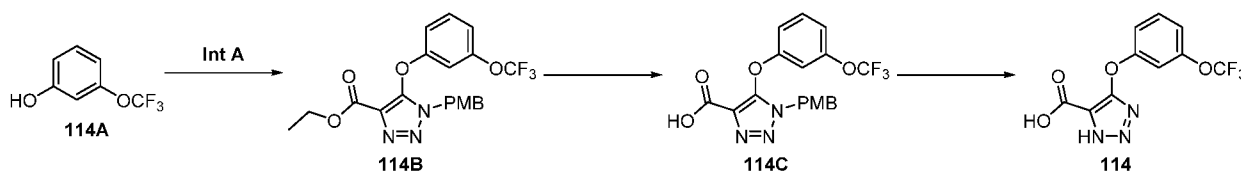
[00882] **Synthesis of 4-(quinolin-7-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (113)**



[00883] Compounds **113B**, **113C**, and **113** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **113A**, **113B**, and **113C** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **113B**: LC-MS (ESI) m/z : 405 $[M+H]^+$. Compound **113C**: LC-MS (ESI) m/z : 377 $[M+H]^+$. Compound **113**: LC-MS (ESI) m/z : 257 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.52 (s, 1H), 7.53-7.62 (m, 1H), 7.65-7.68 (m, 1H), 8.16 (d, $J = 9.2$ Hz, 1H), 8.64 (d, $J = 8.0$ Hz, 1H), 9.00 (d, $J = 4.4$ Hz, 1H).

[00884] **Example 114**

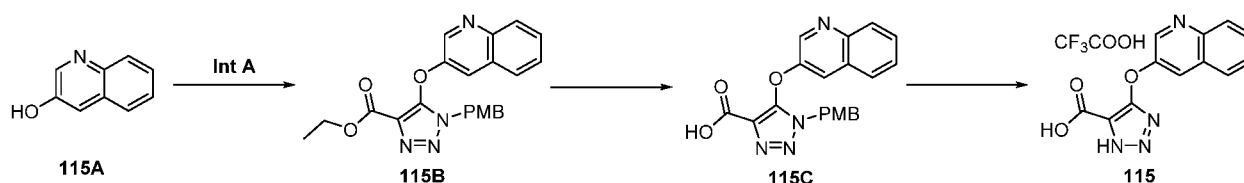
[00885] **Synthesis of 4-(3-(trifluoromethoxy)phenoxy)-1H-1,2,3-triazole-5-carboxylic acid (114)**



[00886] Compounds **114B**, **114C**, and **114** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **114A**, **114B**, and **114C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **114B**: LC-MS (ESI) m/z : 438 $[M+H]^+$. Compound **114C**: LC-MS (ESI) m/z : 410 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 3.32 (s, 3H), 5.28 (s, 2H), 6.74-6.82 (m, 4H), 7.01-7.03 (m, 1H), 7.06-7.09 (m, 2H), 7.35 (t, $J = 8.4$ Hz, 1H). Compound **114**: LC-MS (ESI) m/z : 290 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.09-7.17 (m, 3H), 7.50 (t, $J = 8.4$ Hz, 1H).

[00887] **Example 115**

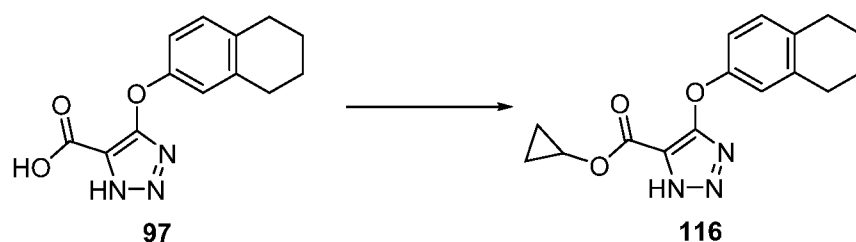
[00888] **Synthesis of 4-(quinolin-3-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (115)**



[00889] Compounds **115B**, **115C**, and **115** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **115A**, **115B**, and **115C** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **115B**: LC-MS (ESI) m/z : 405 $[M+H]^+$. Compound **115C**: LC-MS (ESI) m/z : 377 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 3.56 (s, 3H), 5.41 (s, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.33 (s, 1H), 7.54 (t, $J = 6.8$ Hz, 1H), 7.65 (t, $J = 6.0$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.71 (d, $J = 2.8$ Hz, 1H). Compound **115**: LC-MS (ESI) m/z : 257 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.62 (t, $J = 8.4$ Hz, 1H), 7.72 (t, $J = 8.4$ Hz, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.99 (d, $J = 2.4$ Hz, 1H), 8.04 (d, $J = 8.0$ Hz, 1H), 8.90 (d, $J = 2.8$ Hz, 1H).

[00890] **Example 116**

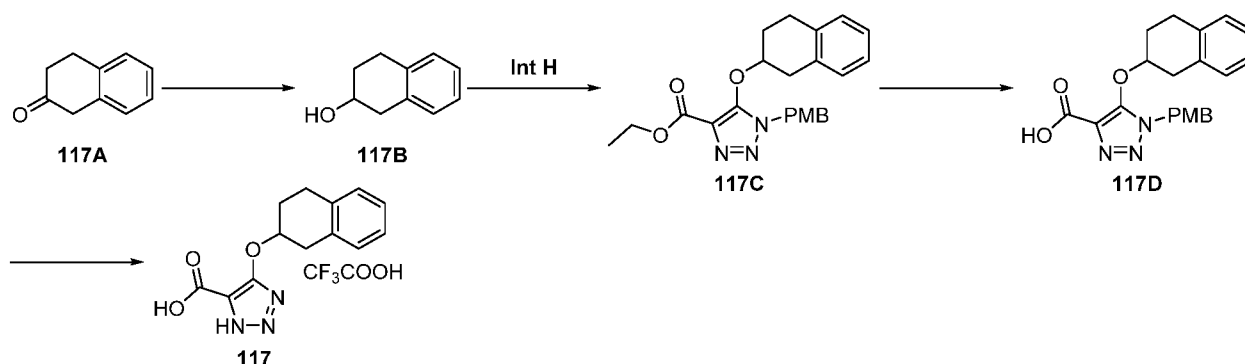
[00891] **Synthesis of cyclopropyl 4-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylate (116)**



[00892] Compound **116** was synthesized by employing the procedure described for Compound **19A** using Compound **97** in lieu of Compound **9A**, LC-MS (ESI) m/z : 300 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.52-1.54 (m, 2H), 1.65-1.67 (m, 2H), 1.77-1.80 (m, 4H), 2.71-2.72 (m, 4H), 4.21-4.23 (m, 1H), 6.63-6.68 (m, 2H), 6.96-6.98 (m, 1H).

[00893] **Example 117**

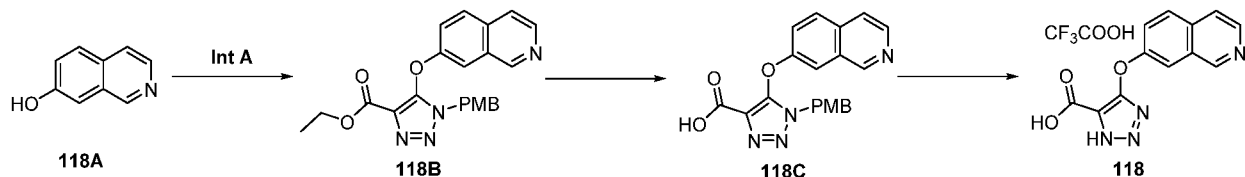
[00894] **Synthesis of 4-((1,2,3,4-tetrahydronaphthalen-2-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (117)**



[00895] Compounds **117B**, **117C**, **117D**, and **117** were synthesized by employing the procedures described for Compounds **57C**, **90C**, **8F**, and **1** using Compounds **117A**, **117B**, **117C**, and **117D** in lieu of Compounds **57B**, **90B**, **8E**, and **1E**. Compound **117B**: LC-MS (ESI) m/z : 131 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.75-1.80 (m, 1H), 2.01-2.15 (m, 1H), 2.80-2.94 (m, 2H), 2.95-2.98 (m, 1H), 3.03-3.18 (m, 1H), 4.15-4.21 (m, 1H), 7.07-7.13 (m, 4H). Compound **117C**: LC-MS (ESI) m/z : 408 $[M+H]^+$. Compound **117D**: LC-MS (ESI) m/z : 380 $[M+H]^+$. Compound **117**: LC-MS (ESI) m/z : 260 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.99-2.03 (m, 1H), 2.08-2.15 (m, 1H), 2.73-2.80 (m, 1H), 2.91-2.98 (m, 2H), 3.19-3.25 (m, 1H), 5.06-5.07 (m, 1H), 7.09-7.11 (m, 4H).

[00896] **Example 118**

[00897] **Synthesis of 4-(isoquinolin-7-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (118)**

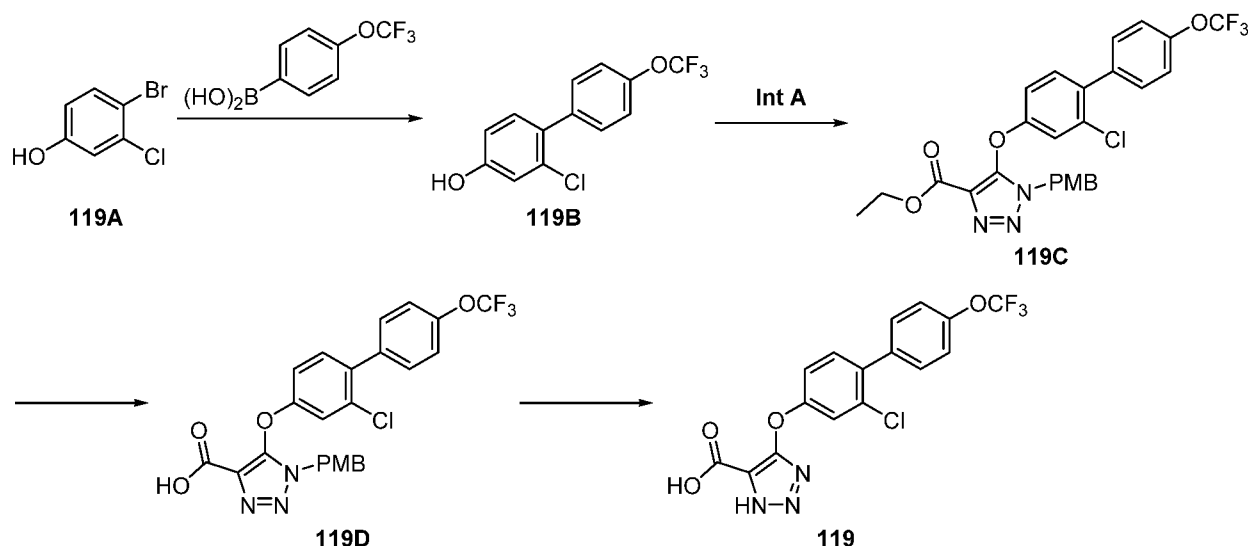


[00898] Compounds **118B**, **118C**, and **118** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **118A**, **118B**, and **118C** in

lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **118B**: LC-MS: (ESI) m/z: 405 $[M+H]^+$. Compound **118C**: LC-MS (ESI) m/z: 377 $[M+H]^+$. Compound **118**: LC-MS (ESI) m/z: 257 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.56 (s, 1H), 7.68 (d, $J = 7.9$ Hz, 1H), 8.01 (s, 1H), 8.35 (d, $J = 8.5$ Hz, 1H), 8.52 (d, $J = 6.1$ Hz, 1H), 9.50 (s, 1H).

[00899] Example 119

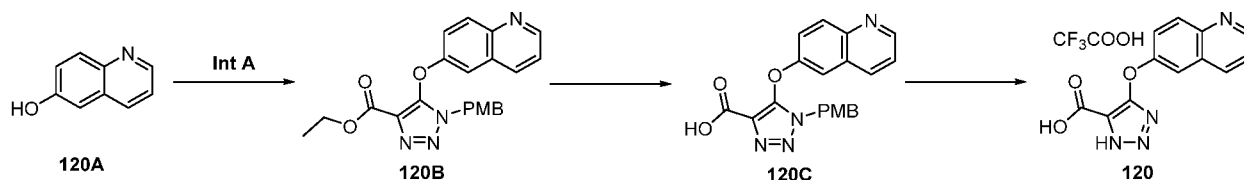
[00900] Synthesis of 4-((2-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (119**)**



[00901] Compounds **119B**, **119C**, **119D**, and **119** were synthesized by employing the procedures described for Compounds **4B**, **86B**, **8F**, and **1** using (4-(trifluoromethoxy)phenyl)boronic acid, Compounds **119A** using 1,4-dioxane and H_2O as solvent, **119B**, **119C**, and **119D** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using toluene/EtOH/ H_2O as solvent, **86A**, **8E**, and **1E**. Compound **119B**: LC-MS (ESI) m/z: 287 $[M+H]^+$. Compound **119C**: LC-MS (ESI) m/z: 548 $[M+H]^+$. Compound **119D**: LC-MS (ESI) m/z: 1061 $[2M+Na]^+$. Compound **119**: LC-MS (ESI) m/z: 400 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 7.13 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.43-7.48 (m, 3H), 7.55-7.59 (m, 2H).

[00902] Example 120

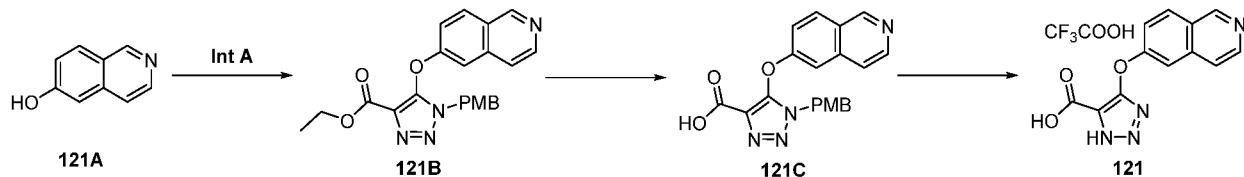
[00903] Synthesis of 4-(quinolin-6-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (120**)**



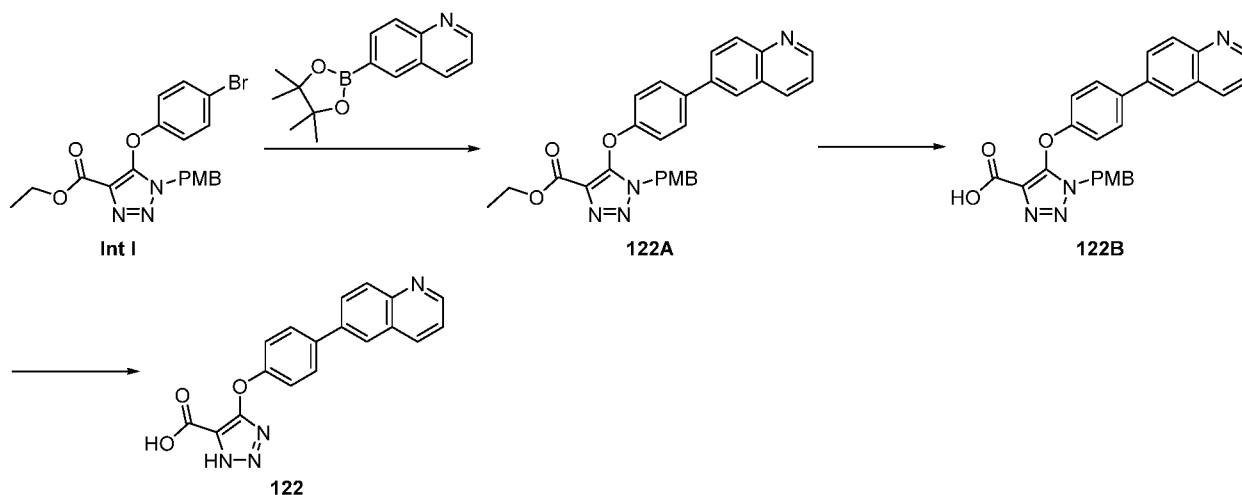
[00904] Compounds **120B**, **120C**, and **120** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **120A**, **120B**, and **120C** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **120B**: LC-MS: (ESI) m/z : 405 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.05 (t, $J = 7.1$ Hz, 3H), 3.61 (s, 3H), 4.09-4.21 (m, 2H), 5.41 (s, 2H), 6.63-6.68 (m, 2H), 6.72 (d, $J = 2.4$ Hz, 1H), 7.13-7.19 (m, 2H), 7.24 (dd, $J = 9.0, 2.5$ Hz, 1H), 7.36 (d, $J = 5.8$ Hz, 1H), 7.94 (d, $J = 9.0$ Hz, 1H), 8.47 (d, $J = 5.8$ Hz, 1H), 9.19 (s, 1H). Compound **120C**: LC-MS (ESI) m/z : 377 $[M+H]^+$. Compound **120**: LC-MS (ESI) m/z : 257 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.55-7.64 (m, 2H), 7.69 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.09 (d, $J = 9.2$ Hz, 1H), 8.43 (d, $J = 7.7$ Hz, 1H), 8.91 (d, $J = 2.6$ Hz, 1H).

[00905] **Example 121**

[00906] **Synthesis of 4-(isoquinolin-6-yloxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**121**)**

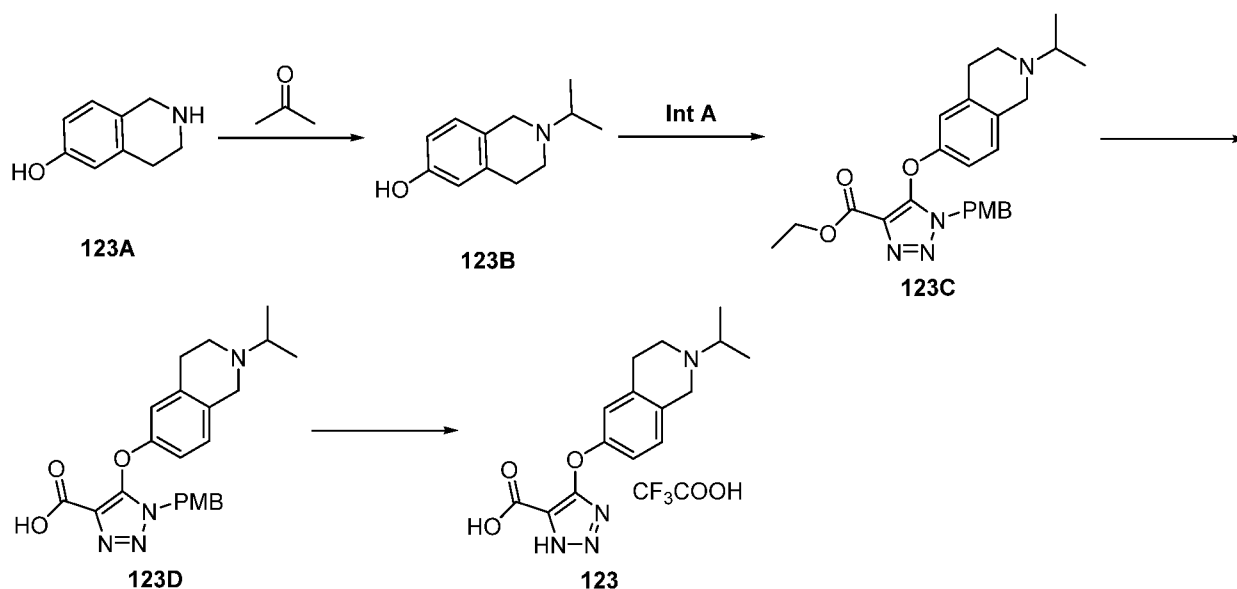


[00907] Compounds **121B**, **121C**, and **121** were synthesized by employing the procedures described for Compounds **86B**, **8F**, and **1** using Compounds **121A**, **121B**, and **121C** in lieu of Compounds **86A**, **8E**, and **1E**. Compound **121B**: LC-MS: (ESI) m/z : 405 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.05 (t, $J = 7.1$ Hz, 3H), 3.61 (s, 3H), 4.02-4.27 (m, 2H), 5.42 (s, 2H), 6.60-6.69 (m, 2H), 6.72 (d, $J = 2.4$ Hz, 1H), 7.16 (d, $J = 8.7$ Hz, 2H), 7.24 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.36 (d, $J = 5.8$ Hz, 1H), 7.94 (d, $J = 9.0$ Hz, 1H), 8.47 (d, $J = 5.8$ Hz, 1H), 9.19 (s, 1H). Compound **121C**: LC-MS (ESI) m/z : 377 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 3.55 (s, 3H), 5.51 (s, 2H), 6.69 (d, $J = 8.7$ Hz, 2H), 7.14 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 2.2$ Hz, 1H), 7.75 (dd, $J = 8.8, 2.4$ Hz, 1H), 8.19 (t, $J = 7.2$ Hz, 1H), 8.50 (d, $J = 9.1$ Hz, 1H), 8.58 (d, $J = 6.4$ Hz, 1H), 9.75 (s, 1H). Compound **121**: LC-MS (ESI) m/z : 257 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.62 (s, 1H), 7.74 (d, $J = 9.0$ Hz, 1H), 8.11 (d, $J = 6.1$ Hz, 1H), 8.41 (d, $J = 9.0$ Hz, 1H), 8.55 (d, $J = 6.2$ Hz, 1H), 9.58 (s, 1H).

[00908] Example 122**[00909] Synthesis of 5-(4-(quinolin-6-yl)phenoxy)-1H-1,2,3-triazole-4-carboxylic acid (122)**

[00910] Compounds **122A**, **122B**, and **122** were synthesized by employing the procedures described for Compounds **8B**, **8F**, and **1** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline, Intermediate **I** using Na_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, Compounds **122A**, and **122B** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, **8E**, and **1E**. Compound **122A**: LC-MS (ESI) m/z : 481 $[\text{M}+\text{H}]^+$. Compound **122B**: LC-MS (ESI) m/z : 453 $[\text{M}+\text{H}]^+$. Compound **122**: LC-MS (ESI) m/z : 333 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.23 (dd, $J = 2.0, 6.8$ Hz, 2H), 7.66 (dd, $J = 2.0, 6.8$ Hz, 1H), 7.85 (dd, $J = 1.6, 6.4$ Hz, 2H), 8.11-8.15 (m, 2H), 8.34 (s, 1H), 8.55 (d, $J = 8.4$ Hz, 1H), 8.96 (d, $J = 4.8$ Hz, 1H).

[00911] Example 123**[00912] Synthesis of 4-((2-isopropyl-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (123)**

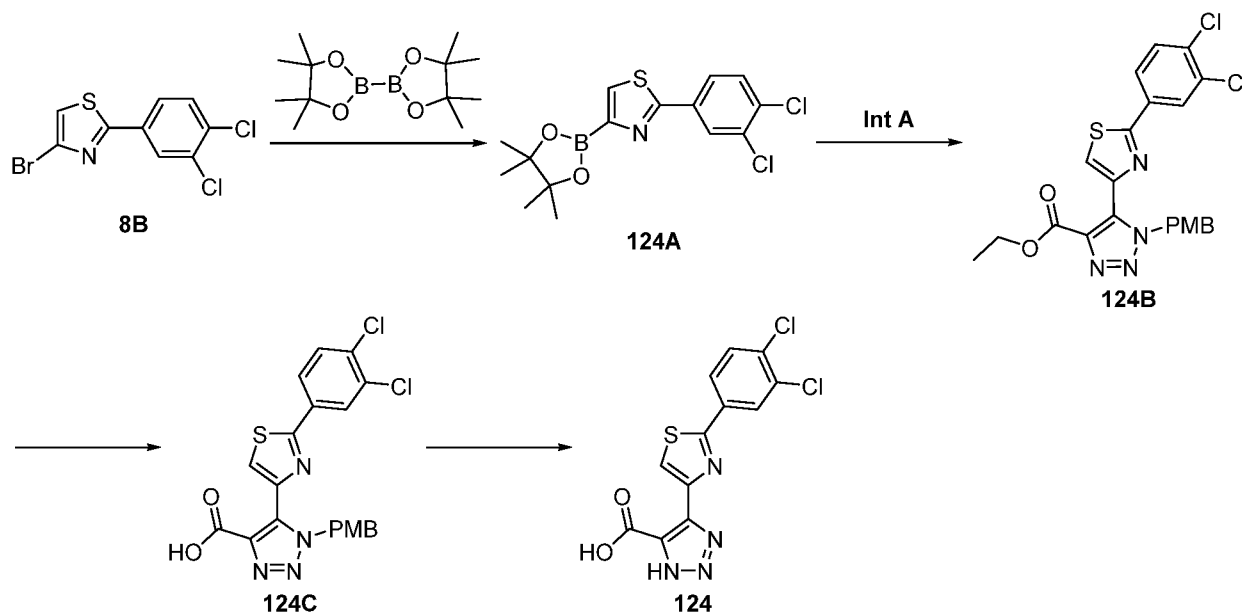


[00913] To a mixture of 1,2,3,4-tetrahydroisoquinolin-6-ol (Compound **123A**) (1.49 g, 10.0 mmol), acetone (3 mL, 50 mmol), and sodium cyanoborohydride (1.26 g, 20 mmol) in methanol (100 mL) was added 60 drops of acetic acid and stirred at room temperature for 16 hours. The mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with ethyl acetate (100 mL x 2). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **123B**. LC-MS (ESI) m/z : 192.

[00914] Compounds **123C**, **123D**, and **123** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **123B** using NMP as solvent, **123C**, and **123D** in lieu of 4-bromophenol using DMF as solvent, Compounds **8E**, and **1E**. Compound **123C**: LC-MS (ESI) m/z : 451. Compound **123D**: LC-MS (ESI) m/z : 423. Compound **123**: LC-MS (ESI) m/z : 303 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.32 (s, 3H), 1.33 (s, 3H), 3.06 (d, $J = 2.4$ Hz, 2H), 3.30 (s, 1H), 3.62-3.66 (m, 2H), 4.37 (s, 1H), 6.96-7.03 (m, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 9.64 (s, 1H).

[00915] Example 124

[00916] Synthesis of 4-(2-(3,4-dichlorophenyl)thiazol-4-yl)-1H-1,2,3-triazole-5-carboxylic acid (**124**)

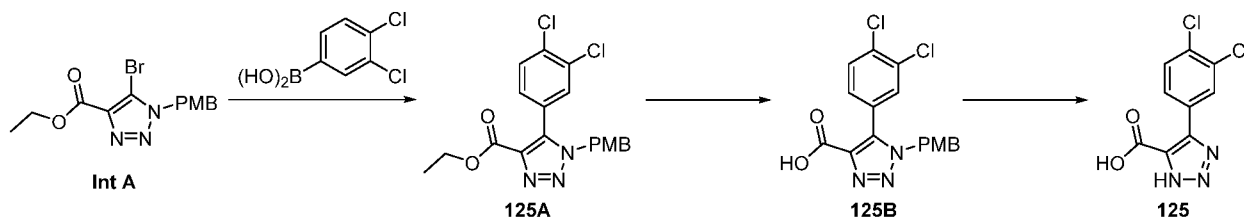


[00917] To a solution of Compound **8B** (309 mg, 1.0 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (254 mg, 1.0 mmol) in 1,4-dioxane (5 mL) were successively added $\text{Pd}_2(\text{dba})_3$ (92 mg, 0.1 mmol), tricyclohexyl phosphine (56 mg, 0.2 mmol) and potassium acetate (196 mg, 2.0 mmol). The mixture was heated at 145 °C in a microwave reactor under nitrogen for 50 minutes. The mixture was allowed to cool down to room temperature and filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL x 2). The combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **124A**, which was used directly for the next step. LC-MS (ESI) m/z : 274 $[\text{M}-82+\text{H}]^+$.

[00918] Compounds **124B**, **124C**, and **124** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using Intermediate **A**, Compound **124A** using K_3PO_4 as base and DMF/ H_2O as solvent, **124B**, and **124C** in lieu of Compound **4A** using Na_2CO_3 as base and toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **8E**, and **1E**. Compound **124B**: LC-MS (ESI) m/z : 489 $[\text{M}+\text{H}]^+$. Compound **124C**: LC-MS (ESI) m/z : 461 $[\text{M}+\text{H}]^+$. Compound **124**: LC-MS (ESI) m/z : 341 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.83 (d, $J = 8.4$ Hz, 1H), 8.02 (d, $J = 8.4$ Hz, 1H), 8.37 (s, 1H), 8.77 (s, 1H).

[00919] **Example 125**

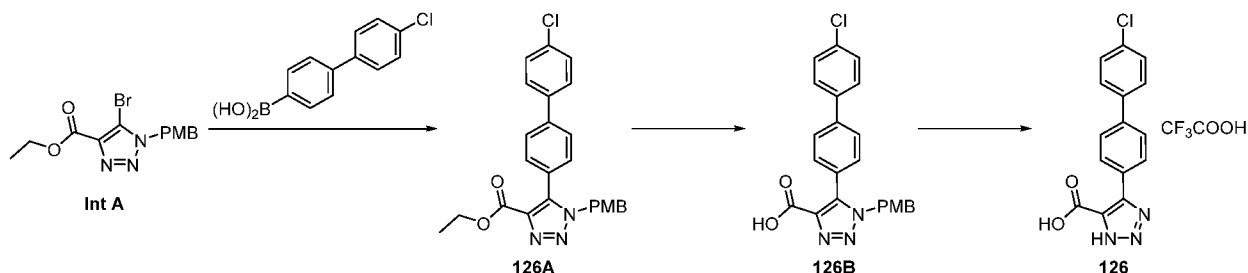
[00920] **Synthesis of 4-(3,4-dichlorophenyl)-1H-1,2,3-triazole-5-carboxylic acid (125)**



[00921] Compounds **125A**, **125B**, and **125** were synthesized by employing the procedures described for Compounds **8B**, **8F**, and **1** using Intermediate **A** using Na_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, Compounds **125A**, and **125B** in lieu of Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, **8E**, and **1E**. Compound **125A**: LC-MS (ESI) m/z : 406 $[\text{M}+\text{H}]^+$. Compound **125B**: LC-MS (ESI) m/z : 378 $[\text{M}+\text{H}]^+$. Compound **125**: LC-MS (ESI) m/z : 258 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.73 (d, $J = 8.4\text{Hz}$, 1H), 7.97 (s, 1H), 8.31 (s, 1H).

[00922] **Example 126**

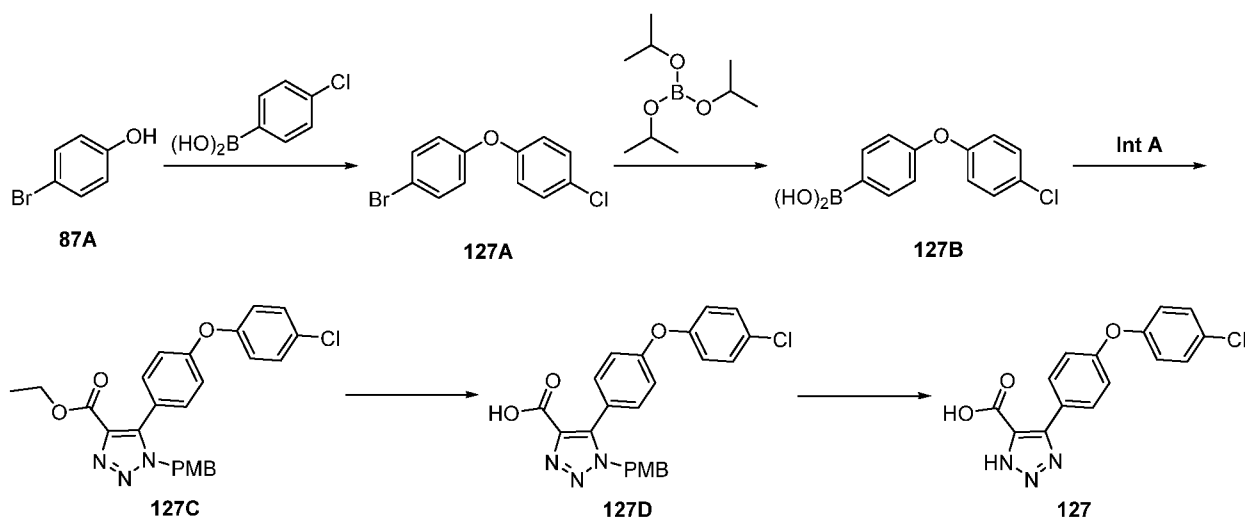
[00923] **Synthesis of 4-(4'-chloro-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**126**)**



[00924] Compounds **126A**, **126B**, and **126** were synthesized by employing the procedures described for Compounds **8B**, **8F**, and **1** using 4'-chlorobiphenyl-4-ylboronic acid using Na_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, Compounds **126A**, and **126B** in lieu of Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, **8E**, and **1E**. Compound **126A**: LC-MS (ESI) m/z : 448 $[\text{M}+\text{H}]^+$. Compound **126B**: LC-MS (ESI) m/z : 420 $[\text{M}+\text{H}]^+$. Compound **126**: LC-MS (ESI) m/z : 300 $[\text{M}+\text{H}]^+$. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.54 (d, $J = 8.8\text{ Hz}$, 4H). 7.78 (d, $J = 8.4\text{ Hz}$, 4H), 7.85-7.91 (m, 3H).

[00925] **Example 127**

[00926] **Synthesis of 4-(4-(4-chlorophenoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (**127**)**



[00927] To a suspension of 4-bromophenol (Compound **87A**) (5.0 g, 29 mmol), 4-chlorophenylboronic acid (6.8 g, 43.5 mmol), and 4 Å molecular sieves (2.0 g) in dichloromethane (200 mL) was added $\text{Cu}(\text{OAc})_2$ (5.26 g, 29 mmol), pyridine (11.5 g, 145 mmol), and DIPEA (18.7 g, 145 mmol), stirred at room temperature for 12 hours, and filtered. The filtrate was concentrated and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to give Compound **127A**. LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 6.86-6.88 (m, 2H), 6.91-6.94 (m, 2H), 7.28-7.30 (m, 2H), 7.42-7.44 (m, 2H).

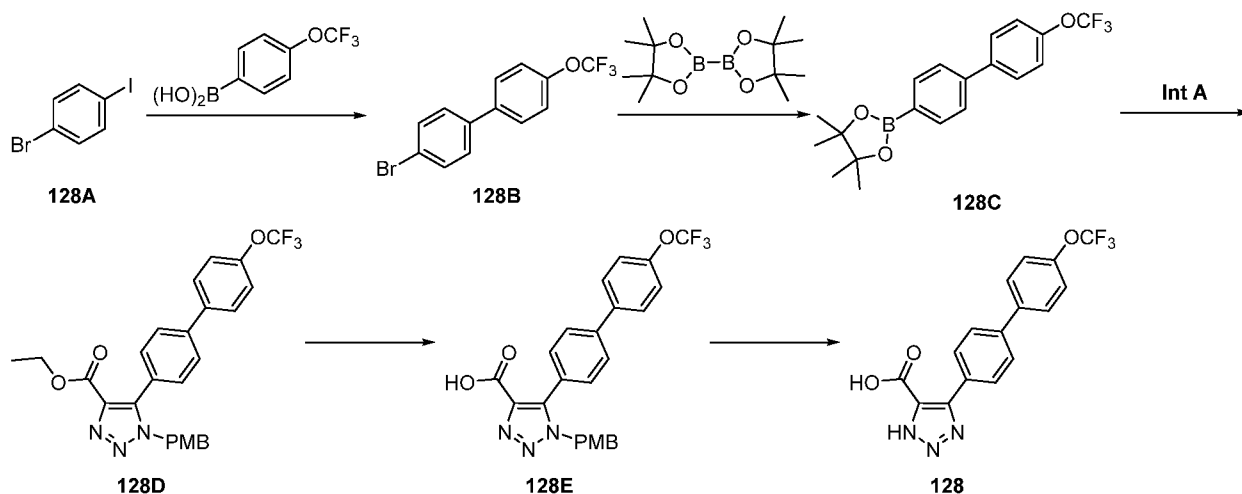
[00928] To a solution of Compound **127A** (660 mg, 2.3 mmol) in anhydrous THF (20 mL) at -78°C under nitrogen was added a solution of $n\text{-BuLi}$ in $n\text{-hexane}$ (2.5 M, 1.1 mL, 2.76 mmol) and stirred at -78°C for 30 minutes. To the solution was added triisopropyl borate (526 mg, 2.76 mmol) and stirred at -78°C for 2 hours. The mixture was quenched with H_2O (10 mL), diluted with 10% aqueous HCl solution (10 mL), stirred at room temperature for additional 30 minutes, and extracted with ethyl acetate (50 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated to give Compound **127B**, which was used directly in the next step. LC-MS (ESI) m/z : non-ionizable compound under routine conditions used.

[00929] Compounds **127C**, **127D**, and **127** were synthesized by employing the procedures described for Compounds **8B**, **8F**, and **1** using Intermediate **A**, Compounds **127B** using toluene/DMF as solvent, **127C**, and **127D** in lieu of Compounds **8A**, (3,4-dichlorophenyl)boronic acid using DME/ H_2O as solvent, **8E**, and **1E**. Compound **127C**: LC-MS (ESI) m/z : 464 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.30 (t, $J = 7.2$ Hz, 3H), 3.77 (s,

3H), 4.31 (q, $J = 7.2$ Hz, 2H), 5.38 (s, 2H), 6.78 (m, 2H), 6.94-6.97 (m, 2H), 7.01-7.04 (m, 4H), 7.16-7.18 (m, 2H), 7.34-7.36 (m, 2H). Compound **127D**: LC-MS (ESI) m/z : 436 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.77 (s, 3H), 5.39 (s, 2H), 6.78-6.81 (m, 2H), 6.97-7.05 (m, 6H), 7.19-7.21 (m, 2H), 7.35-7.37 (m, 2H). Compound **127**: LC-MS (ESI) m/z : 316 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.10-7.13 (m, 4H), 7.46-7.48 (m, 2H), 7.84-7.87 (m, 2H), 13.10 (s, 1H), 15.80 (s, 1H).

[00930] Example 128

[00931] Synthesis of 4-(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-5-carboxylic acid (128**)**

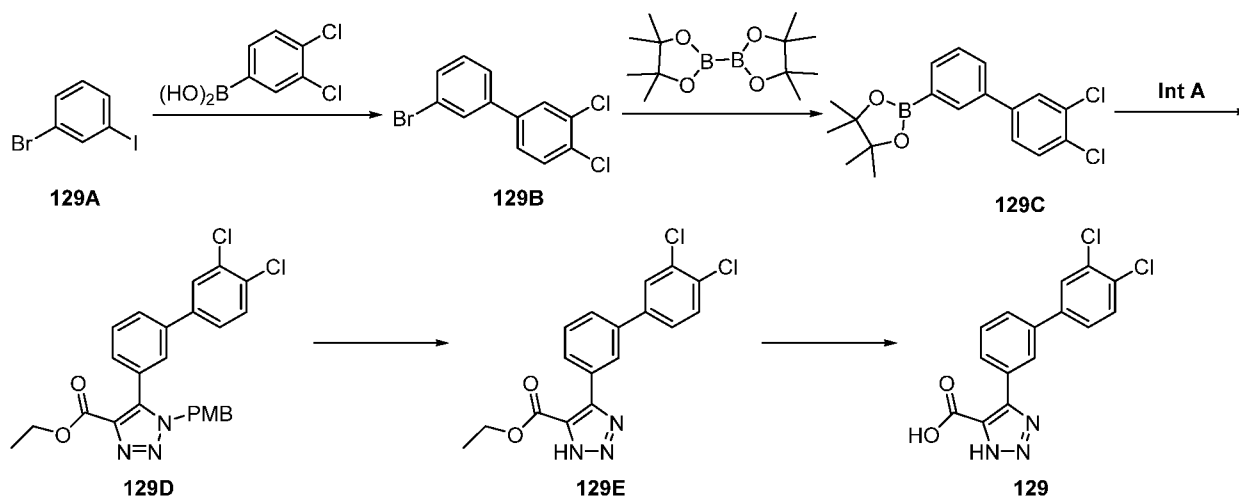


[00932] Compounds **128B**, **128C**, **128D**, **128E**, and **128** were synthesized by employing the procedures described for Compounds **8B**, **27C**, **8B**, **8F**, and **1** using Compounds **128A**, 4-(trifluoromethoxy)phenylboronic acid using Na_2CO_3 as base and toluene/DMF as solvent, **128B**, Intermediate A, **128C** using Na_2CO_3 as base and toluene/DMF as solvent, **128D**, and **128E** in lieu of Compounds **8A**, (3,4-dichlorophenyl)boronic acid using Cs_2CO_3 as base and DME/ H_2O as solvent, **27B**, **8A**, (3,4-dichlorophenyl)boronic acid using Cs_2CO_3 as base and DME/ H_2O as solvent, **8E**, and **1E**. Compound **128B**: LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.30 (dd, $J = 8.8$, 1.2 Hz, 2H), 7.43 (dd, $J = 6.4$, 2.0 Hz, 2H), 7.56-7.60 (m, 4H). Compound **128C**: LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm), 1.38 (s, 12H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.91 (d, $J = 8.0$ Hz, 2H). Compound **128D**: LC-MS (ESI) m/z : 498 $[M+H]^+$. Compound **128E**: LC-MS (ESI)

m/z: 378 [M+H]⁺. Compound **128**: LC-MS (ESI) m/z: 350 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 7.39 (d, J = 8.0 Hz, 2H), 7.75-7.82 (m, 4H), 7.97 (d, J = 8.0 Hz, 2H).

[00933] Example 129

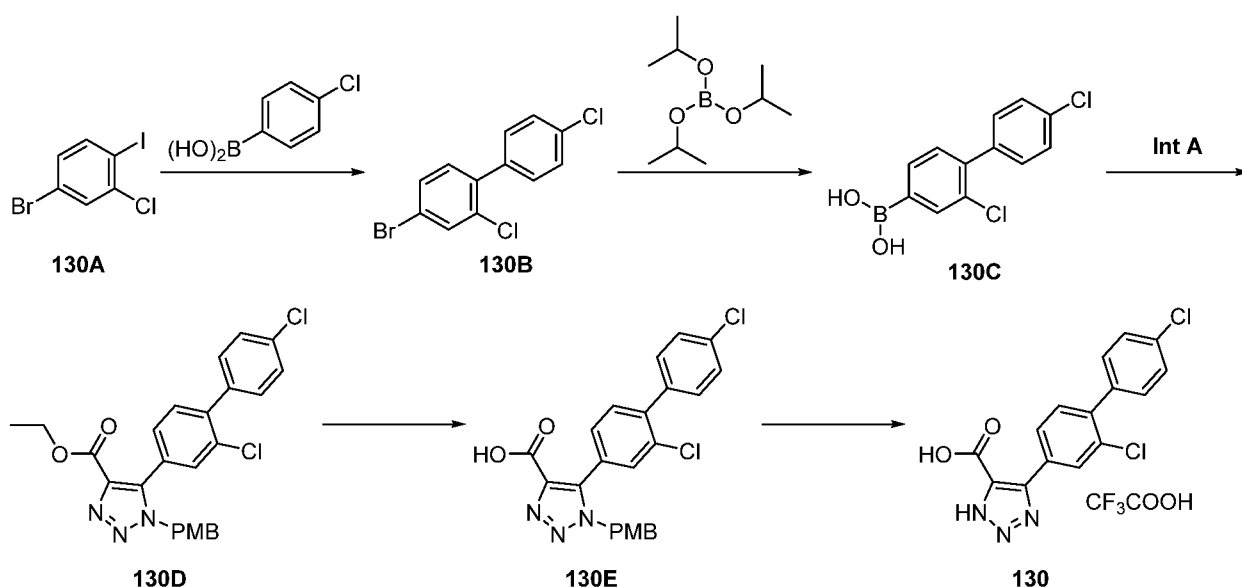
[00934] Synthesis of 4-(3',4'-dichloro-[1,1'-biphenyl]-3-yl)-1H-1,2,3-triazole-5-carboxylic acid (129)



[00935] Compounds **129B**, **129C**, **129D**, **129E**, and **129** were synthesized by employing the procedures described for Compounds **8B**, **27C**, **8B**, **1**, and **8F** using Compounds **129A** using Na₂CO₃ as base and toluene/DMF as solvent, **129B**, Intermediate **A**, **129C** using Na₂CO₃ as base and toluene/DMF as solvent, **129D**, and **129E** in lieu of Compounds **8A** using Cs₂CO₃ as base and DME/H₂O as solvent, **27B**, **8A**, 4-dichlorophenyl)boronic acid using Cs₂CO₃ as base and DME/H₂O as solvent, **1E**, and **8E**. Compound **129B**: LC-MS (ESI) m/z: Non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.33 (t, J = 8.0 Hz, 1H), 7.39 (dd, J = 8.4, 2.0 Hz, 1H), 7.46-7.49 (m, 1H), 7.53 (dd, J = 8.0, 1.6 Hz, 2H), 7.65 (d, J = 2.0 Hz, 1H), 7.69 (t, J = 1.6 Hz, 1H). Compound **129C**: LC-MS (ESI) m/z: Non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm), 1.42 (s, 12H), 7.45-7.51 (m, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 8.00 (s, 1H). Compound **129D**: LC-MS (ESI) m/z: 482 [M+H]⁺. Compound **129E**: LC-MS (ESI) m/z: 362 [M+H]⁺. Compound **129**: LC-MS (ESI) m/z: 334 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 7.57-7.63 (m, 3H), 7.74 (d, J = 8.0 Hz, 1H), 7.87-7.90 (m, 2H), 8.18 (s, 1H).

[00936] Example 130

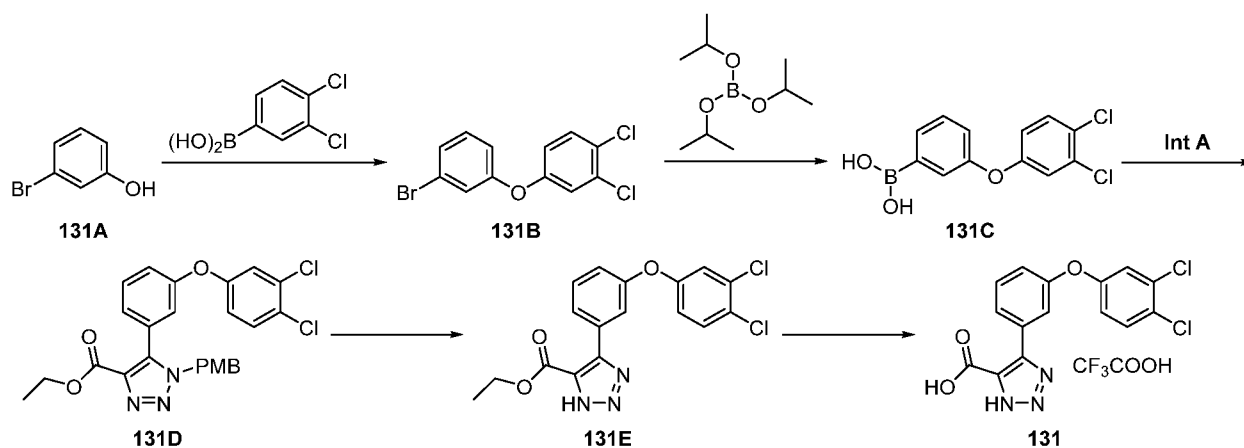
[00937] Synthesis of 4-(2,4'-dichloro-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (130)



[00938] Compounds **130B**, **130C**, **130D**, **130E**, and **130** were synthesized by employing the procedures described for Compounds **8B**, **127C**, **8B**, **8F**, and **1** using Compounds **130A** using K₂CO₃ as base and DMF/H₂O as solvent, **130B**, Intermediate **A**, **130C** using Na₂CO₃ as base and toluene/DMF as solvent, **130D**, and **130E** in lieu of Compounds **8A** using Cs₂CO₃ as base and DME/H₂O as solvent, **127B**, **8A**, (3,4-dichlorophenyl)boronic acid using Cs₂CO₃ as base and DME/H₂O as solvent, **8E**, and **1E**. Compound **130B**: ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 7.15-7.17 (d, *J* = 8.0 Hz, 1H), 7.31-7.33 (m, 2H), 7.38-7.40 (m, 2H), 7.45 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H). Compound **130C**: LC-MS (ESI) *m/z*: 267 [M+H]⁺. Compound **130D**: LC-MS (ESI) *m/z*: 482 [M+H]⁺. Compound **130E**: LC-MS (ESI) *m/z*: 454 [M+H]⁺. Compound **130**: LC-MS (ESI) *m/z*: 334 [M+H]⁺; ¹H-NMR (CD₃OD, 500 MHz): δ (ppm) 7.48-7.49 (m, 5H), 7.94-7.96 (m, 1H), 8.14 (s, 1H).

[00939] **Example 131**

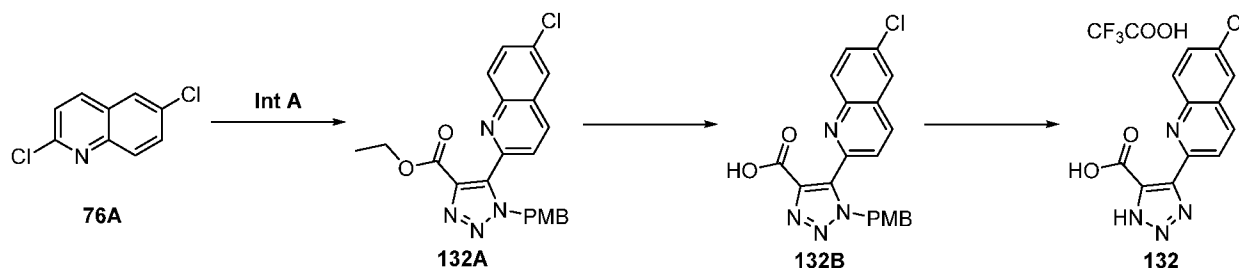
[00940] **Synthesis of 4-(3-(3,4-dichlorophenoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (131)**



[00941] Compounds **131B**, **131C**, **131D**, **131E**, and **131** were synthesized by employing the procedures described for Compounds **127B**, **127C**, **8B**, **8F**, and **1** using 3,4-dichlorophenylboronic acid, Compounds **131A**, **131B**, Intermediate **A**, **131C** using toluene/DMF as solvent, **131D**, and **131E** in lieu of 4-chlorophenylboronic acid, Compounds **127A**, **127B**, **8A**, (3,4-dichlorophenyl)boronic acid using DME/ H_2O as solvent, **8E**, and **1E**. Compound **131B**: LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used. Compound **131C**: LC-MS (ESI) m/z : 283 $[\text{M}+\text{H}]^+$. Compound **131D**: LC-MS (ESI) m/z : 498 $[\text{M}+\text{H}]^+$. Compound **131E**: LC-MS (ESI) m/z : 470 $[\text{M}+\text{H}]^+$. Compound **131**: LC-MS (ESI) m/z : 350 $[\text{M}+\text{H}]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 6.89 (dd, $J = 8.8, 2.8$ Hz, 1H), 7.05 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.10 (d, $J = 3.2$ Hz, 1H), 7.38-7.41 (m, 2H), 7.50-7.51 (m, 1H), 7.57-7.59 (m, 1H).

[00942] Example 132

[00943] Synthesis of 4-(6-chloroquinolin-2-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**132**)



[00944] To a mixture of Compound **76A** (198 mg, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) in xylene (10 mL) was added tributyltin hydride (582 mg, 2.0 mmol) and stirred at 135 °C under nitrogen for 2 hours. After the mixture was cooled down to room temperature, to it was added ethyl 5-bromo-1-(4-

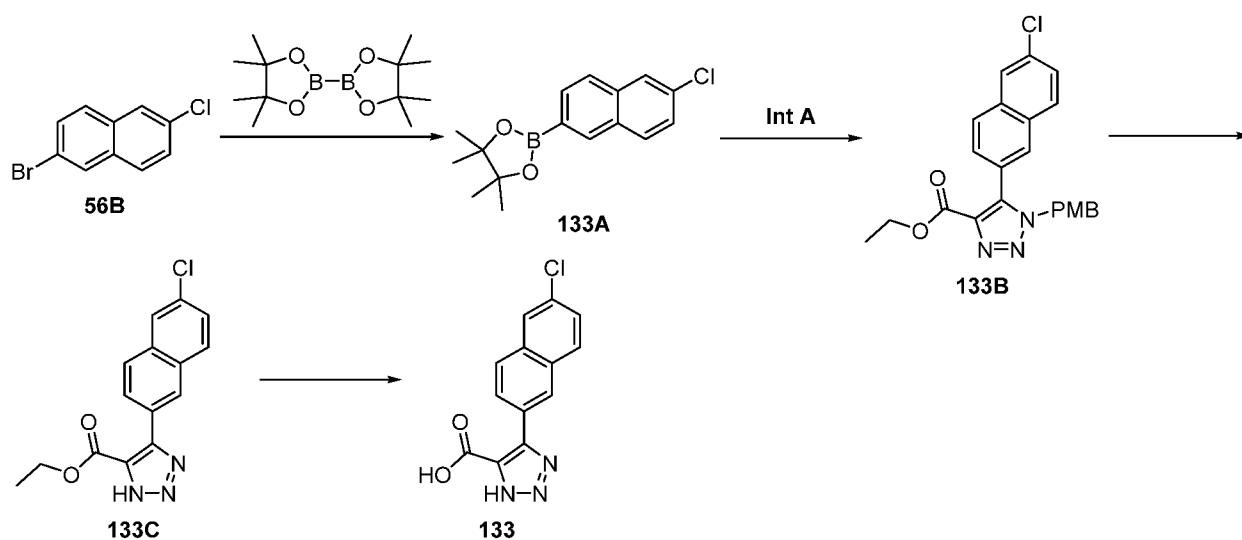
methoxybenzyl)-1H-1,2,3-triazole-4-carboxylate (340 mg, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol,) and stirred at 120 °C under nitrogen for 4 hours. The mixture was cooled down to room temperature, quenched with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 25% v/v) to afford Compound **132A**. LC-MS (ESI) m/z: 423 [M+H]⁺.

[00945] Compounds **132B** and **132** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **132A** and **131B** in lieu of **8E** and **1E**.

Compound **132B**: LC-MS (ESI) m/z: 393 [M-H]⁻. Compound **132**: LC-MS (ESI) m/z: 275 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.92 (d, *J* = 8.8, 2.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 8.53 (d, *J* = 8.8 Hz, 1H), 8.67 (d, *J* = 8.8 Hz, 1H).

[00946] **Example 133**

[00947] **Synthesis of 4-(6-chloronaphthalen-2-yl)-1H-1,2,3-triazole-5-carboxylic acid (133)**

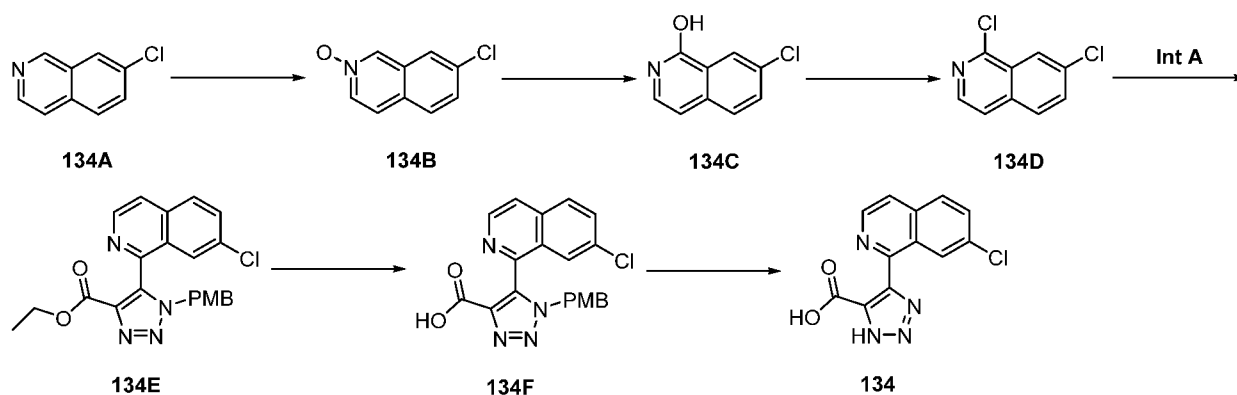


[00948] Compounds **133A**, **133B**, **133C**, and **133** were synthesized by employing the procedures described for Compounds **27C**, **8B**, **1**, and **8F** using Compounds **56B** using DMSO as solvent, Intermediate A, **133A** using Na₂CO₃ as base and 1,4-dioxane/ H₂O as solvent, **133B**, and **133C** in lieu of Compounds **27B** using 1,4-dioxane as solvent, **8A**, 4-dichlorophenyl)boronic acid using Cs₂CO₃ as base and DME/H₂O as solvent, **1E**, and **8E**. Compound **133A**: LC-MS (ESI) m/z: Non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400

MHz): δ (ppm), 1.30 (s, 12H), 7.30-7.31 (m, 1H), 7.32-7.33 (m, 1H), 7.63-7.79 (m, 3H), 8.25 (s, 1H). Compound **133B**: LC-MS (ESI) m/z: 422 [M+H]⁺. Compound **133C**: LC-MS (ESI) m/z: 302 [M+H]⁺. Compound **133**: LC-MS (ESI) m/z: 274 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.56-7.59 (m, 1H), 7.99-7.81 (m, 4H), 8.44 (s, 1H).

[00949] Example 134

[00950] Synthesis of 4-(7-chloroisoquinolin-1-yl)-1H-1,2,3-triazole-5-carboxylic acid (134)



[00951] Compound **134B** was synthesized by employing the procedure described for Compound **20C** using Compound **134A** in lieu of **20B**, LC-MS (ESI) m/z: 180 [M+H]⁺.

[00952] To a solution of Compound **134B** (562 mg, 3.12 mmol) in dry DMF (10 mL) was added 4-methylbenzene-1-sulfonyl chloride (3.57 g, 18.73 mmol) and stirred at 80 °C overnight. The mixture was cooled down to room temperature, poured into a saturated aqueous NaHCO₃ solution (150 mL), stirred at room temperature for 0.5 hour, and extracted with EtOAc (60 mL x 3). The combined extracts were washed with H₂O (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 30% v/v) to afford Compound **134C**. LC-MS (ESI) m/z: 180 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 6.51 (d, *J* = 6.8 Hz, 1H), 7.13 (d, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 2 Hz, 1H), 8.38 (d, *J* = 2.4 Hz, 1H), 10.48 (s, 1H).

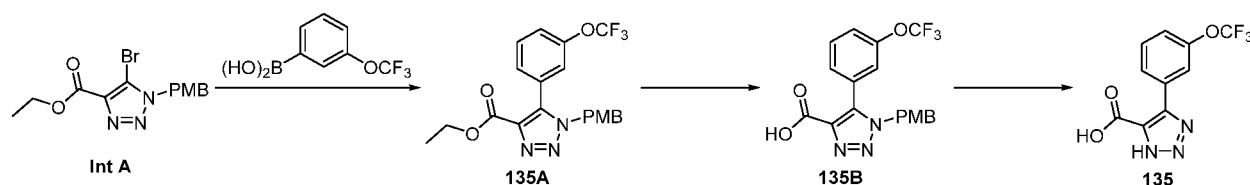
[00953] To a solution of Compound **134C** (280 mg, 3.12 mmol) in dry toluene (10 mL) was added DMF (1 mL) and SOCl₂ (1 mL) and stirred at 80 °C for 3 hours. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 30% v/v) to afford Compound **134D**. LC-MS (ESI) m/z: 198 [M+H]⁺. ¹H-NMR (CDCl₃,

400 MHz): δ (ppm) 7.59 (d, J = 5.6 Hz, 1H), 7.70 (dd, J = 2.4, 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 8.29 (d, J = 5.6 Hz, 1H), 8.34 (d, J = 1.2 Hz, 1H).

[00954] Compounds **134E**, **134F**, and **134** were synthesized by employing the procedures described for Compounds **132A**, **8F**, and **1** using Compounds **134D**, **134E**, and **134F** in lieu of Compounds **76A**, **8E**, and **1E**. Compound **134E**: LC-MS (ESI) m/z : 423 $[M+H]^+$. Compound **134F**: LC-MS (ESI) m/z : 395 $[M+H]^+$. Compound **134**: LC-MS (ESI) m/z : 275 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.93 (dd, J = 1.6, 8.8 Hz, 1H), 8.08 (d, J = 5.6 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.98 (s, 1H).

[00955] Example 135

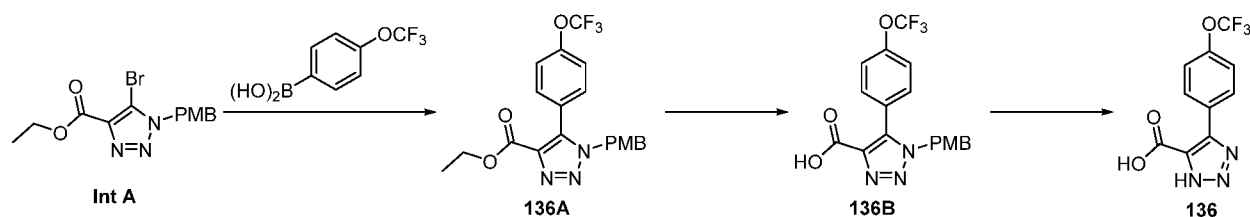
[00956] Synthesis of 4-(3-(trifluoromethoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (**135**)



[00957] Compounds **135A**, **135B**, and **135** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using 3-(trifluoromethoxy)phenylboronic acid, Intermediate **A** using 1,4-dioxane/ H_2O as solvent, Compounds **135A**, and **135B** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **8E**, and **1E**. Compound **135A**: LC-MS (ESI) m/z : 422 $[M+H]^+$. Compound **135B**: LC-MS (ESI) m/z : 394 $[M+H]^+$. Compound **135**: LC-MS (ESI) m/z : 274 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.45 (d, J = 8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.90 (b, 2H).

[00958] Example 136

[00959] Synthesis of 4-(4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (**136**)

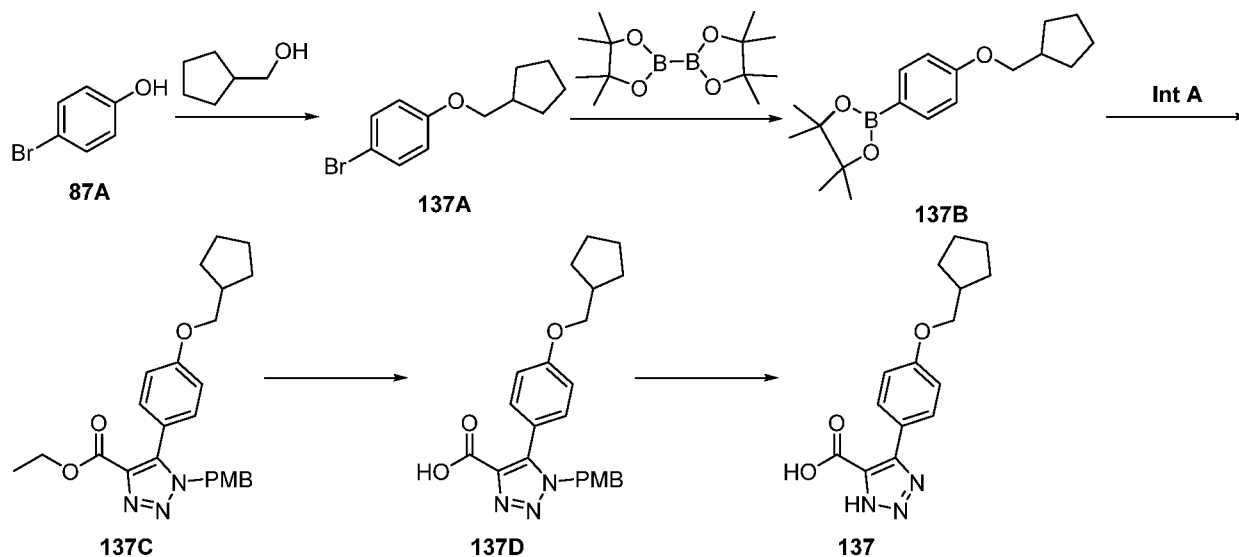


[00960] Compounds **136A**, **136B**, and **136** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using 4-(trifluoromethoxy)phenylboronic acid,

Intermediate **A** using 1,4-dioxane/H₂O as solvent, Compounds **136A**, and **136B** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **136A**: LC-MS (ESI) *m/z*: 422 [M+H]⁺. Compound **136B**: LC-MS (ESI) *m/z*: 394 [M+H]⁺. Compound **136**: LC-MS (ESI) *m/z*: 274 [M+H]⁺. ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.48 (d, *J* = 8.8 Hz, 2H), 7.95 (s, 2H).

[00961] **Example 137**

[00962] **Synthesis of 4-(4-(cyclopentylmethoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (137)**

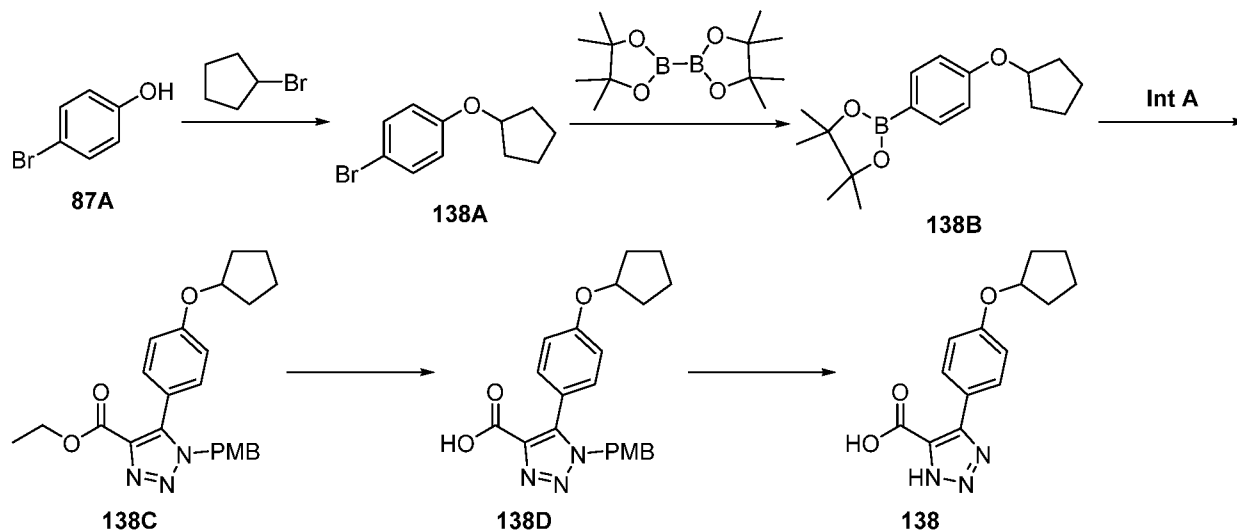


[00963] Compounds **137A**, **137B**, **137C**, **137D**, and **137** were synthesized by employing the procedures described for Compounds **90C**, **27C**, **4B**, **8F**, and **1** using cyclopentylmethanol, Compounds **87A** using DEAD as coupling reagent, **137A**, **137B**, Intermediate **A** using 1,4-dioxane/H₂O as solvent, **137C**, and **137D** in lieu of Compounds **90B**, Intermediate **H** using DIAD as coupling reagent, **27B**, (4-bromophenyl)boronic acid, Compounds **4A** using toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **137A**: LC-MS (ESI) *m/z*: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.32-1.36 (m, 2H), 1.55-1.63 (m, 4H), 1.81-1.83 (m, 2H), 2.32-2.35 (m, 1H), 3.78 (d, *J* = 6.4 Hz, 2H), 6.76 (dd, *J* = 2.4, 6.8 Hz, 2H), 7.35 (dd, *J* = 2.4, 6.8 Hz, 2H). Compound **137B**: LC-MS (ESI) *m/z*: non-ionizable compound under routine conditions used; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.32 (s, 12H), 1.32-1.36 (m, 2H), 1.56-1.64 (m, 4H), 1.81-1.83 (m, 2H), 2.32-2.37 (m, 1H), 3.84 (d, *J* = 6.8 Hz, 2H), 6.88 (dd, *J* = 1.6, 6.4 Hz, 2H), 7.72 (dd, *J* = 1.6, 6.4 Hz, 2H). Compound **137C**: LC-MS (ESI) *m/z*: 436 [M+H]⁺. Compound **137D**: LC-MS (ESI) *m/z*: 408 [M+H]⁺. Compound

137: LC-MS (ESI) m/z : 288 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.31-1.38 (m, 2H), 1.51-1.61 (m, 4H), 1.74-1.82 (m, 2H), 2.28-2.34 (m, 1H), 3.90 (dd, $J = 7.2$ Hz, 2H), 7.0 (dd, $J = 2.8, 6$ Hz, 2H), 7.71 (dd, $J = 2.8, 6$ Hz, 2H).

[00964] Example 138

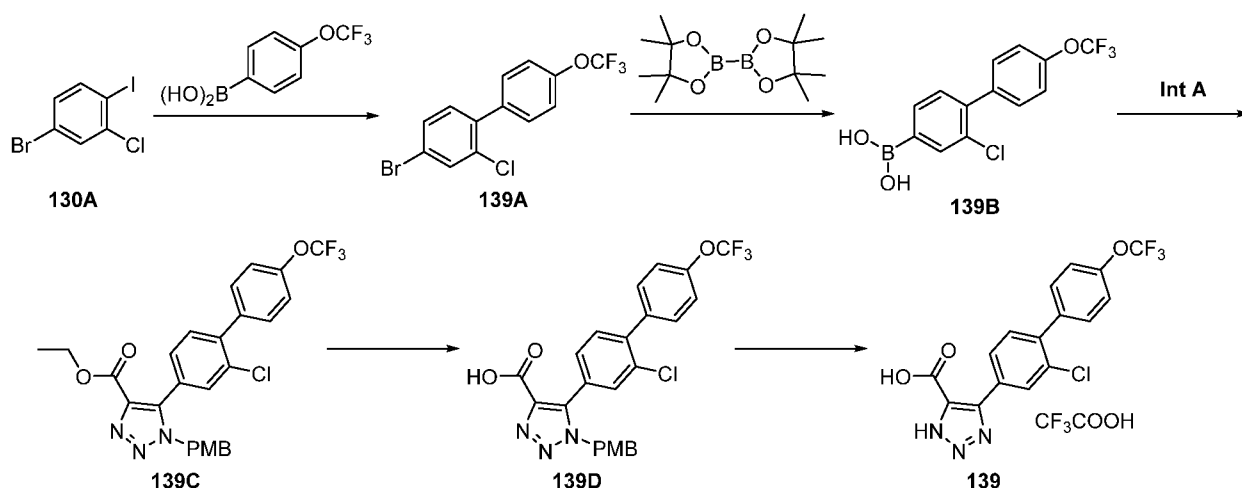
[00965] Synthesis of 4-(4-(cyclopentyloxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (138)



[00966] Compounds **138A**, **138B**, **138C**, **138D**, and **138** were synthesized by employing the procedures described for Compounds **27B**, **27C**, **4B**, **8F**, and **1** using bromocyclopentane at room temperature, Compounds **87A**, **138A**, **138B**, Intermediate **A** using 1,4-dioxane/ H_2O as solvent, **138C**, and **138D** in lieu of 2-bromopropane at 90°C , Compounds **27A**, **27B**, (4-bromophenyl)boronic acid, **4A** using toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **8E**, and **1E**. Compound **138A**: LC-MS (ESI) m/z : 241 $[M+H]^+$, Compound **138B**: LC-MS (ESI) m/z : 289 $[M+H]^+$. Compound **138C**: LC-MS (ESI) m/z : 422 $[M+H]^+$. Compound **138D**: LC-MS (ESI) m/z : 394 $[M+H]^+$. Compound **138**: LC-MS (ESI) m/z : 274 $[M+H]^+$. $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.57-1.62 (m, 2H). 1.70-1.74 (m, 4H), 1.91-1.96 (m, 2H), 4.84-4.87 (m, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 8.05 (s, 2H).

[00967] Example 139

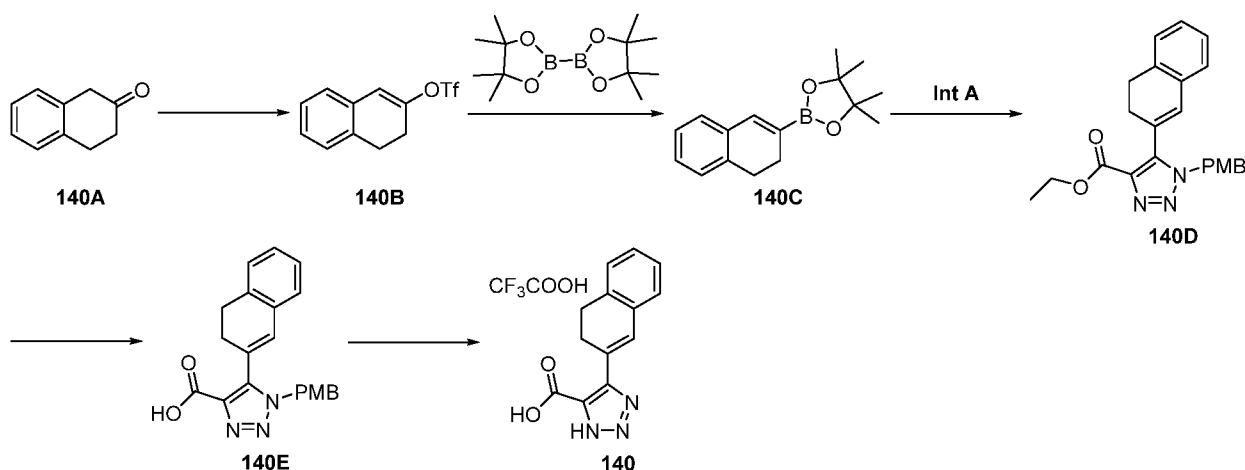
[00968] Synthesis of 4-(2-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (139)



[00969] Compounds **139A**, **139B**, **139C**, **139D**, and **139** were synthesized by employing the procedures described for Compounds **8B**, **27C**, **4B**, **8F**, and **1** using 4-(trifluoromethoxy)phenylboronic acid, Compounds **130A** using K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **139A**, Intermediate A, **139B** using 1,4-dioxane/ H_2O as solvent, **139C**, and **139D** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, **27B**, **4A**, (4-bromophenyl)boronic acid using toluene/EtOH/ H_2O as solvent, **8E**, and **1E**. Compound **139A**: LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.28-7.31 (m, 3H), 7.55 (d, $J = 8.0$ Hz, 2H), 7.63 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H). Compound **139B**: LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. Compound **139C**: LC-MS (ESI) m/z: 532 $[M+H]^+$. Compound **139D**: LC-MS (ESI) m/z: 504 $[M+H]^+$. Compound **139**: LC-MS (ESI) m/z: 384 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.49 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.75 (d, $J = 5.6$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 3H).

[00970] **Example 140**

[00971] **Synthesis of 4-(3,4-dihydronaphthalen-2-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (140)**



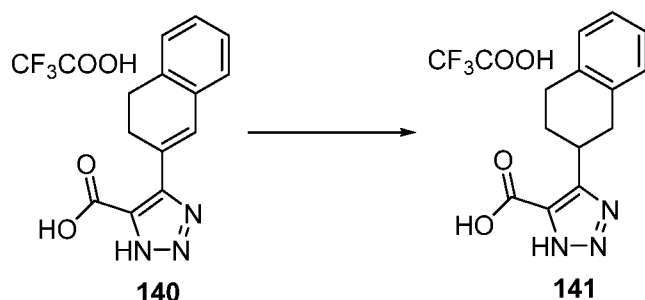
[00972] To a mixture of 3,4-dihydronaphthalen-2(1H)-one (Compound **140A**) (1.5 g, 10.3 mmol) in THF (100 mL) was added *t*-BuOK (2.31 g, 20.6 mmol) at -20 °C under nitrogen and stirred at room temperature for 1 hour. To the mixture was added a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (5.52 g, 15.5 mmol) in dry THF (10 mL) in one portion at -20 °C and stirred at room temperature for 4 hours. It was quenched with a saturated aqueous NH₄Cl solution (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (petroleum ether, 100% v/v) to give Compound **140B**. LC-MS (ESI) *m/z*: 279 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.71 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 7.2 Hz, 2H), 6.49 (s, 1H), 7.08-7.10 (m, 1H), 7.14-7.16 (m, 1H), 7.20-7.22 (m, 2H).

[00973] Compounds **140C**, **140D**, **140E**, and **140** were synthesized by employing the procedures described for Compounds **27C**, **8B**, **8F**, and **1** using Compounds **140B** using DMSO as solvent, Intermediate A, **140C** using 1,4-dioxane/H₂O as solvent, **140D**, and **140E** in lieu of Compounds **27B** using 1,4-dioxane/H₂O as solvent, **8A**, (4-bromophenyl)boronic acid using toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **140C**: LC-MS (ESI) *m/z*: 257 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.22 (s, 12H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 7.12-7.13 (m, 2H), 7.15-7.18 (m, 3H). Compound **140D**: LC-MS (ESI) *m/z*: 390 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.38 (t, *J* = 7.2 Hz, 3H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 5.51 (s, 2H), 6.42 (s, 1H), 6.81-6.83 (m, 2H), 7.01-7.04 (m, 1H), 7.12-7.15 (m, 2H), 7.17-7.23 (m, 3H). Compound **140E**: LC-MS (ESI) *m/z*: 362 [M+H]⁺. Compound **140**: LC-MS (ESI) *m/z*: 242 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400

MHz): δ (ppm) 2.70-2.71 (m, 2H), 2.86-2.90 (m, 2H), 7.18-7.30 (m, 5H), 13.13 (s, 1H), 15.60 (s, 1H).

[00974] Example 141

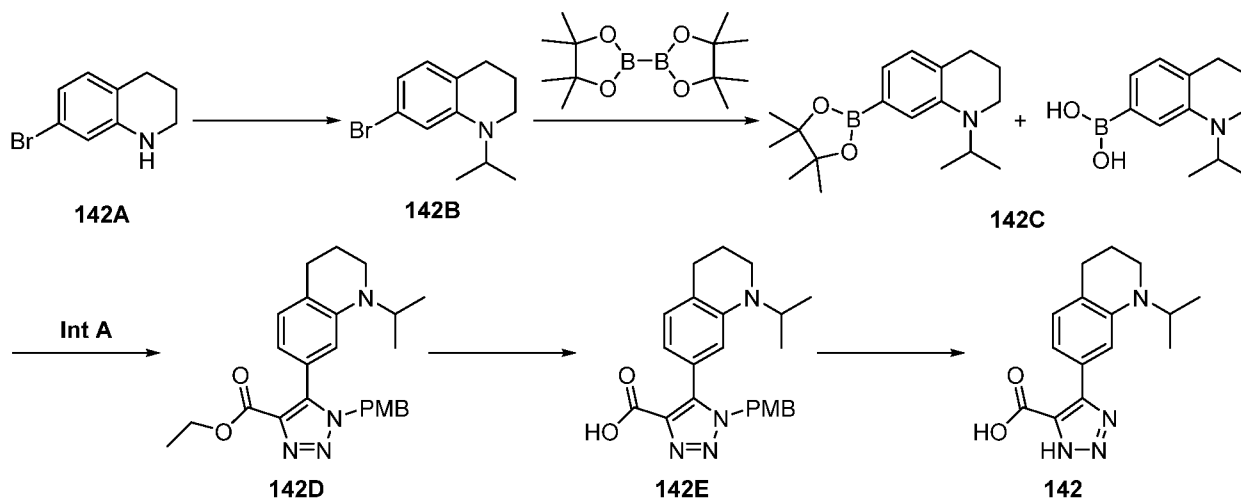
[00975] Synthesis of 4-(1,2,3,4-tetrahydronaphthalen-2-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (141)



[00976] To a mixture of Compound **140** (40 mg, 0.17 mmol) in ethyl acetate (20 mL) was added 10% Pd/C (20 mg) and stirred at room temperature under hydrogen (1 atm) overnight. The mixture was filtered and filtration was concentrated. The residue was purified with preparative HPLC to afford Compound **141**. LC-MS (ESI) m/z : 244 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 1.94-1.99 (m, 1H), 2.08-2.10 (m, 1H), 2.89-2.92 (m, 2H), 2.92-3.04 (m, 2H), 3.60-3.62 (m, 1H), 7.08-7.12 (m, 4H), 13.12 (s, 1H), 15.22 (s, 1H).

[00977] Example 142

[00978] Synthesis of 4-(1-isopropyl-1,2,3,4-tetrahydroquinolin-7-yl)-1H-1,2,3-triazole-5-carboxylic acid (142)



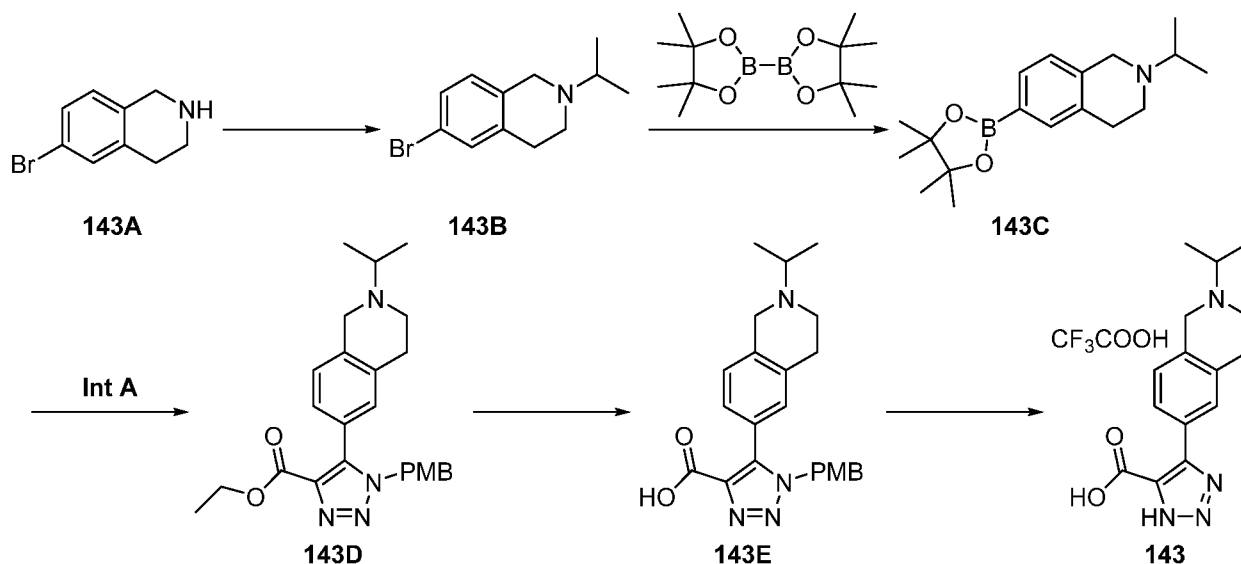
[00979] Compounds **142B**, **142C**, **142D**, **142E**, and **142** were synthesized by employing the procedures described for Compounds **63A**, **27C**, **8B**, **8F**, and **1** using 2-iodopropane,

Compounds **142A** using K_2CO_3 as base, **142B**, Intermediate **A**, **142C** using 1,4-dioxane/ H_2O as solvent, **142D**, and **142E** in lieu of iodomethane, Compounds **61F** using Cs_2CO_3 as base, **27B**, **8A**, (4-bromophenyl)boronic acid using toluene/EtOH/ H_2O as solvent, **8E**, and **1E**.

Compound **142B**: LC-MS (ESI) m/z : 254 $[M+H]^+$. Compound **142C**: LC-MS (ESI) m/z : 302 $[M+H]^+$; 260 $[M+CH_3CN]^+$. Compound **142D**: LC-MS (ESI) m/z : 435 $[M+H]^+$. Compound **142E**: LC-MS (ESI) m/z : 407 $[M+H]^+$. Compound **142**: LC-MS (ESI) m/z : 287 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.14(d, $J = 6.4$ Hz, 6H), 1.82-1.85 (m, 2H), 2.69 (t, $J = 6$ Hz, 2H), 3.15 (t, $J = 6$ Hz, 2H), 4.06-4.10 (m, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 1H), 7.17 (s, 1H).

[00980] Example 143

[00981] Synthesis of 4-(2-isopropyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (143**)**

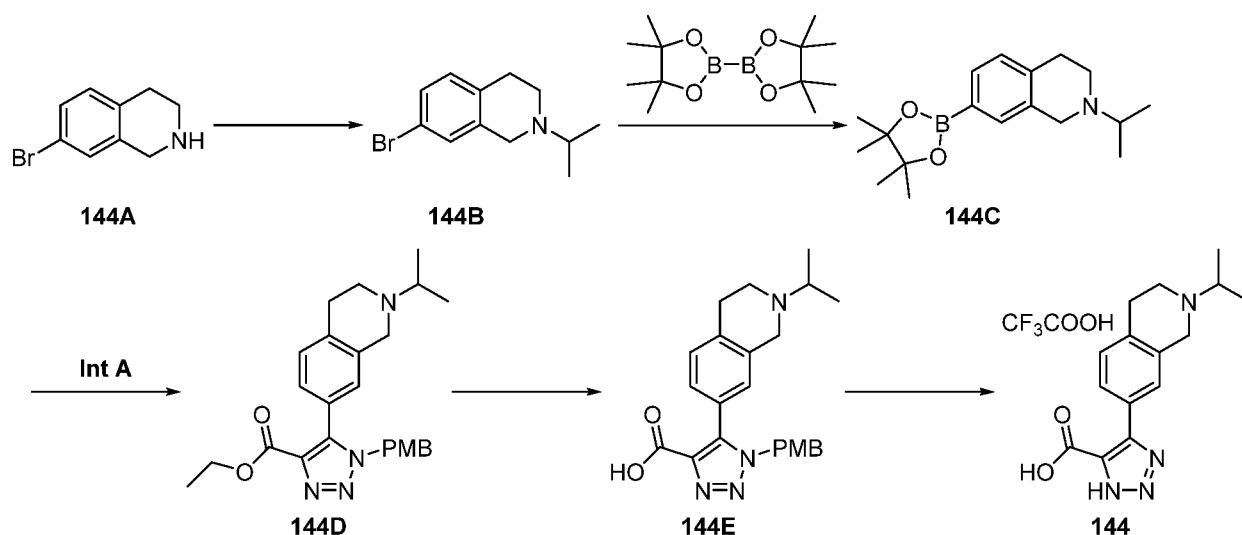


[00982] Compounds **143B**, **143C**, **143D**, **143E**, and **143** were synthesized by employing the procedures described for Compounds **63A**, **27C**, **8B**, **8F**, and **1** using 2-iodopropane, Compounds **143A** using K_2CO_3 as base and acetonitrile as solvent, **143B**, Intermediate **A**, **143C** using 1,4-dioxane/ H_2O as solvent, **143D**, and **143E** in lieu of iodomethane, Compounds **61F** using Cs_2CO_3 as base, **27B**, **8A**, (4-bromophenyl)boronic acid using toluene/EtOH/ H_2O as solvent, **8E**, and **1E**. Compound **143B**: LC-MS (ESI) m/z : 254 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.13 (d, $J = 6.4$ Hz, 6H), 2.74 (t, $J = 6.4$ Hz, 2H), 2.85-2.93 (m, 3H), 3.65 (s, 2H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.20-7.23 (m, 2H). Compound **143C**: LC-MS (ESI) m/z : 302 $[M+H]^+$. Compound **143D**: LC-MS (ESI) m/z : 435 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.17 (d, $J =$

6.8 Hz, 6H), 1.28 (t, $J = 6.8$ Hz, 3H), 2.80 (t, $J = 5.6$ Hz, 2H), 2.87 (t, $J = 5.6$ Hz, 2H), 2.91-2.97 (m, 1H), 3.7-3.79 (m, 5H), 4.30 (q, $J = 6.8$ Hz, 2H), 5.31 (s, 2H), 6.77-6.79 (m, 2H), 6.89 (s, 1H), 6.95-6.99 (m, 3H), 7.12 (d, $J = 8.0$ Hz, 1H). Compound **143E**: LC-MS (ESI) m/z : 407 $[M+H]^+$. Compound **143**: LC-MS (ESI) m/z : 287 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 1.35 (d, $J = 8.4$ Hz, 6H), 3.10-3.37 (m, 3H), 3.65-3.71 (m, 2H), 4.46-4.47 (m, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.60-7.70 (m, 2H), 9.72 (bs, 1H).

[00983] Example 144

[00984] Synthesis of 4-(2-isopropyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (144**)**

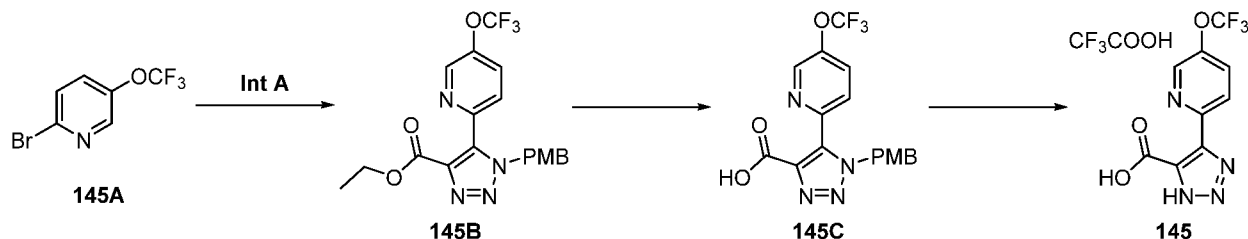


[00985] Compounds **144B**, **144C**, **144D**, **144E**, and **144** were synthesized by employing the procedures described for Compounds **63A**, **27C**, **8B**, **8F**, and **1** using 2-iodopropane, Compounds **144A** using K_2CO_3 as base and acetonitrile as solvent, **144B**, Intermediate **A**, **144C** using K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **144D**, and **144E** in lieu of iodomethane, Compounds **61F** using Cs_2CO_3 as base, **27B**, **8A**, (4-bromophenyl)boronic acid using Cs_2CO_3 as base and toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **8E**, and **1E**. Compound **144B**: LC-MS (ESI) m/z : 254 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.13 (d, $J = 6.8$ Hz, 6H), 2.74-2.77 (m, 2H), 2.81-2.84 (m, 2H), 2.86-2.93 (m, 1H), 3.68 (s, 2H), 6.96 (d, $J = 8.0$ Hz, 1H), 7.18-7.23 (m, 2H). Compound **144C**: LC-MS (ESI) m/z : 302 $[M+H]^+$. Compound **144D**: LC-MS (ESI) m/z : 435 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.15 (d, $J = 6.8$ Hz, 6H), 1.28 (t, $J = 7.2$ Hz, 3H), 2.81 (t, $J = 6.0$ Hz, 2H), 2.89-2.98 (m, 3H), 3.68 (s, 2H), 3.78 (s, 3H), 4.30 (q, $J = 7.2$ Hz, 2H), 5.31 (s, 2H), 6.77-6.82 (m, 3H), 6.96-7.00 (m, 3H), 7.18 (d, $J = 8.0$ Hz, 1H). Compound **144E**: LC-MS (ESI) m/z :

407 [M+H]⁺. Compound **144**: LC-MS (ESI) m/z: 287 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.35 (d, *J* = 8.4 Hz, 6H), 3.10-3.24 (m, 2H), 3.34-3.38 (m, 1H), 3.64-3.71 (m, 2H), 4.46 (s, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.69-7.74 (m, 2H), 10.02 (bs, 1H).

[00986] **Example 145**

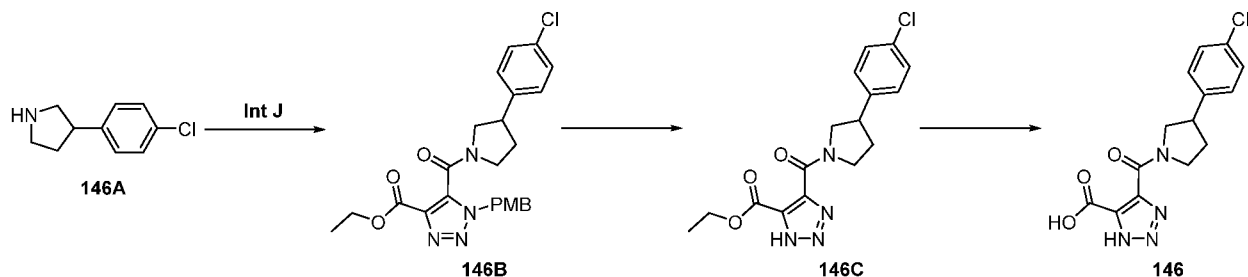
[00987] **Synthesis of 4-(5-(trifluoromethoxy)pyridin-2-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (145)**



[00988] Compounds **145B**, **145C**, and **145** were synthesized by employing the procedures described for Compounds **132A**, **8F**, and **1** using Compounds **145A**, **145B**, and **145C** in lieu of Compounds **76A**, **8E**, and **1E**. Compound **145B**: LC-MS (ESI) m/z: 423 [M+H]⁺. Compound **145C**: LC-MS (ESI) m/z: 395 [M+H]⁺. Compound **145**: LC-MS (ESI) m/z: 275 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 8.21 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.67 (s, 1H).

[00989] **Example 146**

[00990] **Synthesis of 4-(3-(4-chlorophenyl)pyrrolidine-1-carbonyl)-1H-1,2,3-triazole-5-carboxylic acid (146)**

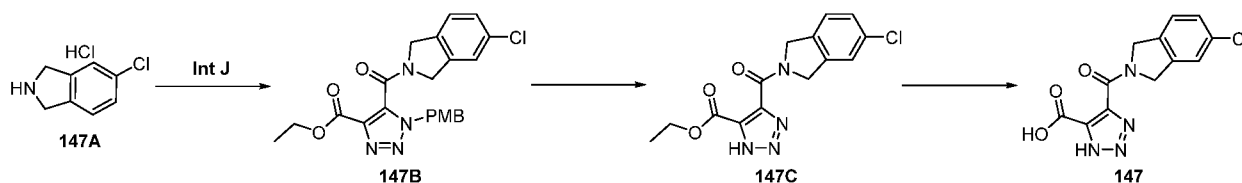


[00991] A mixture of Intermediate **J** (200 mg, 0.66 mmol), Compound **146A**, 3-(4-chlorophenyl)pyrrolidine, (143 mg, 0.79 mmol), HATU (380 mg, 1 mmol), and DIPEA (258 mg, 2 mmol) in DMF (5 mL) was stirred at room temperature overnight. The mixture was diluted with EtOAc (50 mL), washed with brine (15 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with preparative HPLC give Compound **146B**. LC-MS (ESI) m/z: 469 [M+H]⁺.

[00992] Compounds **146C** and **146** were synthesized by employing the procedures described for Compounds **1** and **2** using Compounds **146B** and Compound **146C** in lieu of Compounds **1E** and **1**. Compound **146C**: LC-MS (ESI) m/z : 349 $[M+H]^+$. Compound **146**: LC-MS (ESI) m/z : 321 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.10-2.20 (m, 1H), 2.38-2.47 (m, 1H), 3.53-3.63 (m, 1H), 3.66-3.81 (m, 2H), 3.99-4.44 (m, 2H), 7.32-7.37 (m, 4H).

[00993] **Example 147**

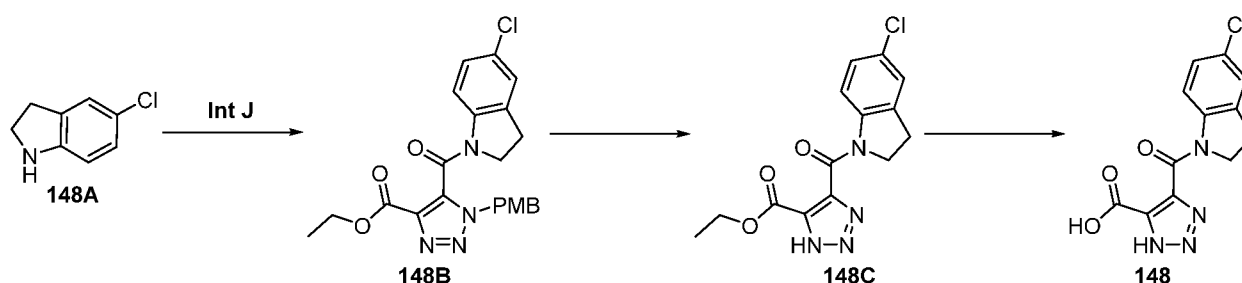
[00994] **Synthesis of 4-(5-chloroisindoline-2-carbonyl)-1H-1,2,3-triazole-5-carboxylic acid (147)**



[00995] Compounds **147B**, **147C**, and **147** were synthesized by employing the procedures described for Compounds **146B**, **1**, and **8F** using Compounds **147A** using DMF as solvent, **147B**, and **147C** in lieu of Compounds **146A** using dichloromethane as solvent, **1E**, and **8E**. Compound **147B**: LC-MS (ESI) m/z : 441 $[M+H]^+$. Compound **147C**: LC-MS (ESI) m/z : 321 $[M+H]^+$. Compound **147**: LC-MS (ESI) m/z : 293 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 4.91-4.93 (m, 2H), 5.37-5.40 (m, 2H), 7.36-7.39 (m, 1H), 7.43-7.47 (m, 1H), 7.52-7.54 (m, 1H).

[00996] **Example 148**

[00997] **Synthesis of 4-(5-chloroindoline-1-carbonyl)-1H-1,2,3-triazole-5-carboxylic acid (148)**

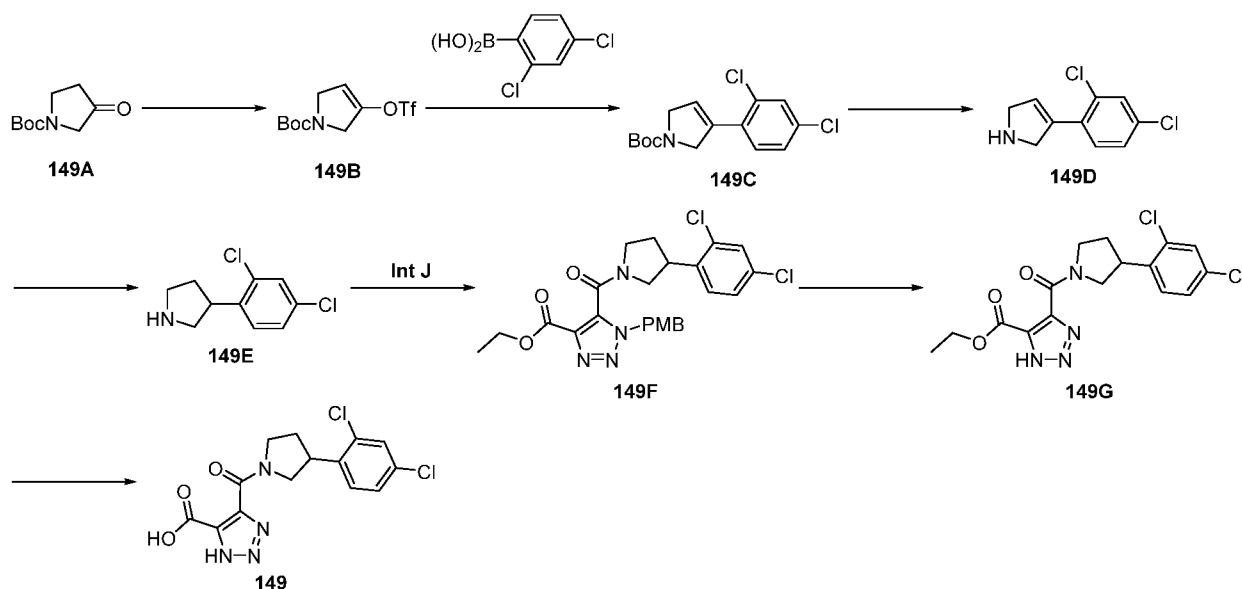


[00998] Compounds **148B**, **148C**, and **148** were synthesized by employing the procedures described for Compounds **146B**, **1**, and **8F** using Compounds **148A**, **148B**, and **148C** in lieu of Compounds **146A**, **1E**, and **8E**. Compound **147B**: LC-MS (ESI) m/z : 441 $[M+H]^+$. Compound **148C**: LC-MS (ESI) m/z : 321 $[M+H]^+$. Compound **148**: LC-MS (ESI) m/z : 293 $[M+H]^+$; $^1\text{H-NMR}$

NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.11 (t, *J* = 8.0 Hz, 2H), 4.23-4.25 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.35 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H).

[00999] Example 149

[001000] Synthesis of 4-(3-(2,4-dichlorophenyl)pyrrolidine-1-carbonyl)-1H-1,2,3-triazole-5-carboxylic acid (149)



[001001] Compounds **149B** and **149C** were synthesized by employing the procedures described for Compounds **140B** and **4B** using Compound **149A** using LiHMDS as base at -78 °C, **149B** using Et₃N as base and DMF as solvent, and 2,4-dichlorophenylboronic acid in lieu of Compound **140A** using tBuOK as base at -20 °C, **4A** using Na₂CO₃ as base and toluene/EtOH/H₂O as solvent, and (4-bromophenyl)boronic acid. Compound **149B**: LC-MS (ESI) *m/z*: 262 [M-55]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.42 (s, 9H), 2.85-3.00 (m, 2H), 3.78 -3.90 (m, 2H), 6.66-6.81 (m, 1H). Compound **149C**: LC-MS (ESI) *m/z*: 258 [M-55]⁺.

[001002] A mixture of Compound **149C** (300 mg, 1 mmol) and HCl solution in EtOAc (3 *M*, 5 mL) was stirred at room temperature for 16 hours. The mixture was concentrated and purified with flash column chromatography on silica gel (methanol in ethyl acetate, 10% v/v) to afford Compound **149D**. LC-MS (ESI) *m/z*: Non-ionizable compound under routine conditions used.

[001003] A mixture of Compound **149D** (100 mg, 1 mmol) and PtO₂ (50 mg) in MeOH (5 mL) was stirred at room temperature under hydrogen (1 atm.) for 16 hours. The mixture was

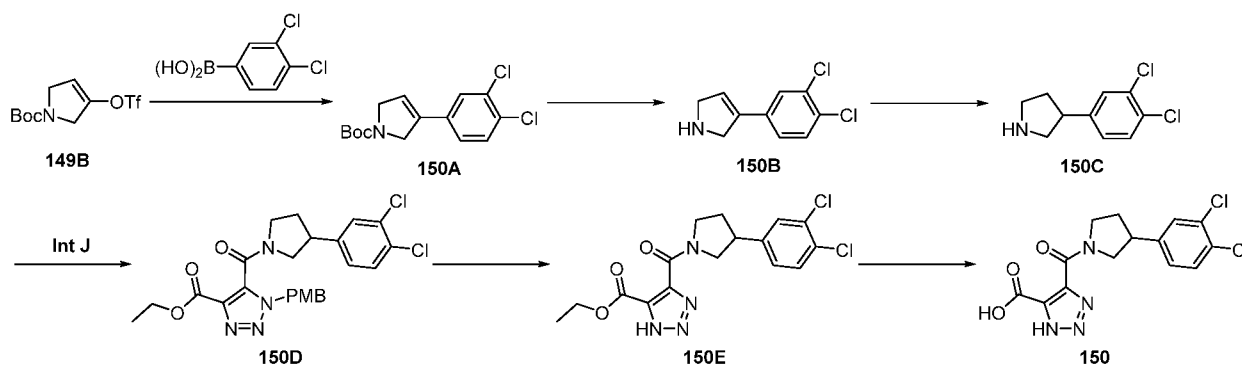
filtered and the filtrate was concentrated to give Compound **149E**. LC-MS (ESI) m/z : 216 $[M+H]^+$.

[001004] Compounds **149F**, **149G**, and **149** were synthesized by employing the procedures described for Compounds **146B**, **1**, and **8F** using Compound **149E** using dichloromethane as solvent, **149F**, and **149G** in lieu of Compound **146A** using DMF as solvent, **1E**, and **8E**.

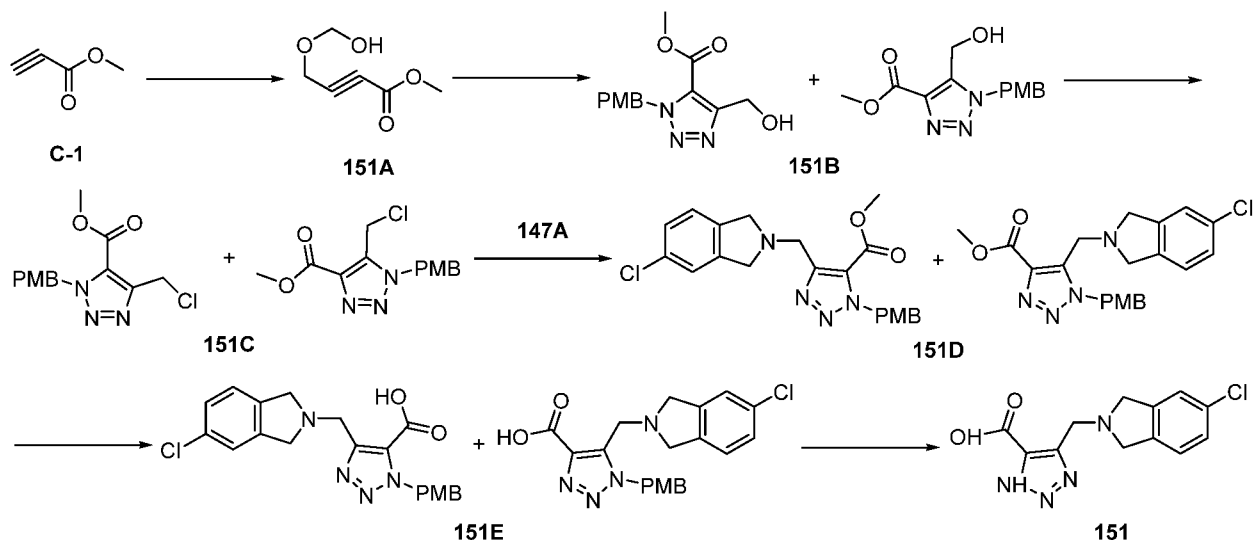
Compound **149F**: LC-MS (ESI) m/z : 503 $[M+H]^+$. Compound **149G**: LC-MS (ESI) m/z : 383 $[M+H]^+$. Compound **149**: LC-MS (ESI) m/z : 355 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.00-2.40 (m, 2H), 3.62-4.15 (m, 5H), 7.32-7.40 (m, 1H), 7.45-7.51 (m, 2H).

[001005] Example 150

[001006] Synthesis of 4-(3-(3,4-dichlorophenyl)pyrrolidine-1-carbonyl)-1H-1,2,3-triazole-5-carboxylic acid (150)



[001007] Compounds **150A**, **150B**, **150C**, **150D**, **150E**, and **150** were synthesized by employing the procedures described for Compounds **4B**, **149D**, **149E**, **146B**, **1**, and **8F** using 3,4-dichlorophenylboronic acid, Compound **149B** using Et_3N as base and DMF as solvent, **150A**, **150B**, **150C** using dichloromethane as solvent, **150D**, and **150E** in lieu of (4-bromophenyl)boronic acid, Compound **4A** using Na_2CO_3 as base and toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **149C**, **149D**, **146A** using DMF as solvent, **1E**, and **8E**. Compound **150A**: LC-MS (ESI) m/z : 258 $[M-55]^+$. Compound **150B**: LC-MS (ESI) m/z : 214 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 4.28-4.30 (m, 2H), 4.45-4.47 (m, 2H), 6.47 (s, 1H), 7.47 (d, $J = 2.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.71 (d, $J = 2.0$ Hz, 1H). Compound **150C**: LC-MS (ESI) m/z : 216 $[M+H]^+$. Compound **150D**: LC-MS (ESI) m/z : 503 $[M+H]^+$. Compound **150E**: LC-MS (ESI) m/z : 383 $[M+H]^+$. Compound **150**: LC-MS (ESI) m/z : 355 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.00-2.11 (m, 1H), 2.27-2.44 (m, 1H), 3.54-4.17 (m, 5H), 7.25-7.34 (m, 1H), 7.45-7.56 (m, 2H).

[001008] Example 151**[001009] Synthesis of 4-((5-chloroisindolin-2-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid (151)**

[001010] To a solution of Intermediate **C-1** (3.34 g, 40 mmol) and paraformaldehyde (1.44 g, 48 mmol) in DMSO (20 mL) was added a solution of trimethylbenzylammonium hydroxide (0.668 g, 4 mmol) in DMSO (20 mL) over 10 minutes. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water (100 mL) and extracted with ethylacetate/hexane (1:3 in volume, 100 mL x 3). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate- hexane eluent to afford Compound **151A**. LC-MS (ESI) m/z: 145 [M+H]⁺. ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 5.49 (s, 2H), 4.97 (t, *J* = 1.6 Hz, 1H), 4.56 (d, *J* = 1.2 Hz, 2H), 3.72 (s, 3H).

[001011] A mixture of Compound **151A** (340 mg, 2.36 mmol) and 1-(azidomethyl)-4-methoxybenzene (500 mg, 3.07 mmol) in toluene (15 mL) was stirred at 110 °C for 48 hours. The reaction mixture was concentrated and purified by column chromatography on silica gel using ethyl acetate- hexane as eluent to afford a Mixture **151B**. LC-MS (ESI) m/z: 278 [M+H]⁺.

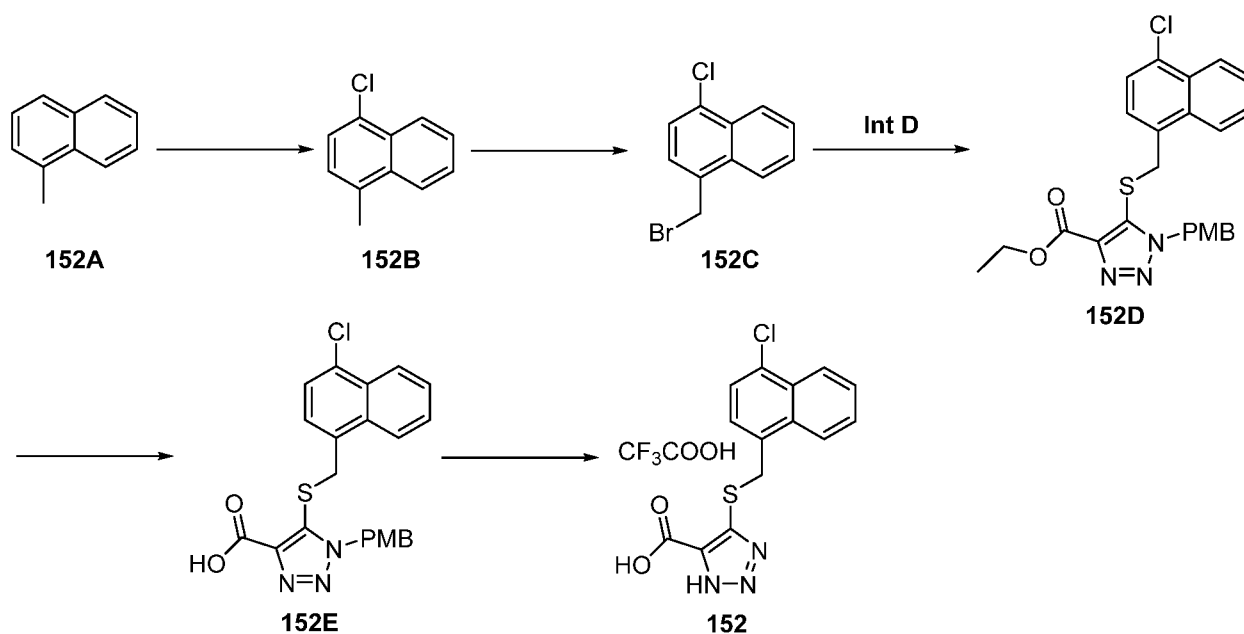
[001012] A Mixture **151B** (60 mg, 0.217 mmol) and thionyl chloride (0.45 mL) in methylene chloride (10 mL) was stirred at 50 °C for 5 hours. The reaction mixture was concentrated to give **151C**, which was used directly in the next step without further purification. LC-MS (ESI) m/z: 296 [M+H]⁺.

[001013] A Mixture **151C** (74 mg, 0.217 mmol), 5-chloroisindoline (38 mg, 0.248 mmol), and K_2CO_3 (60 mg, 0.435 mmol) in DMF (6 mL) was stirred at 60 °C for 5 hours. The mixture was poured into water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined extracts were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with preparative HPLC to afford a Mixture **151D**. LC-MS (ESI) m/z : 413 $[M+H]^+$.

[001014] Mixture **151E** and Compound **151** were synthesized by employing the procedures described for Compounds **8F** and **1** using Mixtures **151D** and **151E** in lieu of Compounds **8E** and **1E**. Mixture **151E**: LC-MS (ESI) m/z : 399. Compound **151**: LC-MS (ESI) m/z : 279 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 4.80 (s, 2H), 4.81 (s, 2H), 4.97 (s, 2H), 7.38-7.40 (m, 1H), 7.42-7.46 (m, 2H).

[001015] Example 152

[001016] Synthesis of 4-(((4-chloronaphthalen-1-yl)methyl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**152**)



[001017] To a mixture of 1-methylnaphthalene (Compound **152A**) (1.46 g, 10 mmol) and $SnCl_4$ (5.2 g, 20 mmol) in dichloromethane (40 mL) was added $Pb(OAc)_4$ (4.4 g, 10 mmol) at 0 °C and stirred at room temperature overnight. The mixture was diluted with Et_2O (80 mL) and filtered. The filtrate was concentrated under reduced pressure. The residue was purified with reverse phase chromatography using eluent (methanol in water, 60% v/v) to afford Compound

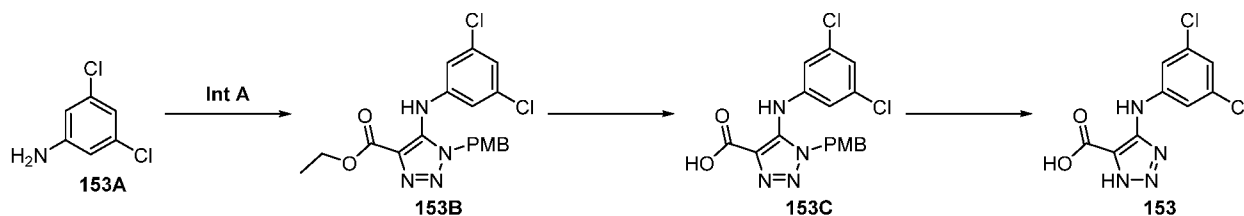
152B. LC-MS (ESI) m/z: Non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.66 (s, 3H), 7.20-7.24 (m, 1H), 7.44 (d, $J = 8.0$ Hz, 1H), 7.56-7.60 (m, 2H), 7.98 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 8.0$ Hz, 1H).

[001018] To a mixture of Compound **152B** (1.76 g, 10 mmol) and N-Bromosuccinimide (1.94 g, 11 mmol) in carbon tetrachloride (40 mL) was added BPO (50 mg) at 0 °C and heated at reflux overnight. The mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to afford Compound **152C**. LC-MS (ESI) m/z: Non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 4.93 (s, 2H), 7.45-7.51 (m, 2H), 7.65-7.69 (m, 2H), 8.16 (d, $J = 8.0$ Hz, 1H), 8.35 (d, $J = 8.0$ Hz, 1H).

[001019] Compounds **152D**, **152E**, and **152** were synthesized by employing the procedures described for Compounds **35D**, **8F**, and **1** using Compounds **152C**, **152D**, and **152E** in lieu of Compounds **35C**, **8E**, and **1E**. Compound **152D**: LC-MS (ESI) m/z: 468 $[\text{M}+\text{H}]^+$. Compound **152E**: LC-MS (ESI) m/z: 440 $[\text{M}+\text{H}]^+$. Compound **152**: LC-MS (ESI) m/z: 320 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 4.85 (s, 2H), 7.58-7.65 (m, 2H), 7.71-7.74 (m, 2H), 8.23-8.29 (m, 2H).

[001020] **Example 153**

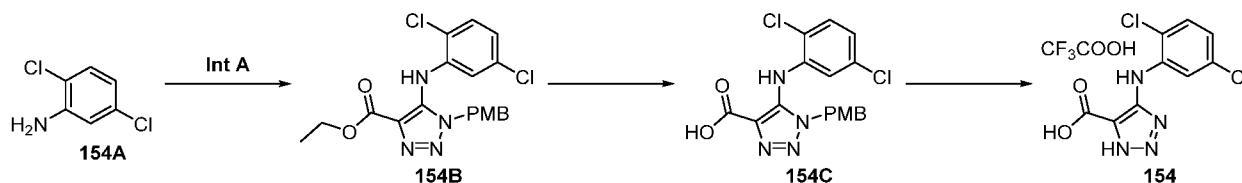
[001021] **Synthesis of 4-((3,5-dichlorophenyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (153)**



[001022] Compounds **153B**, **153C**, and **153** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate A, Compound **153A** using K_3PO_4 as base, **153B**, and **153C** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **153B**: LC-MS (ESI) m/z: 421 $[\text{M}+\text{H}]^+$. Compound **153C**: LC-MS (ESI) m/z: 301 $[\text{M}+\text{H}]^+$. Compound **153**: LC-MS (ESI) m/z: 273 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz,): δ (ppm) 6.93-6.94 (m, 1H), 7.64-7.65 (m, 2H), 9.26 (brs, 1H).

[001023] **Example 154**

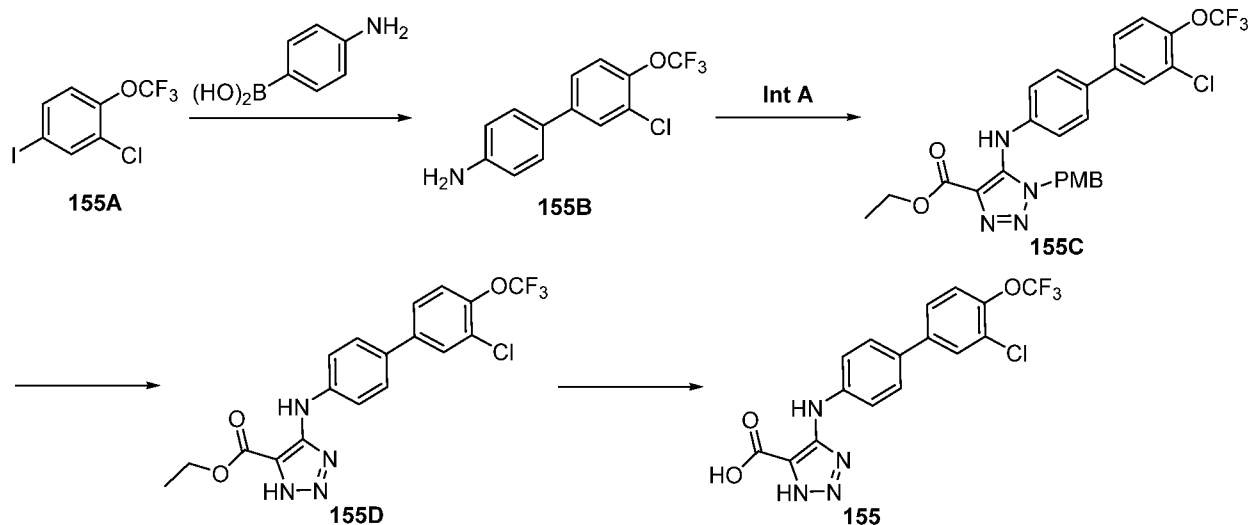
[001024] Synthesis of 4-((2,5-dichlorophenyl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (154)



[001025] Compounds **154B**, **154C**, and **154** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **154A** using K_3PO_4 as base, **154B**, and **154C** in lieu of Compounds **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **8E**, and **1E**. Compound **154B**: LC-MS (ESI) m/z : 421 $[M+H]^+$. Compound **154C**: LC-MS (ESI) m/z : 301 $[M+H]^+$. Compound **154**: LC-MS (ESI) m/z : 273 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.01 (dd, $J_1 = 4.0$ Hz, $J_2 = 8.4$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 8.38 (s, 1H), 8.85 (s, 1H).

[001026] Example 155

[001027] Synthesis of 4-((3'-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (155)

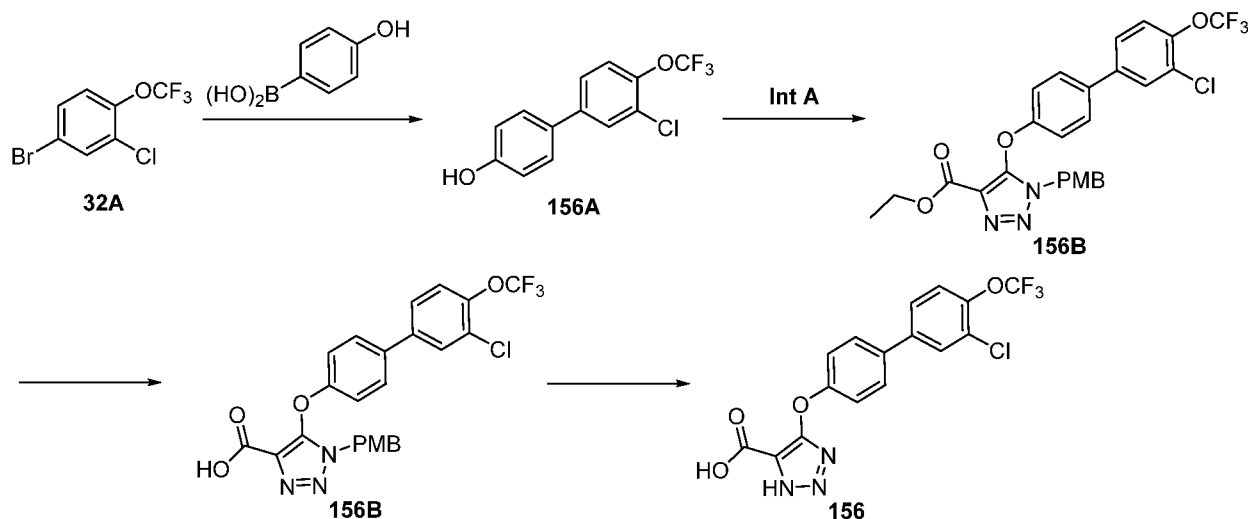


[001028] Compounds **155B**, **155C**, **155D**, and **155** were synthesized by employing the procedures described for Compounds **4B**, **6B**, **1**, and **8F** using 4-aminophenylboronic acid, Compounds **155A**, Intermediate **A**, **155B** using K_3PO_4 as base, **155C**, and **155D** in lieu of (4-bromophenyl)boronic acid, Compounds **4A**, **6A**, 1-methylpiperazine using $t\text{-BuONa}$ as base, **1E**, and **8E**. Compound **155B**: LC-MS (ESI) m/z : 288 $[M+H]^+$. Compound **155C**: LC-MS (ESI) m/z :

547 [M+H]⁺. Compound **155D**: LC-MS (ESI) m/z: 427 [M+H]⁺. Compound **155**: LC-MS (ESI) m/z: 399 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.59-7.61 (m, 1H), 7.70-7.71 (m, 5H), 7.95-7.96 (m, 1H), 8.36 (brs, 1H), 13.40 (brs, 1H), 14.97 (brs, 1H).

[001029] Example 156

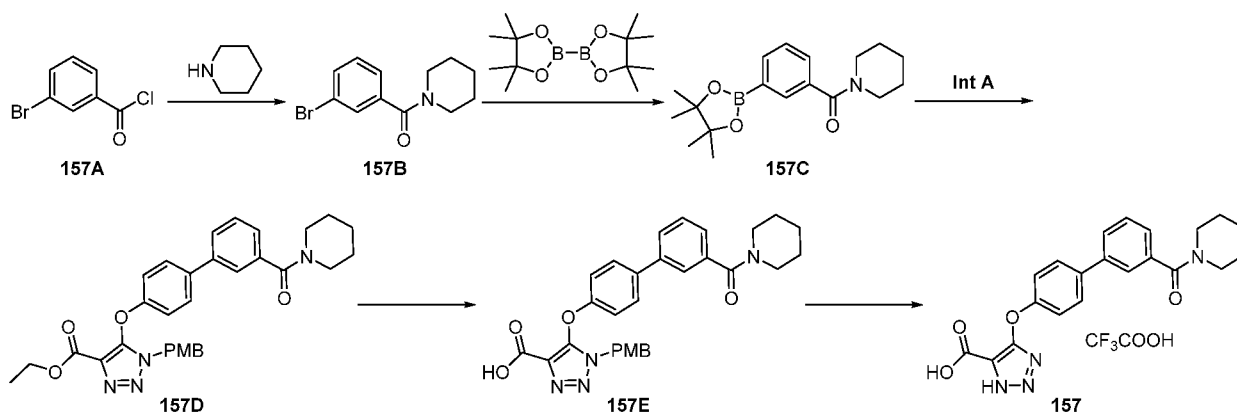
[001030] Synthesis of 4-((3'-chloro-4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (156)



[001031] Compounds **156B**, **156C**, **156D**, and **156** were synthesized by employing the procedures described for Compounds **8B**, Intermediate **I**, **8F**, and **1** using 4-hydroxyphenylboronic acid, Compounds **32A** using K₂CO₃ as base and 1,4-dioxane/H₂O as solvent, **156A**, **156B**, and **156C** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** using Cs₂CO₃ as base and DME/H₂O as solvent, 4-bromophenol, **8E**, and **1E**. Compound **156B**: LC-MS (ESI) m/z: 287 [M-H]⁻. Compound **156C**: LC-MS (ESI) m/z: 548 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.13, 1.41 (t, *J* = 7.2 Hz, 3H), 3.73, 3.75 (s, 3H), 4.20, 4.43 (q, *J* = 7.2 Hz, 2H), 5.38, 5.54 (s, 2H), 6.75-6.88 (m, 4H), 7.19-7.27 (m, 3H), 7.38-7.60 (m, 4H). Compound **156D**: LC-MS (ESI) m/z: 518 [M-H]⁻. Compound **156**: LC-MS (ESI) m/z: 400 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.15-7.19 (m, 2H), 7.63 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.72-7.77 (m, 3H), 7.98 (d, *J* = 2 Hz, 1H), 13.34 (b, 1H), 15.32 (b, 1H).

[001032] Example 157

[001033] Synthesis of 4-((3'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (157)

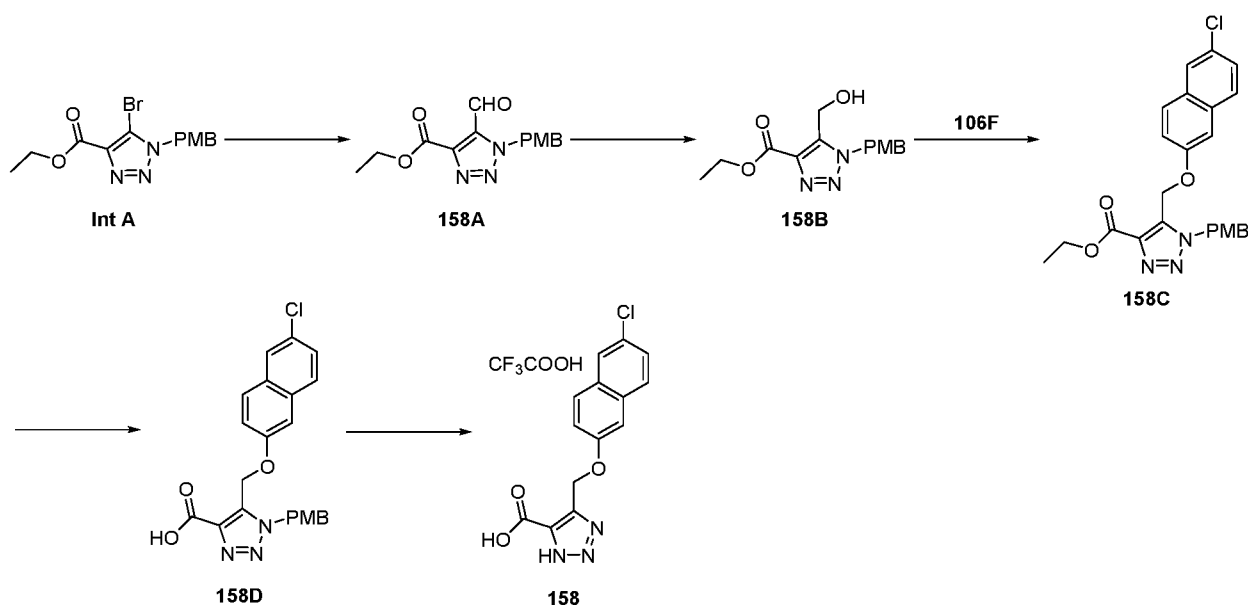


[001034] To a mixture of 3-bromobenzoyl chloride (Compound **157A**) (1.09 g, 5 mmol) and DIPEA (3.22 g, 25 mol) in dichloromethane (10 mL) was added piperidine (2.12 g, 25 mmol) at -10 °C and stirred at room temperature for 2 hours. The mixture was washed successively with an aqueous HCl solution (1N, 20 mL), water (10 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **157B**. LC-MS (ESI) *m/z*: 268 [M+H]⁺.

[001035] Compounds **157C**, **157D**, **157E**, and **157** were synthesized by employing the procedures described for Compounds **27C**, **4B**, **8F**, and **1** using Compounds **157B**, Intermediate **I**, **157C** using 1,4-dioxane/H₂O as solvent, **157D**, and **157E** in lieu of Compounds **27B**, **4A**, (4-bromophenyl)boronic acid using toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **157C**: LC-MS (ESI) *m/z*: 316 [M+H]⁺. Compound **157D**: LC-MS (ESI) *m/z*: 541 [M+H]⁺. Compound **157E**: LC-MS (ESI) *m/z*: 513 [M+H]⁺. Compound **157**: LC-MS (ESI) *m/z*: 393 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.47-1.60 (m, 6H), 3.29 (s, 2H), 3.59 (s, 2H), 7.15 (d, *J* = 4.4 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.68-7.72 (m, 3H), 13.21 (s, 1H), 15.30 (s, 1H).

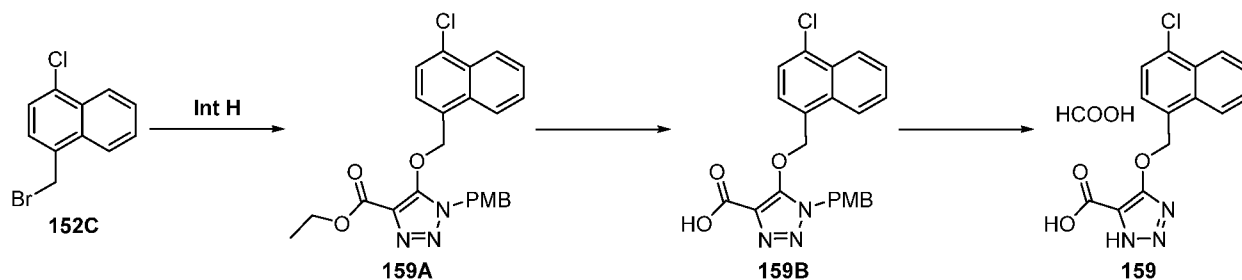
[001036] **Example 158**

[001037] **Synthesis of 4-(((6-chloronaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (158)**

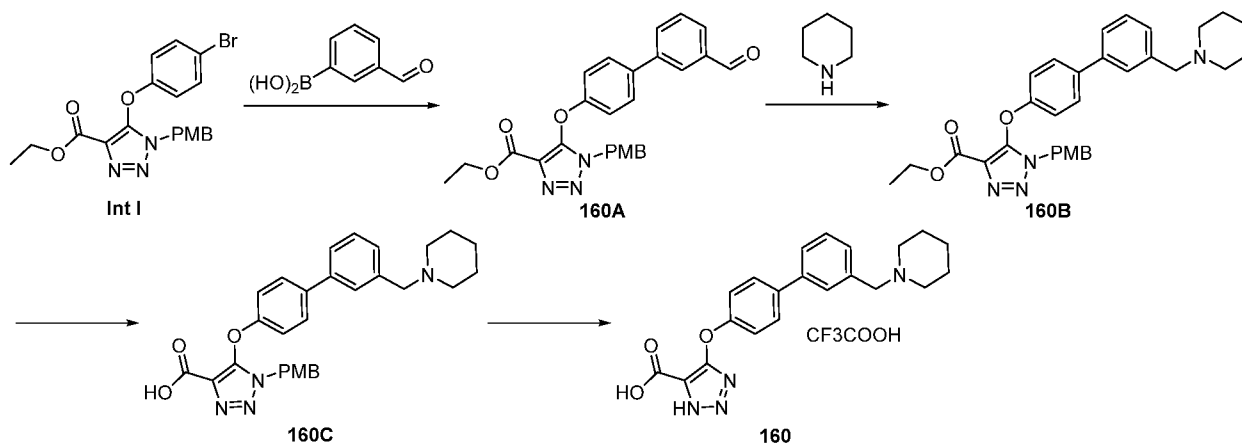


[001038] To a mixture of Intermediate **A** (3.39 g, 10 mmol) in anhydrous THF (100 mL) was added a solution of *n*-BuLi in hexane (2.5 M, 4.0 mL, 10 mmol) at -78 °C under nitrogen and stirred at -78 °C for 10 minutes. To the mixture was added DMF (730 mg, 100 mmol) and stirred at -78 °C for 1 hour. It was quenched with a saturated aqueous NH₄Cl solution (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with water (100 mL) and brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **158A**. LC-MS (ESI) *m/z*: 290 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.45 (t, *J* = 7.2 Hz, 3H), 3.78 (s, 3H), 4.50 (q, *J* = 7.2 Hz, 2H), 5.86 (s, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 8.8 Hz, 2H), 10.48 (s, 1H).

[001039] Compounds **158B**, **158C**, **158D**, and **158** were synthesized by employing the procedures described for Compounds **57C**, **90C**, **8F**, and **1** using Compounds **158A** using EtOAc as solvent, **158B** using DEAD, **106F**, **158C**, and **158D** in lieu of Compounds **57B** using MeOH as solvent, **90B** using DIAD, Intermediate **H**, **8E**, and **1E**. Compound **158B**: LC-MS (ESI) *m/z*: 292 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.45 (t, *J* = 7.2 Hz, 3H), 3.80-3.84 (m, 4H), 4.47 (q, *J* = 7.2 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 5.58 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 2H). Compound **158C**: LC-MS (ESI) *m/z*: 452 [M+H]⁺. Compound **158D**: LC-MS (ESI) *m/z*: 424 [M+H]⁺. Compound **158**: LC-MS (ESI) *m/z*: 304 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 5.49 (s, 2H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 8.8, 2.4 Hz, 2H), 7.98 (d, *J* = 2.0 Hz, 1H).

[001040] Example 159**[001041] Synthesis of 4-((4-chloronaphthalen-1-yl)methoxy)-1H-1,2,3-triazole-5-carboxylic acid formate (159)**

[001042] Compounds **159A**, **159B**, and **159** were synthesized by employing the procedures described for Intermediate **I**, Compounds **8F**, and **1** using Compounds **152C**, **159A**, and **159B** in lieu of 4-bromophenol, Compounds **8E**, and **1E**. Compound **159A**: LC-MS (ESI) m/z : 452 $[M+H]^+$. Compound **159B**: LC-MS (ESI) m/z : 424 $[M+H]^+$. Compound **159**: LC-MS (ESI) m/z : 302 $[M-H]^-$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 6.20 (s, 2H), 7.00-7.07 (m, 1H), 7.61-7.80 (m, 3H), 8.12 (s, 1H), 8.24-8.27 (m, 1H), 8.35-8.41 (m, 1H).

[001043] Example 160**[001044] Synthesis of 4-((3'-(piperidin-1-ylmethyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (160)**

[001045] Compound **160A** was synthesized by employing the procedure described for Compound **4B** using 3-formylphenylboronic acid and Intermediate **I** in lieu of (4-bromophenyl)boronic acid and Compound **4A**, LC-MS (ESI) m/z : 458 $[M+H]^+$. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 0.93 (t, $J = 7.2$ Hz, 3H), 3.67 (s, 3H), 4.01-4.07 (m, 2H), 5.47 (s,

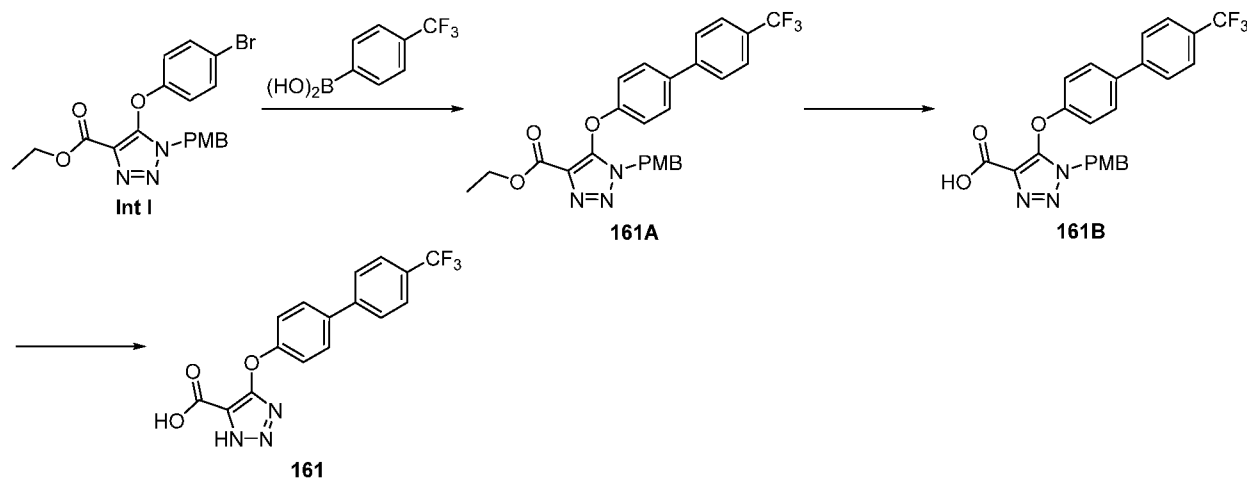
2H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.66-7.71 (m, 3H), 7.88 (d, $J = 7.2$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 8.14 (s, 1H), 10.08 (s, 1H).

[001046] A mixture of Compound **160A** (160 mg, 0.35 mmol), piperidine (36 mg, 0.42 mol) and anhydrous magnesium sulfate (500 mg) in dichloromethane (10 mL) was stirred at 20 °C under nitrogen for 0.5 hour. To the mixture was added NaBH_3CN (26 mg, 0.42 mol) and stirred at 20 °C for 15 hours. It was filtered and the filtrate was concentrated. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 60% v/v) to give Compound **160B**. LC-MS (ESI) m/z : 527 $[\text{M}+\text{H}]^+$.

[001047] Compounds **160C** and **160** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **160B** and **160C** in lieu of Compounds **8E** and **1E**. Compound **160C**: LC-MS (ESI) m/z : 499 $[\text{M}+\text{H}]^+$. Compound **160**: LC-MS (ESI) m/z : 379 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.33-1.42 (m, 1H), 1.57-1.70 (m, 3H), 1.81-1.84 (m, 2H), 2.87 (s, 2H), 3.34-3.37 (m, 2H), 4.34 (s, 2H), 7.20 (d, $J = 8.8$ Hz, 2H), 7.46 (d, $J = 7.2$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 1H), 7.80 (s, 1H), 9.45 (s, 1H), 13.23 (s, 1H), 15.30 (s, 1H).

[001048] Example 161

[001049] Synthesis of 4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (161)

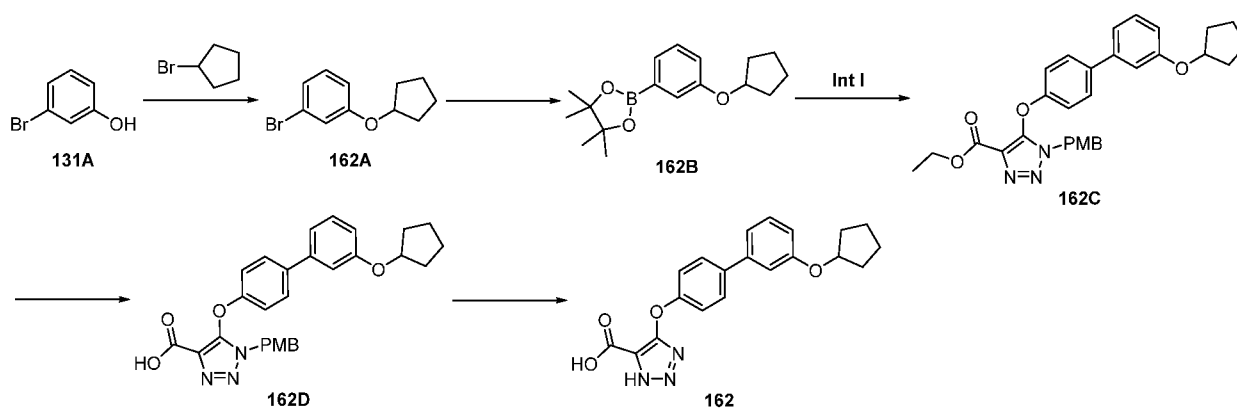


[001050] Compounds **161A**, **161B**, and **161** were synthesized by employing the procedures described for Compounds **4B**, **8F**, and **1** using 4-(trifluoromethyl)phenylboronic acid, Intermediate **I** using K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, Compounds **161A**, and **161B** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** using Na_2CO_3 as base and

toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **161A**: LC-MS (ESI) m/z: 498 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.13 (t, J = 7.2 Hz, 3H), 3.73 (s, 3H), 4.21 (q, J = 7.2 Hz, 2H), 5.39 (s, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H). Compound **161B**: LC-MS (ESI) m/z: 492 [M+Na]⁺. Compound **161**: LC-MS (ESI) m/z: 350 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.20 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H).

[001051] Example 162

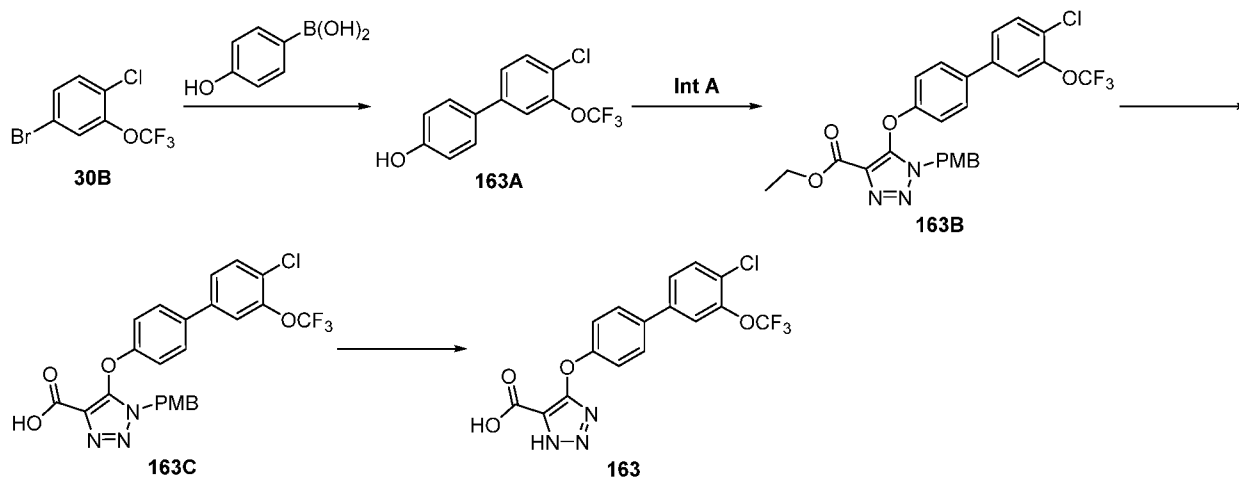
[001052] Synthesis of 4-((3'-(cyclopentyloxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (162**)**



[001053] Compounds **162A**, **162B**, **162C**, **162D**, and **162** were synthesized by employing the procedures described for Compounds **27B**, **27C**, **8B**, **8F**, and **1** using bromocyclopentane, Compounds **131A**, **162A**, **162B**, Intermediate **I** using Na₂CO₃ as base and 1,4-dioxane/H₂O as solvent, **162C**, and **162D** in lieu of 2-bromopropane, Compounds **27A**, **27B**, (4-bromophenyl)boronic acid, **8A** using Cs₂CO₃ as base and DME/H₂O as solvent, **8E**, and **1E**. Compound **162A**: LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. Compound **162B**: LC-MS (ESI) m/z: 289 [M+H]⁺. Compound **162C**: LC-MS (ESI) m/z: 514 [M+H]⁺. Compound **162D**: LC-MS (ESI) m/z: 486 [M+H]⁺. Compound **162**: LC-MS (ESI) m/z: 366 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.59-1.75 (m, 6H), 1.92-1.95 (m, 2H), 4.90-4.91 (m, 1H), 6.88 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.10-7.18 (m, 4H), 7.34 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H).

[001054] Example 163

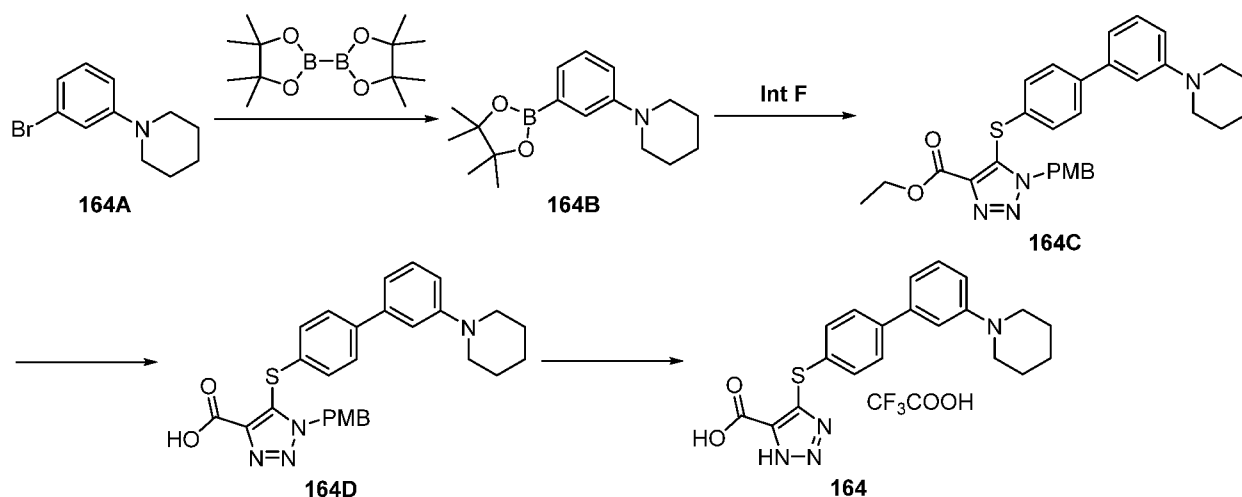
[001055] Synthesis of 4-((4'-chloro-3'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid (163)



[001056] Compounds **163A**, **163B**, **163C**, and **163** were synthesized by employing the procedures described for Compounds **8B**, Intermediate **I**, **8F**, and **1** using 4-hydroxyphenylboronic acid, Compounds **30B** using K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **163A**, **163B**, and **163C** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, 4-bromophenol, **8E**, and **1E**. Compound **163A**: LC-MS (ESI) m/z : 287 $[M-H]^-$. Compound **163B**: LC-MS (ESI) m/z : 548 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, $J = 7.2$ Hz, 3H), 3.73 (s, 3H), 4.21 (q, $J = 7.2$ Hz, 2H), 5.38 (s, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.37-7.45 (m, 4H), 7.53 (d, $J = 8.4$ Hz, 1H). Compound **163C**: LC-MS (ESI) m/z : 518 $[M-H]^-$. Compound **163**: LC-MS (ESI) m/z : 400 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.18 (d, $J = 8.8$ Hz, 2H), 7.73-7.76 (m, 4H), 7.82 (s, 1H).

[001057] Example 164

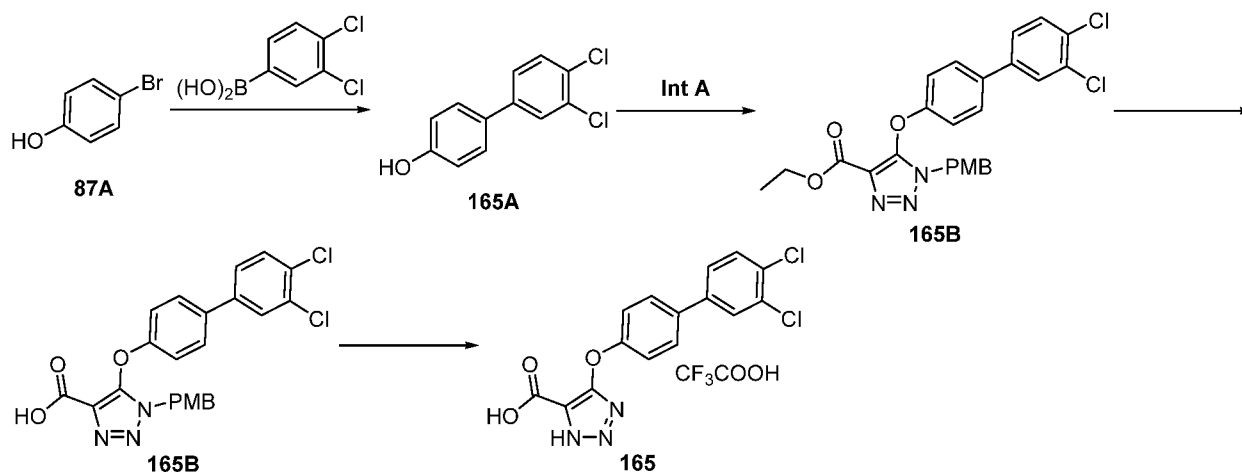
[001058] Synthesis of 4-((3'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (164)



[001059] Compounds **164B**, **164C**, **164D**, and **164** were synthesized by employing the procedures described for Compounds **27C**, **4B**, **8F**, and **1** using Compounds **164A**, **164B**, Intermediate **F** using K₃PO₄ as base and DME/H₂O as solvent, **164C**, and **164D** in lieu of Compounds **27B**, (4-bromophenyl)boronic acid, **4A** using Na₂CO₃ as base and toluene/EtOH/H₂O as solvent, **8E**, and **1E**. Compound **164B**: LC-MS (ESI) m/z: 288 [M+H]⁺. Compound **164C**: LC-MS (ESI) m/z: 529 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ 1.24-1.28 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.70-1.74 (m, 4H), 3.19-3.22 (m, 4H), 3.71 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.56 (s, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.92-6.96 (m, 2H), 7.04-7.07 (m, 3H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.28-7.31 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H). Compound **164D**: LC-MS (ESI) m/z: 499 [M-H]⁻. Compound **164**: LC-MS (ESI) m/z: 381 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.54-1.57 (m, 2H), 1.64-1.66 (m, 4H), 3.23-3.25 (m, 4H), 7.01-7.10 (m, 2H), 7.20-7.23 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 13.53 (bs, 1H), 15.81 (bs, 1H).

[001060] Example 165

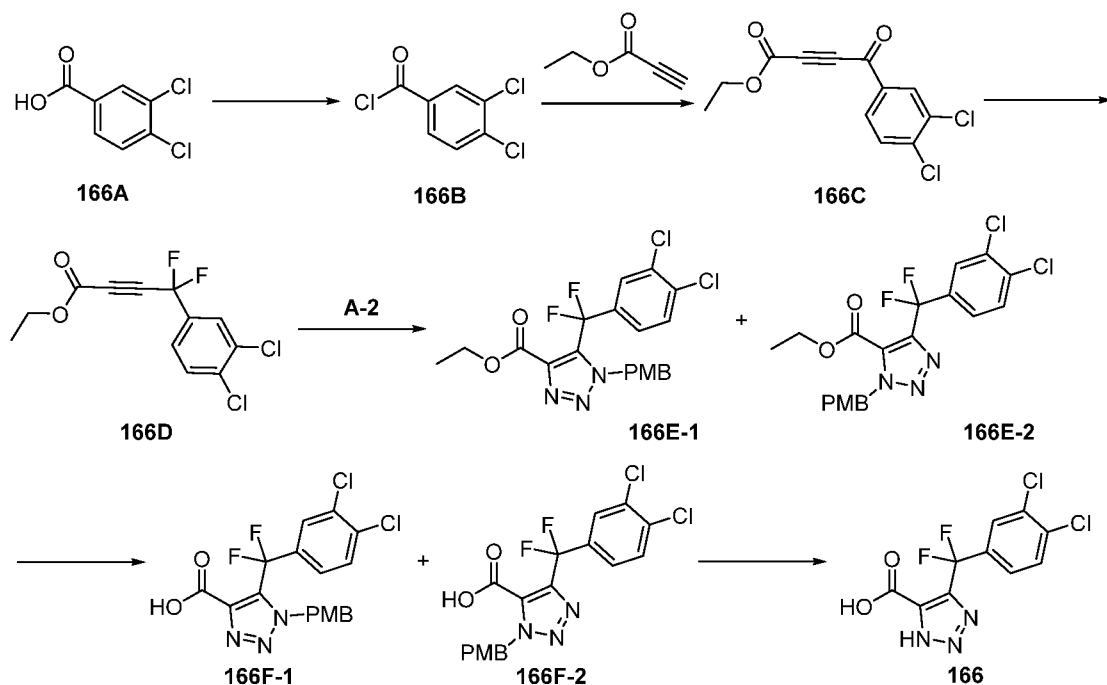
[001061] Synthesis of 4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**165**)



[001062] Compounds **165A**, **165B**, **165C**, and **165** were synthesized by employing the procedures described for Compounds **8B**, Intermediate **I**, **8F**, and **1** using Compounds **87A** using Na_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **165A**, **165B**, and **165C** in lieu of Compounds **8A** using Cs_2CO_3 as base and DME/ H_2O as solvent, 4-bromophenol, **8E**, and **1E**. Compound **165A**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 6.89- 6.92 (m, 2H), 7.33- 7.36 (m, 1H), 7.41-7.47 (m, 3H), 7.61 (d, $J = 2.4$ Hz, 1H). Compound **165B**: LC-MS (ESI) m/z : 498 $[\text{M}+\text{H}]^+$. Compound **163C**: LC-MS (ESI) m/z : 470 $[\text{M}+\text{H}]^+$. Compound **165**: LC-MS (ESI) m/z : 350 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.14 (d, $J = 8.8$ Hz, 2H), 7.63-7.66 (m, 1H), 7.68- 7.73 (m, 3H), 7.91 (d, $J = 2.0$ Hz, 1H).

[001063] **Example 166**

[001064] **Synthesis of 4-((3,4-dichlorophenyl)difluoromethyl)-1H-1,2,3-triazole-5-carboxylic acid (166)**



[001065] A mixture of 3,4-dichlorobenzoic acid (Compound **166A**) (6.0 g, 28.7 mmol) and sulfurous dichloride (100 mL) was heated at 80 °C for 4 hours. The reaction mixture was concentrated to give a crude Compound **166B**, which was used directly for next step without further purification.

[001066] A mixture of ethyl propiolate (2.82 g, 28.8 mmol), CuI (5.97 g, 31.4 mmol), DIPEA (4.2 g, 32.6 mmol), and Compound **166B** (6.0 g, 28.8 mmol) in THF (70 mL) was stirred at room temperature for 16 hours. The reaction mixture was filtered through Celite and the filtrate was concentrated under the reduced pressure. The residue was purified by column chromatography (silica gel, eluted with petroleum ether/ethyl acetate: 1/0 to 20/1) to give Compound **166C**. LC-MS (ESI) m/z : 271 $[M+H]^+$.

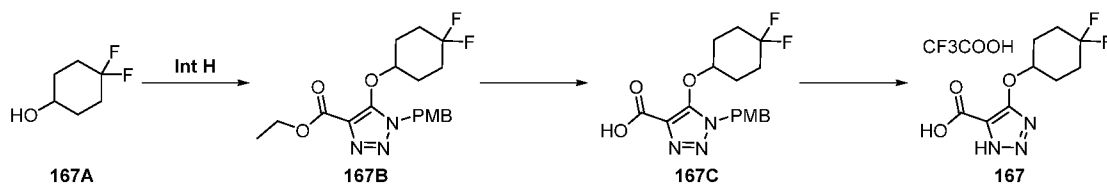
[001067] To Compound **166C** (900 mg, 3.33 mmol) was added DAST (5 mL) and two drops of ethanol (95%). The reaction mixture was stirred at 60 °C for 16 hours. After cooled down to room temperature, to the mixture was added pentane (50 mL), followed by slowly addition of HCl solution (1%, 50 mL). The organic layers were separated, washed with water (100 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude Compound **166D**, which was used directly for next step without further purification. LC-MS (ESI) m/z : non-ionizable compound under routine conditions used.

[001068] A mixture of Compound **166D** (850 mg, 2.9 mmol) and Intermediate **A-2** (608 mg, 3.73 mmol) in THF (10 mL) was stirred at 60 °C for 8 hours. The reaction mixture was concentrated and purified with preparative HPLC to afford a Mixture of **166E-1** and **166E-2**. LC-MS (ESI) m/z : 456 $[M+H]^+$.

[001069] Mixture of **166F-1** and **166F-2**, and Compound **166** were synthesized by employing the procedures described for Compounds **8F** and **1** using Mixtures of **166E-1** and **166E-2**, and **166F-1** and **166F-2** in lieu of Compounds **8E** and **1E**. Mixture of **166F-1** and **166F-2**: which was used directly for next step without further purification. LC-MS (ESI) m/z : 877 $[2M+Na]^+$. Compound **166**: LC-MS (ESI) m/z : 308 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.50 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.8$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 1.6$ Hz, 1H).

[001070] Example 167

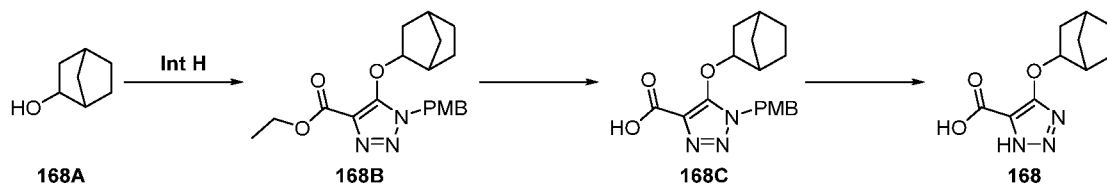
[001071] Synthesis of 4-((4,4-difluorocyclohexyl)oxy)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (167**)**



[001072] Compounds **167B**, **167C**, and **167** were synthesized by employing the procedures described for Compounds **90C**, **8F**, and **1** using Compounds **167A**, **167B**, and **167C** in lieu of Compounds **90B**, **8E**, and **1E**. Compound **167B**: LC-MS (ESI) m/z : 396 $[M+H]^+$. Compound **167C**: LC-MS (ESI) m/z : 368 $[M+H]^+$. Compound **167**: LC-MS (ESI) m/z : 248 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.91-2.11 (m, 8H), 4.85 (s, 1H), 12.89 (s, 1H), 14.78 (s, 1H).

[001073] Example 168

[001074] Synthesis of 4-(bicyclo[2.2.1]heptan-2-yloxy)-1H-1,2,3-triazole-5-carboxylic acid (168**)**

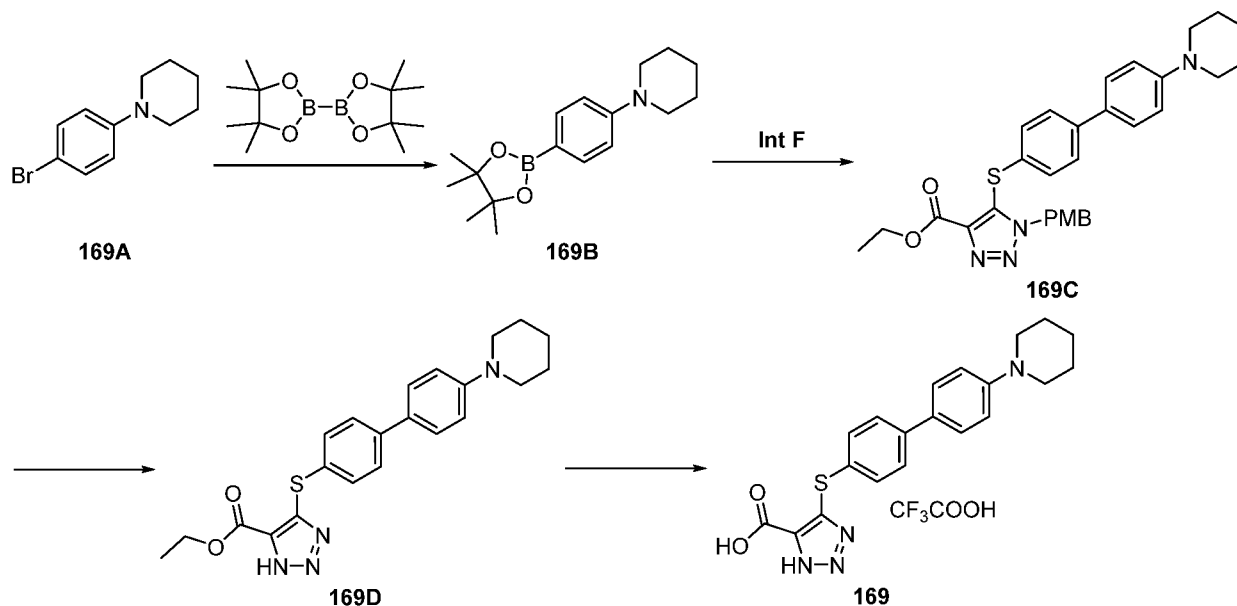


[001075] Compounds **168B**, **168C**, and **168** were synthesized by employing the procedures described for Compounds **90C**, **8F**, and **1** using Compounds **168A**, **168B**, and **168C** in lieu of

Compounds **90B**, **8E**, and **1E**. Compound **168B**: LC-MS (ESI) m/z : 372 $[M+H]^+$. Compound **168C**: LC-MS (ESI) m/z : 344 $[M+H]^+$. Compound **168**: LC-MS (ESI) m/z : 224 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.03 (dt, $J = 13.2$ Hz, 1H), 1.31 (t, $J = 9.8$ Hz, 3H), 1.42 (d, $J = 9.9$ Hz, 1H), 1.54 (dd, $J = 8.3$ Hz, 1H), 1.85 (t, $J = 13.0$ Hz, 1H), 2.02 (dd, $J = 8.8$ Hz, 1H), 2.21 (s, 1H), 2.57 (s, 1H), 4.90 (d, $J = 9.6$ Hz, 1H).

[001076] **Example 169**

[001077] **Synthesis of 4-((4'-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**169**)**

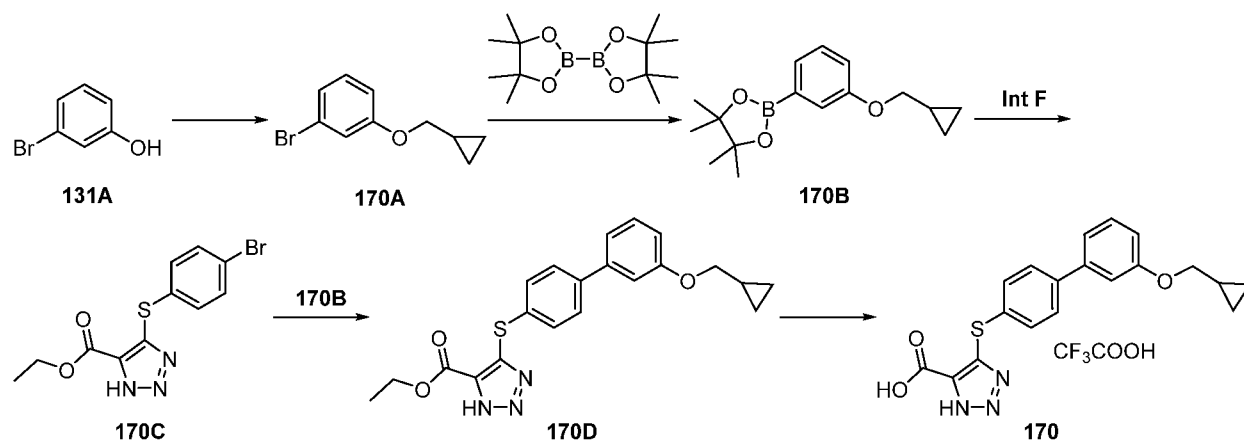


[001078] Compounds **169B**, **169C**, **169D**, and **169** were synthesized by employing the procedures described for Compounds **27C**, **4B**, **1**, and **8F** using Compounds **169A**, **169B**, Intermediate **F** with K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **169C**, and **169D** in lieu of Compounds **27B**, (4-bromophenyl)boronic acid, **4A** with Na_2CO_3 as base and toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **1E**, and **8E**. Compound **169B**: LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.33 (s, 12H), 1.61-1.63 (m, 2H), 1.66-1.72 (m, 4H), 3.24-3.28 (m, 4H), 6.90 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 2H). Compound **169C**: LC-MS (ESI) m/z : 529 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.33 (t, $J = 7.2$ Hz, 3H), 1.60-1.65 (m, 2H), 1.70-1.74 (m, 4H), 3.21-3.24 (m, 4H), 3.72 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 5.56 (s, 2H), 6.76 (d, $J = 8.8$ Hz, 2H), 6.98 (d, $J = 8.8$ Hz, 2H), 7.06 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.8$ Hz, 2H), 7.37-7.44 (m, 4H). Compound **169D**: LC-MS (ESI) m/z : 409 $[M+H]^+$. Compound **169**: LC-MS (ESI) m/z : 381 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ

(ppm) 1.81-1.84 (m, 2H), 2.02-2.08 (m, 4H), 2.64-2.68 (m, 4H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.68-7.71 (m, 4H), 7.87 (d, $J = 8.4$ Hz, 2H).

[001079] Example 170

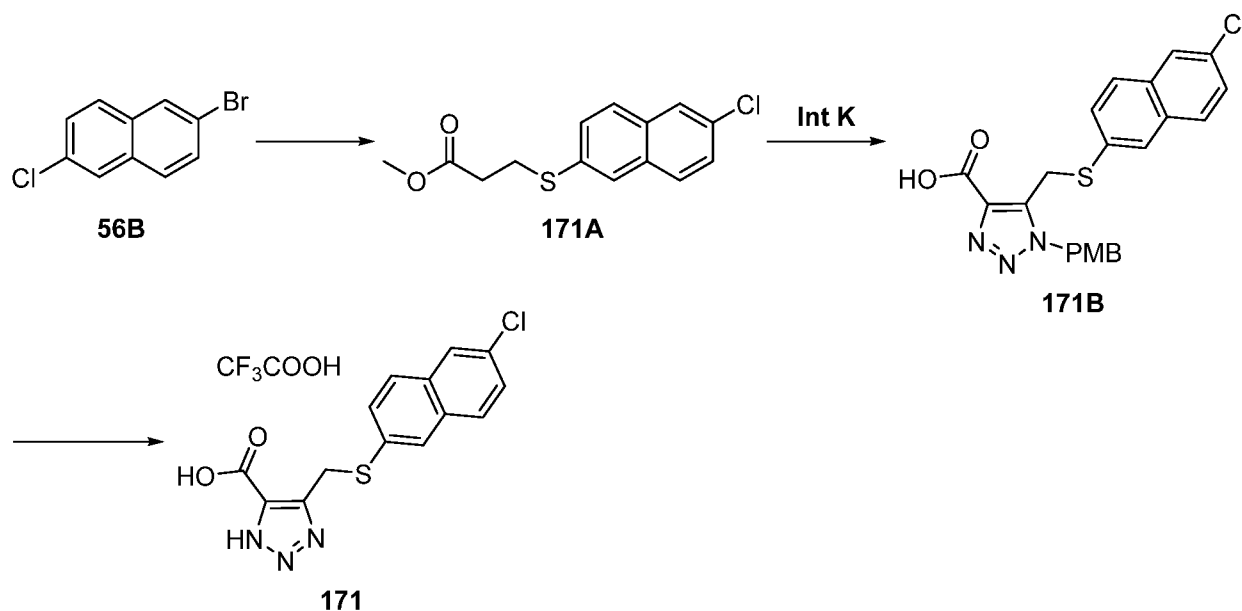
[001080] Synthesis of 4-((3'-(cyclopropylmethoxy)-[1,1'-biphenyl]-4-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (170)



[001081] Compounds **170A**, **170B**, **170C**, **170D**, and **170** were synthesized by employing the procedures described for Compounds **29B**, **27C**, **1**, **4B**, and **8F** using (bromomethyl)cyclopropane, Compounds **131A**, **170A**, Intermediate **F**, **170B**, **170C** with K_3CO_3 as base and 1,4-dioxane/ H_2O as solvent, and **170D** in lieu of iodoethane, Compounds **29A**, **27B**, **1E**, (4-bromophenyl)boronic acid, **4A** with Na_2CO_3 as base and toluene/ $EtOH/H_2O$ as solvent, and **8E**. Compound **170A**: LC-MS (ESI) m/z : Non-ionizable compound under routine conditions used. Compound **170B**: LC-MS (ESI) m/z : 275 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.33-0.37 (m, 2H), 0.61-0.65 (m, 2H), 1.26-1.30 (m, 1H), 1.36 (s, 12H), 3.85 (d, $J = 6.8$ Hz, 2H), 7.02-7.05 (m, 1H), 7.29-7.33 (m, 2H), 7.40 (d, $J = 7.6$ Hz, 1H). Compound **170C**: LC-MS (ESI) m/z : 328 $[M+H]^+$. Compound **170D**: LC-MS (ESI) m/z : 396 $[M+H]^+$. Compound **170**: LC-MS (ESI) m/z : 368 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 0.35-0.40 (m, 2H), 0.61-0.66 (m, 2H), 1.28-1.31 (m, 1H), 3.89 (d, $J = 6.4$ Hz, 2H), 6.92 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 7.15 (t, $J = 2.0$ Hz, 1H), 7.19 (d, $J = 8.0$ Hz, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H).

[001082] Example 171

[001083] Synthesis of 4-(((6-chloronaphthalen-2-yl)thio)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (171)



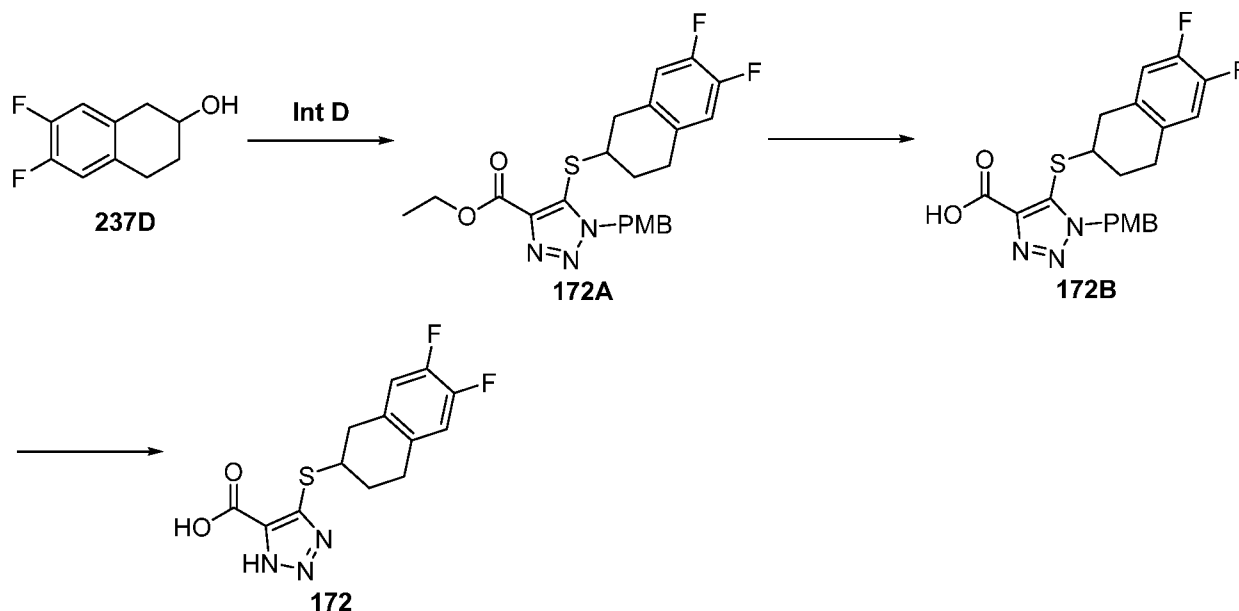
[001084] Compound **171A** was synthesized by employing the procedure described for Intermediate **D-1** using Compounds **56B** in lieu of Intermediate **A**, LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 2.69 (t, $J = 7.2$ Hz, 2H), 3.28 (t, $J = 7.2$ Hz, 2H), 3.69 (s, 3H), 7.41-7.48 (m, 2H), 7.69 (dd, $J = 8.8$ Hz, 2.4 Hz, 2H), 7.77 (d, $J = 10.4$ Hz, 2H).

[001085] To a solution of Compound **171A** (70 mg, 0.25 mmol) in dry THF (10 mL) at -78°C and under nitrogen was added potassium *tert*-butoxide (56 mg, 0.5 mmol) and stirred at -78°C for 30 minutes, and then stirred at room temperature for 1 hour. A solution of Intermediate **K** (88 mg, 0.25 mmol) in dry THF (2 mL) was added. The resulting mixture was stirred at room temperature overnight and concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (methanol in CH_2Cl_2 , 20% v/v) to afford Compound **171B**. LC-MS (ESI) m/z : 440 $[\text{M}+\text{H}]^+$.

[001086] Compound **171** was synthesized by employing the procedure described for Compound **1** using Compound **171B** in lieu of Compound **1E**, LC-MS (ESI) m/z : 320 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 4.60 (s, 2H), 7.50-7.54 (m, 2H), 7.33 (dd, $J = 8.8$, 3.2 Hz, 2H), 7.94 (s, 1H), 8.01 (d, $J = 2.0$ Hz, 1H).

[001087] **Example 172**

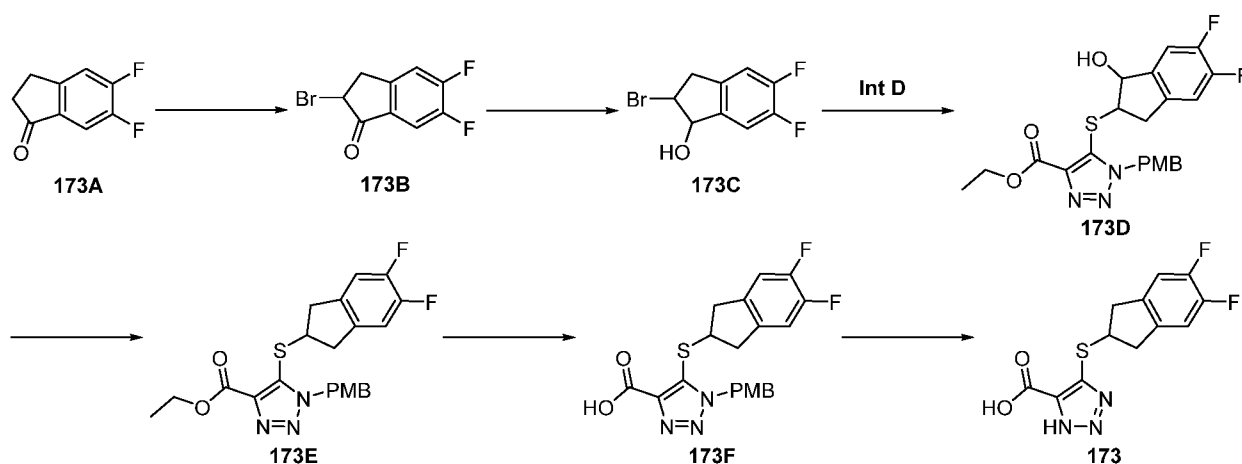
[001088] Synthesis of 4-((6,7-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (172)



[001089] Compounds **172A**, **172B**, and **172** were synthesized by employing the procedures described for Compounds **90C**, **8F**, and **1** using Intermediate **D**, Compounds **237D** with DEAD, **172A**, and **172B** in lieu of Intermediate **H**, Compounds **90B** with DIAD, **8E**, and **1E**. Compound **172A**: LC-MS (ESI) m/z : 460 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.25 (t, $J = 7.6$ Hz, 3H), 1.70-1.75 (m, 1H), 1.94-1.98 (m, 1H), 2.47-2.54 (m, 1H), 2.65-2.69 (m, 1H), 2.75-2.80 (m, 2H), 3.75 (s, 3H), 3.79-3.84 (m, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 5.5 (d, $J = 14.8$ Hz, 2H), 6.66 (q, $J = 2.8$, 8 Hz, 1H), 6.81-6.86 (m, 3H), 7.20 (d, $J = 8.8$ Hz, 2H). Compound **172B**: LC-MS (ESI) m/z : 432 $[M+H]^+$. Compound **172**: LC-MS (ESI) m/z : 312 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 1.84-1.89 (m, 1H), 2.16-2.19 (m, 1H), 2.82-2.85 (m, 3H), 3.21-3.22 (m, 1H), 3.97-3.99 (m, 1H), 7.14-7.19 (m, 2H), 13.24 (s, 1H), 15.60 (s, 1H).

[001090] Example 173

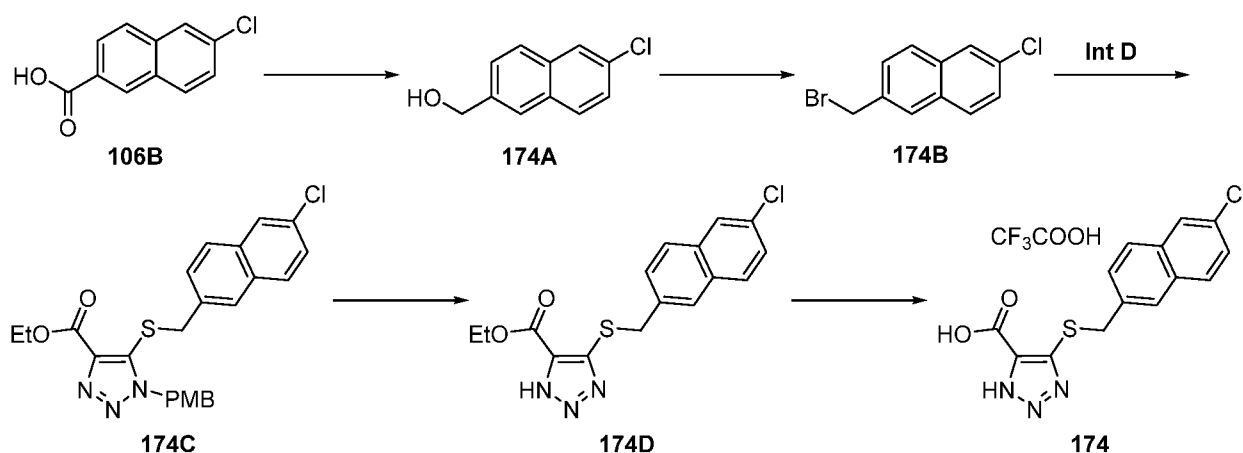
[001091] Synthesis of 4-((5,6-difluoro-2,3-dihydro-1H-inden-2-yl)thio)-1H-1,2,3-triazole-5-carboxylic acid (173)



[001092] Compounds **173B**, **173C**, **173D**, **173E**, **173F**, and **170** were synthesized by employing the procedures described for Compounds **57B**, **57C**, **57D**, **57E**, **8F**, and **1** using Compounds **173A**, **173B**, **173C** with K_3CO_3 as base and DMF as solvent, **173D**, **173E**, and **170F** in lieu of Compounds **57A**, **57B**, **57C** with Na_2CO_3 as base and NMP as solvent, **57D**, **8E**, and **1E**. Compound **173B**: LC-MS (ESI) m/z : 247 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 3.38 (d, J = 18 Hz, 1H), 3.81 (dd, J = 7.6, 18.8 Hz, 1H), 4.66 (dd, J = 3.2, 7.2 Hz, 1H), 7.24-7.28 (m, 1H), 7.61-7.65 (m, 1H). Compound **173C**: LC-MS (ESI) m/z : 231 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 2.47-2.50 (m, 1H), 3.29-3.43 (m, 2H), 4.92-4.93 (m, 2H), 7.04-7.08 (m, 1H), 7.22-7.26 (m, 1H). Compound **173D**: LC-MS (ESI) m/z : 462 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ 1.44 (t, J = 7.2 Hz, 3H), 2.58-2.65 (m, 1H), 3.03-3.09 (m, 1H), 3.43 (d, J = 5.2 Hz, 1H), 3.57-3.63 (m, 1H), 3.78 (s, 3H), 4.47 (q, J = 7.2 Hz, 2H), 4.90-4.93 (m, 1H), 5.64 (s, 2H), 6.84-6.91 (m, 3H), 7.08-7.12 (m, 1H), 7.23-7.25 (m, 2H). Compound **173E**: LC-MS (ESI) m/z : 446 $[M+H]^+$. Compound **173F**: LC-MS (ESI) m/z : 418 $[M+H]^+$. Compound **173**: LC-MS (ESI) m/z : 298 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 2.89-2.94 (m, 2H), 3.45-3.51 (m, 2H), 4.41-4.44 (m, 1H), 7.29-7.34 (m, 2H).

[001093] **Example 174**

[001094] **Synthesis of 4-(((6-chloronaphthalen-2-yl)methyl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (174)**



[001095] To a solution of 6-chloro-2-naphthoic acid (**106B**) (1.00 g, 10.00 mmol) in THF (20 mL) was added LiAlH_4 (295 mg, 2.77 mmol) in several portions. The mixture was stirred at room temperature for 16 hours, quenched with water (0.3 mL), NaOH solution (15% in water, 0.3 mL), and water (0.9 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 0% to 40% v/v) to afford Compound **174A**. LC-MS (ESI) m/z : 175 $[\text{M}-\text{OH}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 4.66 (d, $J = 6.0$ Hz, 2H), 5.35 (t, $J = 6.0$ Hz, 1H), 7.48-7.53 (m, 2H), 7.86-7.89 (m, 2H), 7.94 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 2.4$ Hz, 1H).

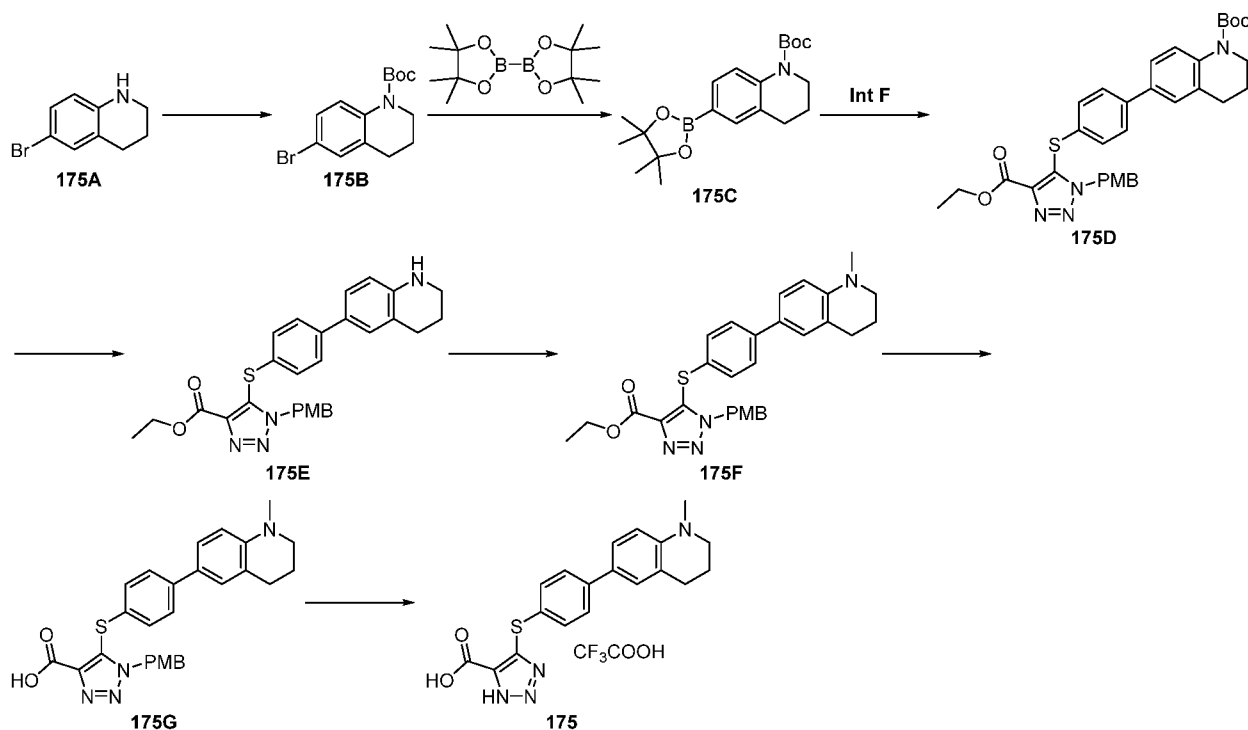
[001096] To a solution of Compound **174A** (190 mg, 0.99 mmol) and PPh_3 (337 mg, 1.29 mmol) in dichloromethane (5 mL) was added NBS (230 mg, 1.29 mmol). The mixture was stirred at room temperature under nitrogen for 16 hours and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (tetrahydrofuran in petroleum ether, from 0% to 20% v/v) to give Compound **174B**. LC-MS (ESI) m/z : non-ionizable compound under routine conditions used; $^1\text{H-NMR}$ CDCl_3 , 400 MHz): δ (ppm) 4.64 (s, 2H), 7.43 (d, $J = 8.8$ Hz, 1H), 7.53 (d, $J = 8.4$ Hz, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.81 (s, 2H).

[001097] Compounds **174C**, **174D**, and **174** were synthesized by employing the procedures described for Compounds **57D**, **1**, and **8F** using Compounds **174B** with K_3CO_3 as base and DMF as solvent, **174C**, and **174D** in lieu of Compounds **57C** with Na_2CO_3 as base and NMP as solvent, **1E**, and **8E**. Compound **174C**: LC-MS (ESI) m/z : 468 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.31 (t, $J = 7.2$ Hz, 3H), 3.68 (s, 3H), 4.27-4.32 (m, 2H), 4.34 (s, 2H), 5.33 (s, 2H), 6.72 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.49-7.52 (m, 2H), 7.82 (d, $J = 8.8$ Hz, 2H), 8.01 (s, 1H). Compound **174D**: LC-MS (ESI) m/z :

348 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.40 (t, J = 7.2 Hz, 3H), 4.39-4.45 (m, 2H), 4.53 (s, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.70-7.73 (m, 2H), 7.79 (s, 1H), 7.83 (s, 1H). Compound **174**: LC-MS (ESI) m/z : 320 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 4.52 (s, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.95 (s, 1H), 8.01 (s, 1H).

[001098] Example 175

[001099] Synthesis of 4-((4-(1-methyl-1,2,3,4-tetrahydroquinolin-6-yl)phenyl)thio)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (175**)**



[001100] To a solution of 6-bromo-1,2,3,4-tetrahydroquinoline (**175A**) (1.3 g, 6.1 mmol) in toluene (20 mL) was added Boc₂O (1.6 g, 7.4 mmol). The reaction mixture was stirred at 110 °C overnight and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to furnish Compound **175B**. LC-MS (ESI) m/z : 255 [M-56]⁺.

[001101] Compounds **175C** and **175D** were synthesized by employing the procedures described for Compounds **27C** and **4B** using Compounds **175B**, Intermediate **F**, and **175C** with K₃PO₄ as base and 1,4-dioxane as solvent in lieu of Compounds **27B** and **4A**, (4-bromophenyl)boronic acid with Na₂CO₃ as base and toluene/EtOH/H₂O as solvent. Compound **175C**: LC-MS (ESI) m/z : 382 [M+Na]⁺. Compound **175D**: LC-MS (ESI) m/z : 601 [M+H]⁺; ¹H-

NMR (CDCl₃, 400 MHz): δ (ppm) 1.33 (t, J = 7.2 Hz, 3H), 1.55 (s, 9H), 1.93-2.00 (m, 2H), 2.80-2.85 (m, 2H), 3.72-3.77 (m, 5H), 4.35-4.40 (m, 2H), 5.55 (d, J = 4.0 Hz, 2H), 6.76 (d, J = 14.4 Hz, 2H), 7.04-7.17 (m, 4H), 7.23 (d, J = 5.6 Hz, 1H), 7.28-7.31 (m, 1H), 7.37-7.40 (m, 2H), 7.74-7.78 (m, 1H).

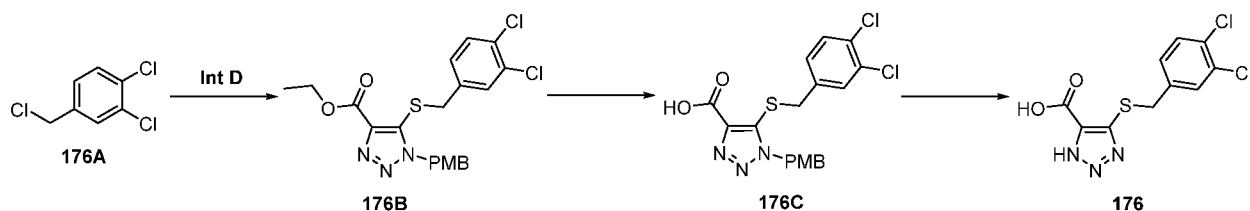
[001102] A mixture of Compound **175D** (560 mg, 0.93 mmol) and TFA (1 mL) in dichloromethane (4 mL) was stirred at 20 °C for 3 hours. The mixture was concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **175E**. LC-MS (ESI) m/z : 501 [M+H]⁺.

[001103] To a mixture of Compound **175E** (300 mg, 0.6 mmol) and (CH₂O)_n (180 mg, 6 mmol) in dichloromethane (10 mL) was added TFA (0.43 mL, 3 mmol) and TES (0.74 mL, 10 mmol) and stirred at room temperature under nitrogen overnight. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 20 % to 30% v/v) to furnish Compound **175F**. LC-MS (ESI) m/z : 515 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.32 (t, J = 7.2 Hz, 3H), 2.12-2.18 (m, 2H), 2.93 (t, J = 6.4 Hz, 2H), 3.11 (s, 3H), 3.46 (t, J = 5.6 Hz, 2H), 3.72 (s, 3H), 4.34-4.39 (m, 2H), 5.57 (s, 2H), 6.75 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.14-7.27 (m, 4H), 7.33-7.37 (m, 3H).

[001104] Compounds **175G** and **175** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **175F** and **175G** in lieu of Compounds **8E** and **1E**. Compound **175G**: LC-MS (ESI) m/z : 487 [M+H]⁺. Compound **175**: LC-MS (ESI) m/z : 367 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.90 (t, J = 6.4 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.87 (s, 3H), 3.23 (t, J = 5.6 Hz, 2H), 6.65 (d, J = 8.8 Hz, 1H), 7.26 (s, 1H), 7.34 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H).

[001105] Example 176

[001106] Synthesis of 4-((3,4-dichlorobenzyl)thio)-1H-1,2,3-triazole-5-carboxylic acid (176)

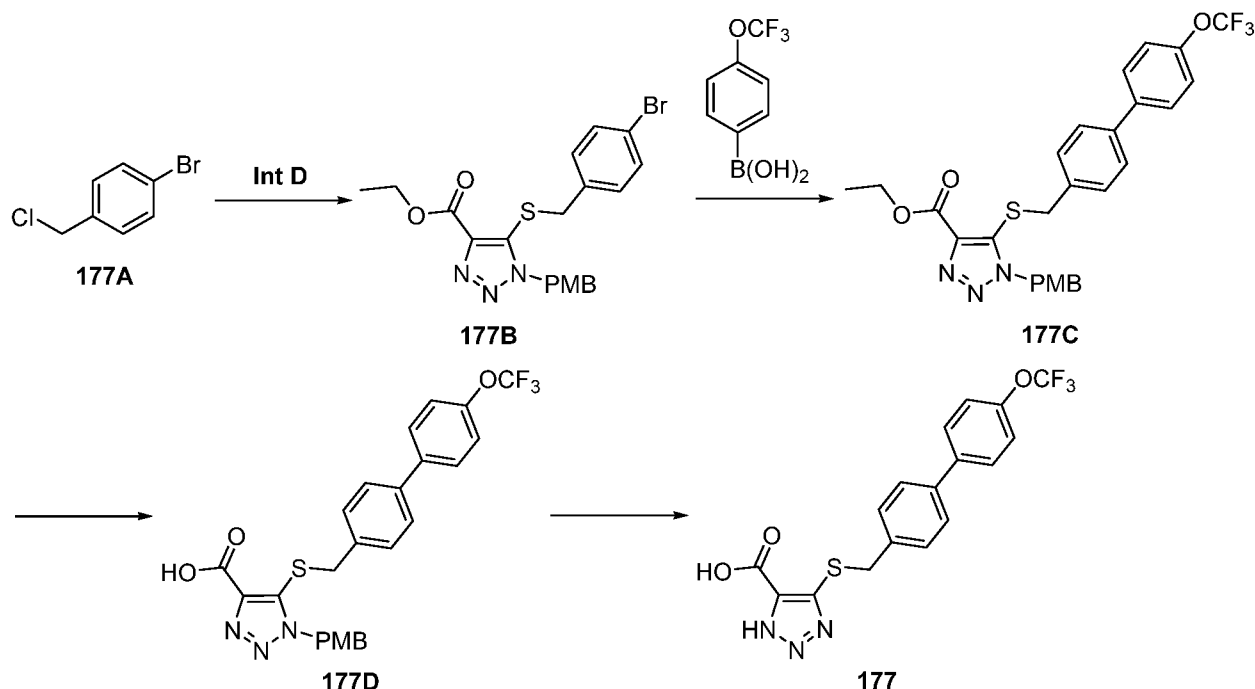


[001107] Compounds **176B**, **176C**, and **176** were synthesized by employing the

procedures described for Compounds **57D**, **8F**, and **57E** using Compounds **176A** with K_3CO_3 as base and DMF as solvent, **176B**, and **176C** in lieu of Compounds **57C** with Na_2CO_3 as base and NMP as solvent, **8E**, and **57D**. Compound **176B**: LC-MS (ESI) m/z : 452 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.47 (t, J = 6.8 Hz, 3H), 3.80 (s, 3H), 4.03 (s, 2H), 4.48 (q, J = 7.2 Hz, 2H), 5.39 (s, 2H), 6.82-6.85 (m, 3H), 7.13-7.27 (m, 4H). Compound **176C**: LC-MS (ESI) m/z : 424 $[M+H]^+$. Compound **176**: LC-MS (ESI) m/z : 304 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 4.34 (s, 2H), 7.39 (dd, J = 8.4, 1.6 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H).

[001108] **Example 177**

[001109] **Synthesis of 4-(((4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)methyl)thio)-1H-1,2,3-triazole-5-carboxylic acid (177)**

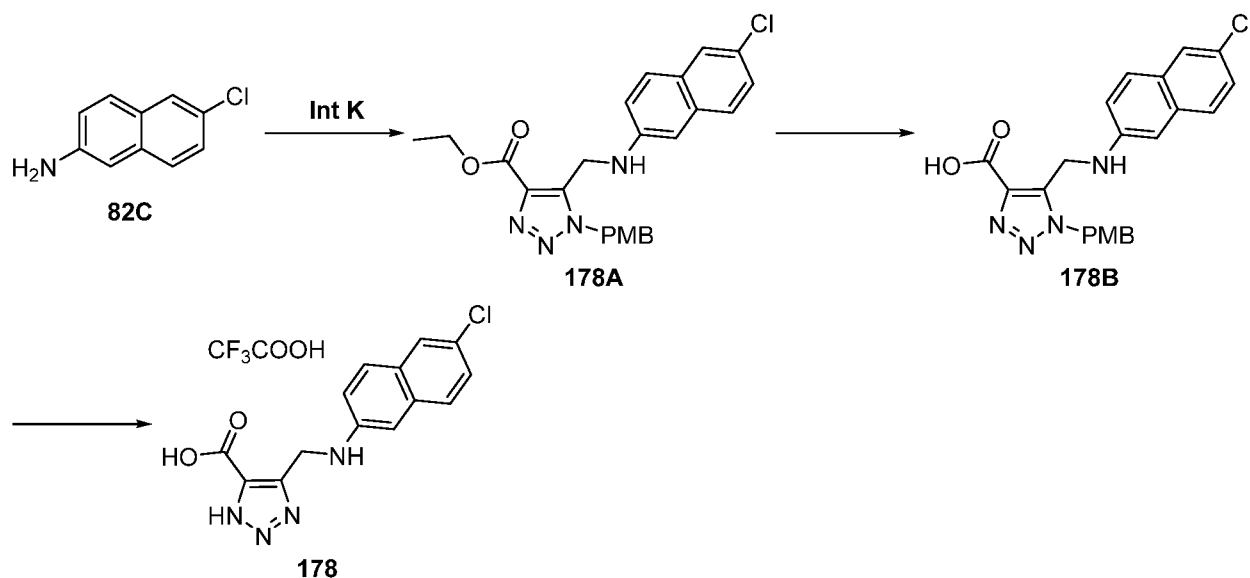


[001110] Compounds **177B**, **177C**, **177D**, and **177** were synthesized by employing the procedures described for Compounds **57D**, **4B**, **8F**, and **57E** using Compounds **177A** with K_3CO_3 as base and DMF as solvent, **177B** with K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **177C**, and **177D** in lieu of Compounds **57C** with Na_2CO_3 as base and NMP as solvent, **4A** with Na_2CO_3 as base and toluene/ $EtOH/H_2O$ as solvent, **8E** and **57D**. Compound **177B**: LC-MS (ESI) m/z : 462 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.46 (t, J = 6.8 Hz, 3H), 3.79 (s, 3H), 4.05 (s, 2H), 4.47 (q, J = 6.8 Hz, 2H), 5.30 (s, 2H), 6.81-6.83 (m, 2H), 6.89-6.92 (m, 2H), 7.11

(d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 6.8$ Hz, 2H). Compound **177C**: LC-MS (ESI) m/z : 544 $[M+H]^+$. Compound **177D**: LC-MS (ESI) m/z : 516 $[M+H]^+$. Compound **177**: LC-MS (ESI) m/z : 396 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 4.38 (s, 2H), 7.42 (dd, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 7.6$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 2H),

[001111] Example 178

[001112] Synthesis of 4-(((6-chloronaphthalen-2-yl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (178**)**



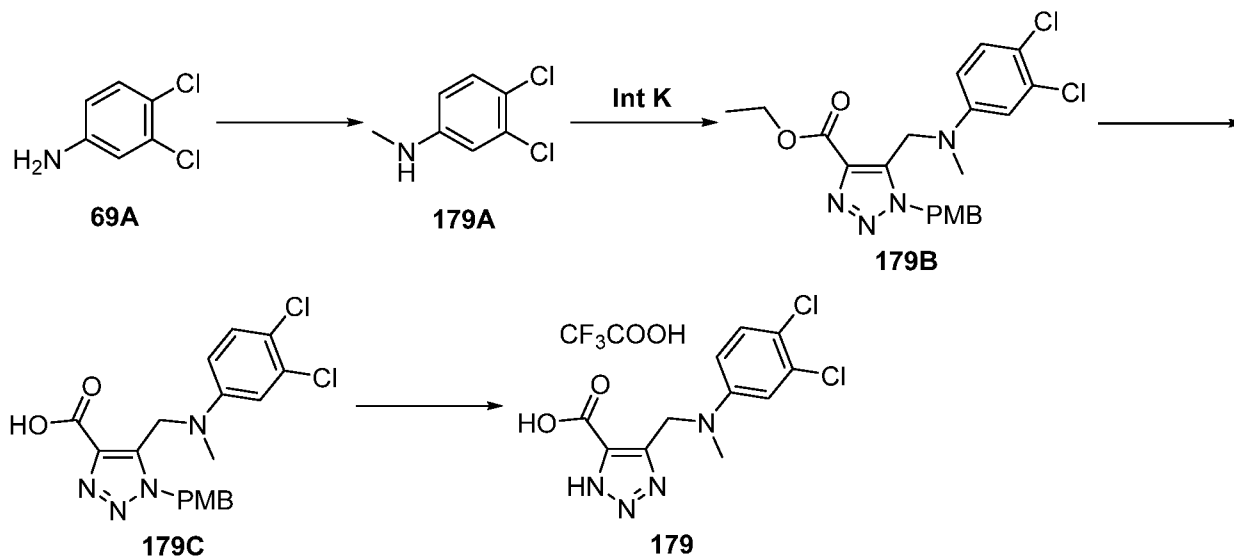
[001113] To a mixture of Intermediate **K** (950 mg, 2.69 mmol) in anhydrous DMF (30 mL) was added K_2CO_3 (557 mg, 4.04 mmol) and Compound **82C** (476 mg, 2.69 mmol). The mixture was stirred at room temperature under nitrogen overnight, diluted with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 40% v/v) to furnish Compound **178A**. LC-MS (ESI) m/z : 451 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.44 (t, $J = 7.2$ Hz, 3H), 3.80 (s, 3H), 4.28-4.32 (m, 1H), 4.48 (q, $J = 7.2$ Hz, 2H), 4.64 (d, $J = 7.2$ Hz, 2H), 5.65 (s, 2H), 6.76-6.86 (m, 4H), 7.14 (d, $J = 8.8$ Hz, 2H), 7.31-7.34 (m, 1H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.67 (s, 1H).

[001114] Compounds **178B** and **178** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **178A** and **178B** in lieu of Compounds **8E** and **1E**. Compound **178B**: LC-MS (ESI) m/z : 423 $[M+H]^+$. Compound **178**: LC-MS (ESI) m/z :

303 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 4.72 (s, 2H), 6.61 (s, 1H), 6.90 (s, 1H), 7.17 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.37 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 13.33 (s, 1H), 15.63 (s, 1H).

[001115] Example 179

[001116] Synthesis of 4-(((3,4-dichlorophenyl)(methyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (179)



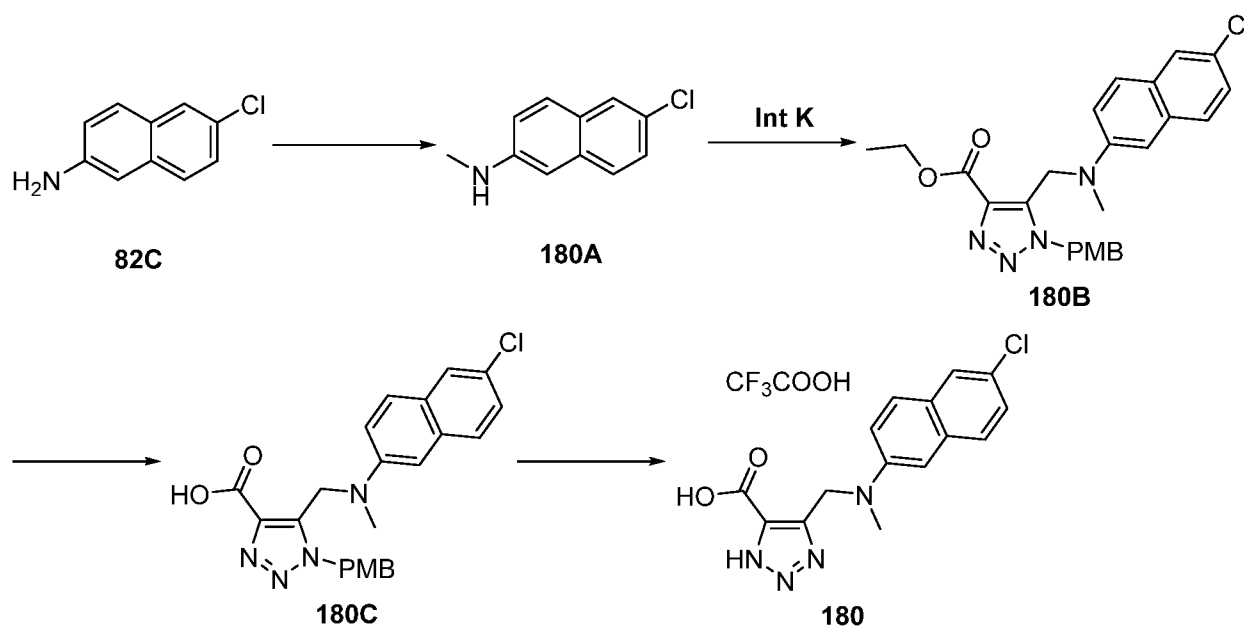
[001117] To a solution of 3,4-dichloroaniline (**69A**) (324 mg, 2.0 mmol) in MeOH (5 mL) was added MeONa (540 mg, 10.0 mmol), paraformaldehyde (120 mg, 4.0 mmol), and Molecular sieves (4 Angstroms, 200 mg). The mixture was stirred at room temperature under nitrogen overnight, and then sodium borohydride (151 mg, 4 mmol) was added. The mixture was heated at reflux for 1 hour, cooled down to room temperature, filtered through Celite, and concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to afford Compound **179A**. LC-MS (ESI) *m/z*: 176 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.82 (s, 3H), 3.80 (s, 1H), 6.44 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.66 (d, *J* = 2.8 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H).

[001118] Compounds **179B**, **179C**, and **179** were synthesized by employing the procedures described for Compounds **178A**, **8F**, and **1** using Compounds **179A**, **179B**, and **179C** in lieu of Compounds **82C**, **8E** and **1E**. Compound **179B**: LC-MS (ESI) *m/z*: 449 [M+H]⁺. Compound **179C**: LC-MS (ESI) *m/z*: 421 [M+H]⁺. Compound **179**: LC-MS (ESI) *m/z*: 301

[M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.05 (s, 3H), 4.86 (s, 2H), 6.74 (s, 1H), 6.96 (s, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 13.38 (s, 1H), 15.38 (s, 1H).

[001119] Example 180

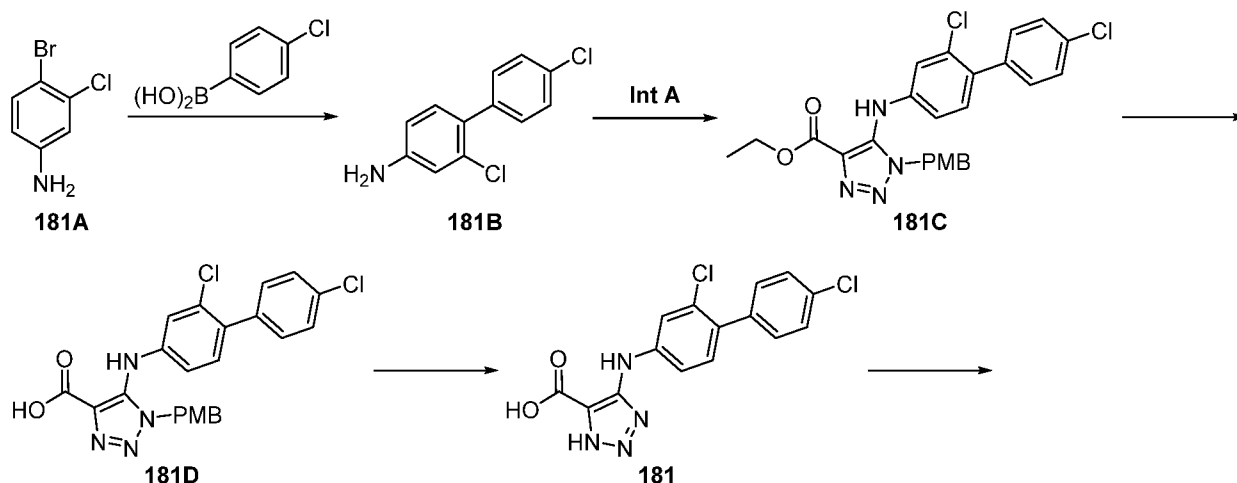
[001120] Synthesis of 4-(((6-chloronaphthalen-2-yl)(methyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (180)



[001121] Compounds 180A, 180B, 180C, and 180 were synthesized by employing the procedures described for Compounds 179A, 178A, 8F, and 1 using Compounds 82C, 180A, 180B, and 180C in lieu of Compounds 69A, 82C, 8E and 1E. Compound 180A: LC-MS (ESI) *m/z*: 192 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.94 (s, 3H), 3.95 (s, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.65 (d, *J* = 2.4 Hz, 1H). Compound 180B: LC-MS (ESI) *m/z*: 465 [M+H]⁺. Compound 180C: LC-MS (ESI) *m/z*: 437 [M+H]⁺. Compound 180: LC-MS (ESI) *m/z*: 317 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 3.14 (s, 3H), 4.97 (s, 2H), 7.03 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.65-7.72 (m, 2H), 7.80 (s, 1H), 13.39 (s, 1H), 15.29 (s, 1H).

[001122] Example 181

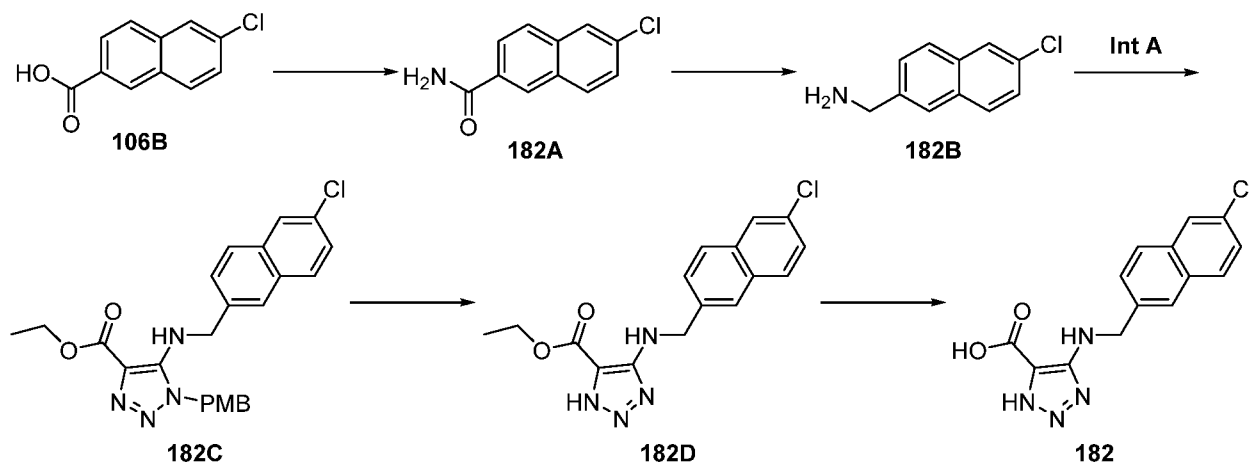
[001123] Synthesis of 4-((2,4'-dichloro-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (181)



[001124] Compounds **181B**, **181C**, **181D**, and **181** were synthesized by employing the procedures described for Compounds **8B**, **6B**, **8F**, and **1** using (4-chlorophenyl)boronic acid, Compounds **181A** with Na_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, Intermediate A, **181B** with K_3PO_4 as base, **181C**, and **181D** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** with Cs_2CO_3 as base and DME/ H_2O as solvent, **6A**, 1-methylpiperazine with $t\text{-BuONa}$ as base, **8E** and **1E**. Compound **181B**: LC-MS (ESI) m/z : 238 $[\text{M}+\text{H}]^+$. Compound **181C**: LC-MS (ESI) m/z : 497 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.05 (t, $J = 14.4$ Hz, 3H), 3.7 (s, 3H), 4.12 (q, $J = 7.2$ Hz, 2H), 5.44 (s, 2H), 6.66-6.63 (m, 1H), 6.70 (d, $J = 2.4$ Hz, 1H), 6.86 (t, $J = 8.8$ Hz, 2H), 7.14 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 1H), 7.39 (q, $J = 1.6$ Hz, 2H), 7.49 (q, $J = 2$ Hz, 2H), 8.8 (s, 1H). Compound **181D**: LC-MS (ESI) m/z : 469 $[\text{M}+\text{H}]^+$. Compound **181**: LC-MS (ESI) m/z : 349 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.33 (d, $J = 8.4$ Hz, 1H), 7.5 (q, $J = 8.4$ Hz, 4H), 7.63 (q, $J = 1.6$ Hz, 1H), 7.94 (s, 1H), 8.46 (s, 1H), 13.44 (s, 1H), 15.01 (s, 1H).

[001125] Example 182

[001126] Synthesis of 4-(((6-chloronaphthalen-2-yl)methyl)amino)-1H-1,2,3-triazole-5-carboxylic acid (182**)**



[001127] Compound **182A** was synthesized by employing the procedure described for Compound **106C** using NH₄Cl with DMF as solvent in lieu of N,O-dimethylhydroxylamine hydrochloride with dichloromethane as solvent, LC-MS (ESI) m/z: 206 [M+H]⁺.

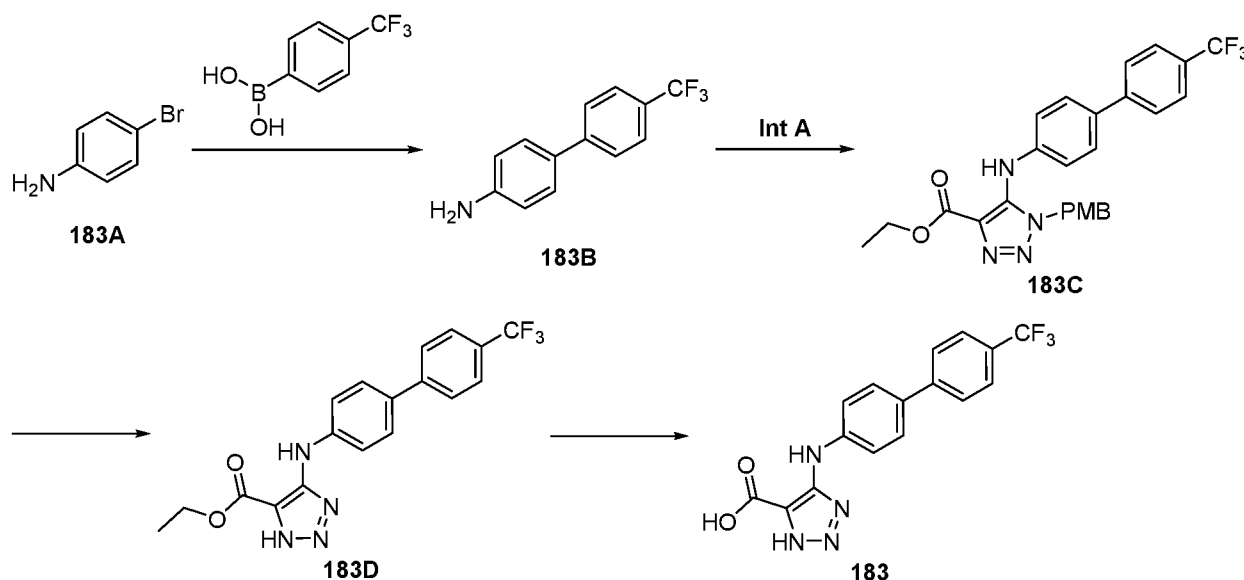
[001128] To a solution of Compound **182A** (2.00 g, 9.75 mmol) in THF (10 mL) at room temperature was dropped a solution of BH₃ in THF (1 M, 49 mL, 48.78 mmol) and stirred at 65 °C for 16 hours. After cooled down to room temperature, the mixture was quenched with water (10 mL) and methanol (10 mL), concentrated under reduced pressure. The residue was purified with reverse phase chromatography using eluent (acetonitrile in water, from 0% to 100% v/v) to afford Compound **182B**. LC-MS (ESI) m/z: 175 [M-NH₂]⁺; ¹H-NMR (CDCl₃, 400 MHz,): δ (ppm) 4.03 (s, 2H), 7.41 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 7.72-7.81 (m, 4H).

[001129] Compounds **182C**, **182D**, and **182** were synthesized by employing the procedures described for Compounds **6B**, **1**, and **8F** using Intermediate **A**, Compounds **182B** with K₃PO₄ as base and DMF as solvent, **182C**, and **182D** in lieu of Compounds **6A**, 1-methylpiperazine with t-BuONa as base and toluene as solvent, **1E** and **8E**. Compound **182C**: LC-MS (ESI) m/z: 451 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz,): δ (ppm) 1.23 (t, J = 7.2 Hz, 3H), 3.72 (s, 3H), 4.20-4.26 (m, 2H), 4.75 (d, J = 6.8 Hz, 2H), 5.43 (s, 2H), 6.86 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.76-7.79 (m, 2H), 7.98(s, 1H). Compound **182D**: LC-MS (ESI) m/z: 331 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz,): δ (ppm) 1.35 (t, J = 7.2 Hz, 3H), 4.39-4.44 (m, 2H), 4.68 (s, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.72-7.80 (m, 4H). Compound **182**: LC-MS (ESI) m/z:

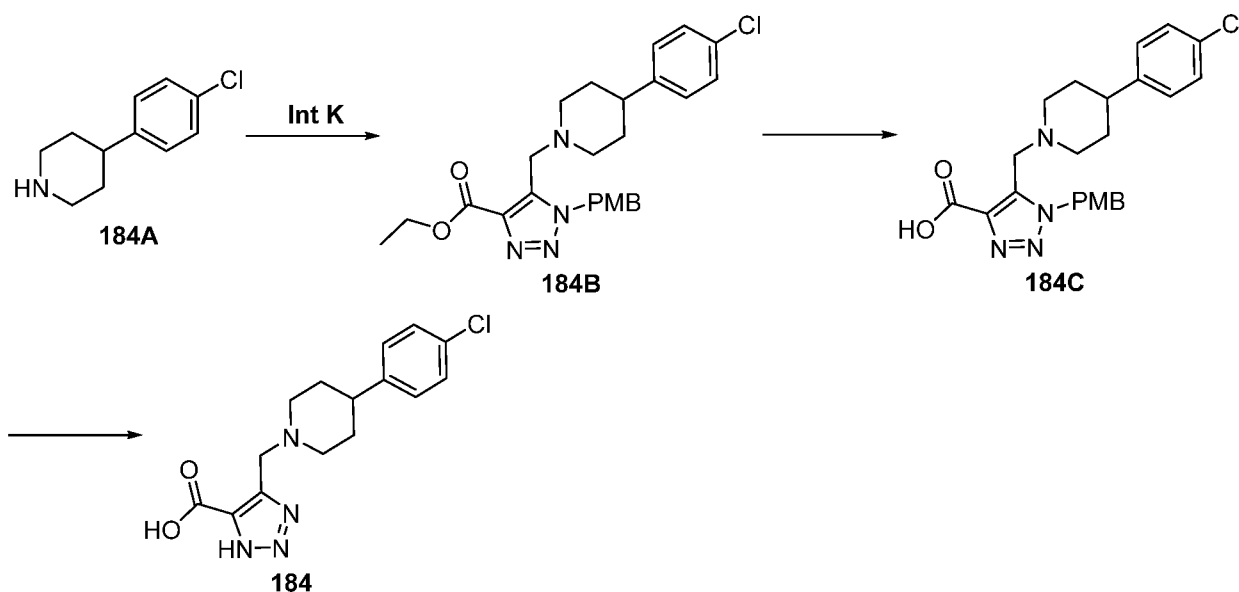
303 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 4.65 (s, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.77-7.85 (m, 4H).

[001130] Example 183

[001131] Synthesis of 4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (183)



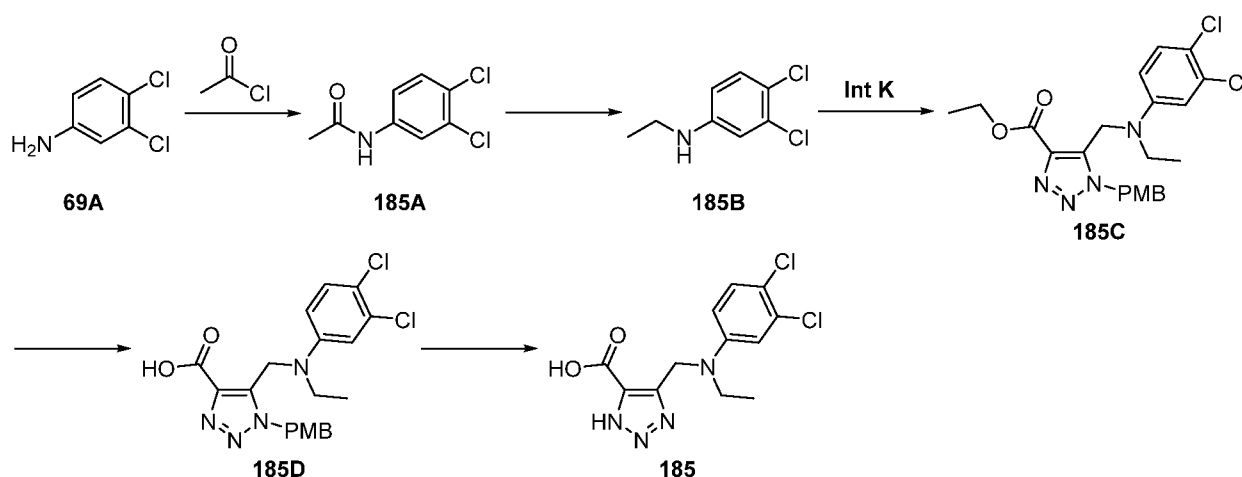
[001132] Compounds **183B**, **183C**, **183D**, and **183** were synthesized by employing the procedures described for Compounds **4B**, **6B**, **1**, and **8F** using (4-(trifluoromethyl)phenyl)boronic acid, Compounds **183A** with K₂CO₃ as base and DMF/H₂O as solvent, Intermediate A, **183B** with K₃PO₄ as base, **183C**, and **183D** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** with Na₂CO₃ as base and toluene/EtOH/H₂O as solvent, **6A**, 1-methylpiperazine with t-BuONa as base, **1E** and **8E**. Compound **183B**: LC-MS: (ESI) m/z : 238 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 6.77-6.79 (m, 2H), 7.43-7.45 (m, 2H), 7.64 (s, 4H). Compound **183C**: LC-MS (ESI) m/z : 497 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.42 (t, J = 7.2 Hz, 3H), 3.76 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 5.24 (s, 2H), 6.74 (J = 8.7 Hz, 2H), 6.86 (J = 8.7 Hz, 2H), 6.92 (J = 8.4 Hz, 2H), 7.18 (s, 1H), 7.55 (J = 8.4 Hz, 2H), 7.67-7.73 (m, 4H). Compound **183D**: LC-MS (ESI) m/z : 377 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.34 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 7.68-7.73 (m, 4H), 7.76 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.2 Hz, 2H), 8.30 (s, 1H). Compound **183**: LC-MS (ESI) m/z : 349 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 7.62-7.68 (m, 4H), 7.73 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H).

[001133] Example 184**[001134] Synthesis of 4-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid (184)**

[001135] Compounds **184B**, **184C**, and **184** were synthesized by employing the procedures described for Compounds **178A**, **8F**, and **1** using Compounds **184A**, **184B**, and **184C** in lieu of Compounds **82C**, **8E** and **1E**. Compound **184B**: LC-MS (ESI) m/z : 469 $[M+H]^+$.

Compound **184C**: LC-MS (ESI) m/z : 441 $[M+H]^+$. Compound **184**: LC-MS (ESI) m/z : 321 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.55-1.70 (m, 4H), 2.13-2.19 (m, 2H), 2.46-2.49 (m, 1H), 2.99-3.02 (m, 2H), 3.86 (s, 2H), 7.23-7.25 (m, 2H), 7.31-7.33 (m, 2H).

[001136] Example 185**[001137] Synthesis of 4-(((3,4-dichlorophenyl)(ethyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid (185)**



[001138] To a solution of 3,4-dichloroaniline (**69A**) (1.62 g, 10.0 mmol) in acetone (100 mL) was added K_2CO_3 (4.14 g, 30.0 mmol) and acetyl chloride (1.18 g, 15.0 mmol). The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **185A**. LC-MS (ESI) m/z : 204 $[\text{M}+\text{H}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 2.20 (s, 3H), 7.33 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 2.4$ Hz, 1H).

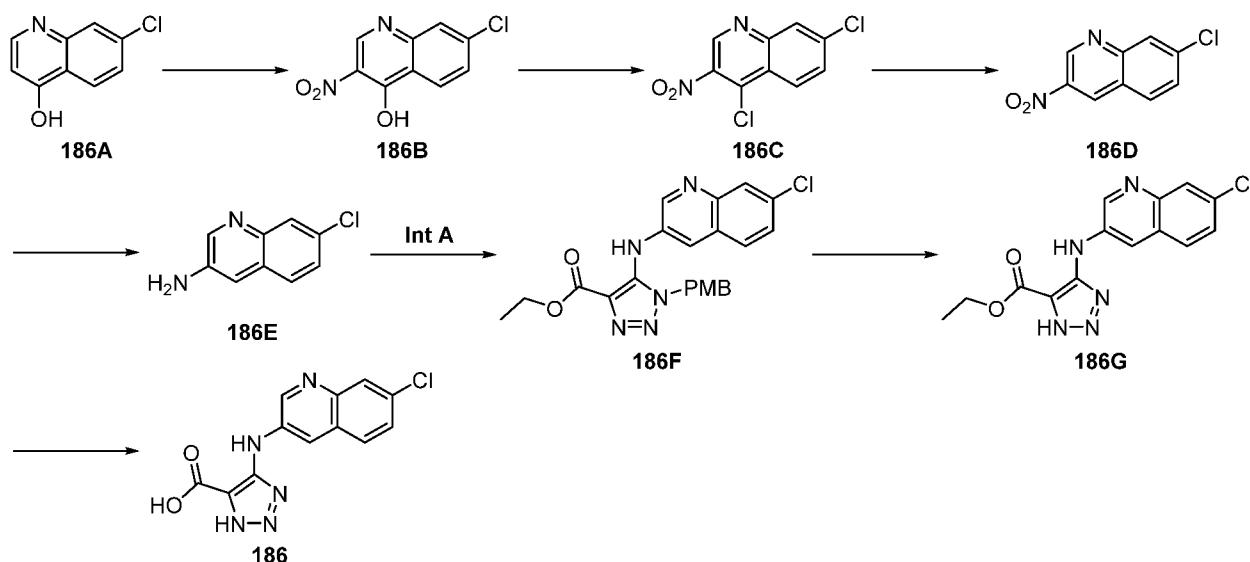
[001139] To a solution of Compound **185A** (612 mg, 3.0 mmol) in anhydrous THF (30 mL) was added LiAlH_4 (456 mg, 12 mmol) and stirred at 30 °C for 3 hours. The reaction mixture was quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ and stirred at room temperature for 30 minutes. The resulting suspension was filtered through Celite and the cake was washed with ethyl acetate (50 mL x 3). The combined filtrates was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 40% v/v) to furnish Compound **185B**. LC-MS (ESI) m/z : 190 $[\text{M}+\text{H}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 1.26 (t, $J = 7.2$ Hz, 3H), 3.12 (q, $J = 7.2$ Hz, 2H), 3.64 (s, 1H), 6.43 (dd, $J = 8.8, 1.8$ Hz, 1H), 6.66 (d, $J = 1.8$ Hz, 1H), 7.18 (d, $J = 8.8$ Hz, 1H).

[001140] Compounds **185C**, **185D**, and **185** were synthesized by employing the procedures described for Compounds **178A**, **8F**, and **1** using Compounds **185B**, **185C**, and **185D** in lieu of Compounds **82C**, **8E** and **1E**. Compound **185C**: LC-MS (ESI) m/z : 463 $[\text{M}+\text{H}]^+$. Compound **185D**: LC-MS (ESI) m/z : 435 $[\text{M}+\text{H}]^+$. Compound **185**: LC-MS (ESI) m/z : 315

$[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.09 (t, $J = 7.2$ Hz, 3H), 3.49 (q, $J = 7.2$ Hz, 2H), 4.79 (s, 2H), 6.67 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 2.8$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H).

[001141] Example 186

[001142] Synthesis of 4-((7-chloroquinolin-3-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid (186)



[001143] To a stirred solution of 7-chloroquinolin-4-ol (**186A**) (5 g, 27.9 mmol) in HOAc (100 mL) was added HNO_3 (63%, 5.41 g, 55.8 mmol) and stirred at 125 °C overnight. After cooled down to room temperature, the mixture was concentrated under reduced pressure, the residue was diluted with EtOH (20 mL), the resulting solid was collected and dried under vacuum to afford Compound **186B**. LC-MS: (ESI) m/z : 225 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 7.53 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.74 (d, $J = 2.0$ Hz, 1H), 8.22 (d, $J = 8.8$ Hz, 1H), 9.23 (s, 1H), 12.99 (s, 1H).

[001144] A mixture of Compound **186B** (5 g, 22.32 mmol) and POCl_3 (50 mL) was stirred at 115 °C overnight. The mixture was evaporated under reduced pressure and the residue was diluted with dichloromethane (50 mL) and washed with brine (30 mL x 2). The organic layer wash dried over anhydrous Na_2SO_4 , filtered and concentrated to give a crude Compound **186C**, which was used directly in next step without further purification. LC-MS (ESI) m/z : 243 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 7.78 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.24 (d, $J = 2.0$ Hz, 1H), 8.39 (d, $J = 8.8$ Hz, 1H), 9.29 (s, 1H).

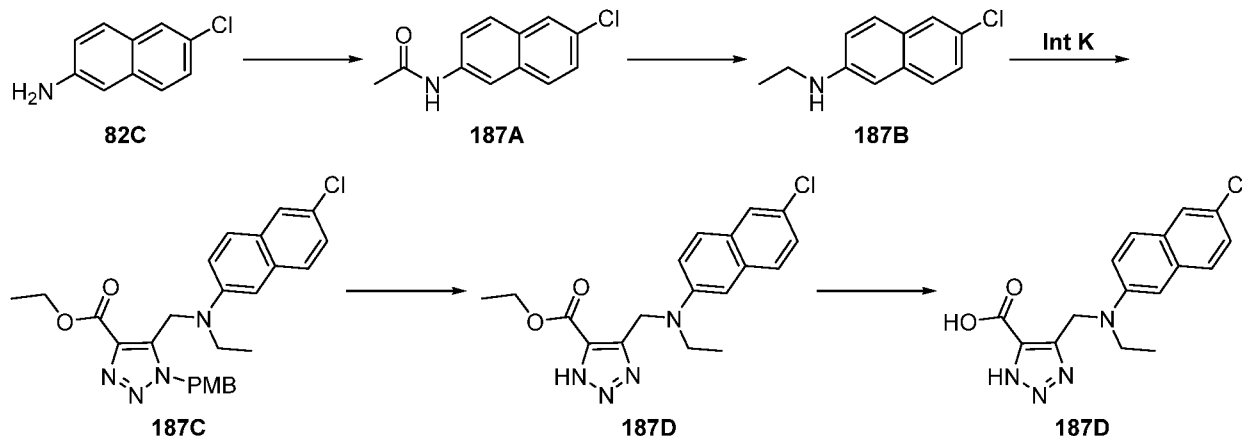
[001145] A solution of Compound **186C** (4 g, 16.5 mmol) and *p*-toluenesulfonylhydrazine (6.1 g, 33 mmol) in CHCl_3 (100 mL) was stirred at room temperature for 24 hours. The mixture was filtered. The solid was washed with cold CHCl_3 and dried under vacuum to afford the hydrazino intermediate as solid. The intermediate was mixed with aqueous NaOH solution (0.5 *N*, 50 mL) and heated at 80 °C for 1 hour. After cooled down to room temperature, the resulting mixture was extracted with dichloromethane (30 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4 , concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 10% v/v) to afford Compound **186D**. LC-MS (ESI) *m/z*: 209 $[\text{M}+\text{H}]^+$; ^1H -NMR (CDCl_3 , 400 MHz): δ (ppm) 7.71 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 8.26 (d, *J* = 2.0 Hz, 1H), 9.04 (d, *J* = 2.4 Hz, 1H), 9.67 (d, *J* = 2.4 Hz, 1H).

[001146] To a solution of Compound **186D** (200 mg, 0.96 mmol) in MeOH (10 mL) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.25 g, 4.8 mmol) and stirred at 100 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 50% v/v) to leave a crude product, which was further purified with reverse phase chromatography using eluent (acetonitrile in water, from 0% to 20% v/v) afford Compound **186E**. LC-MS (ESI) *m/z*: 179 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.28 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.70-7.73 (m, 1H), 7.82 (s, 1H), 8.50 (s, 1H).

[001147] Compounds **186F**, **186G**, and **186** were synthesized by employing the procedures described for Compounds **6B**, **1**, and **8F** using Intermediate **A**, Compounds **186E** with as Cs_2CO_3 base and DMF as solvent at 150 °C in a microwave reactor, **186F**, and **186G** in lieu of Compounds **6A**, 1-methylpiperazine with as *t*-BuONa base and toluene as solvent at 120 °C, **1E** and **8E**. Compound **186F**: LC-MS (ESI) *m/z*: 438 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 0.87 (t, *J* = 7.2 Hz, 3H), 3.60 (s, 3H), 4.01 (q, *J* = 7.2 Hz, 2H), 5.48 (s, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 2.6 Hz, 1H), 7.46-7.49 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 2.6 Hz, 1H), 9.13 (s, 1H). Compound **186G**: LC-MS (ESI) *m/z*: 318 $[\text{M}+\text{H}]^+$. Compound **186**: LC-MS (ESI) *m/z*: 290 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.50 (d, *J* = 8.8 Hz, 1H), 7.87-7.90 (m, 2H), 8.63 (s, 1H), 8.87 (s, 1H), 9.74 (s, 1H).

[001148] **Example 187**

[001149] Synthesis of 4-(((6-chloronaphthalen-2-yl)(ethyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid (187)



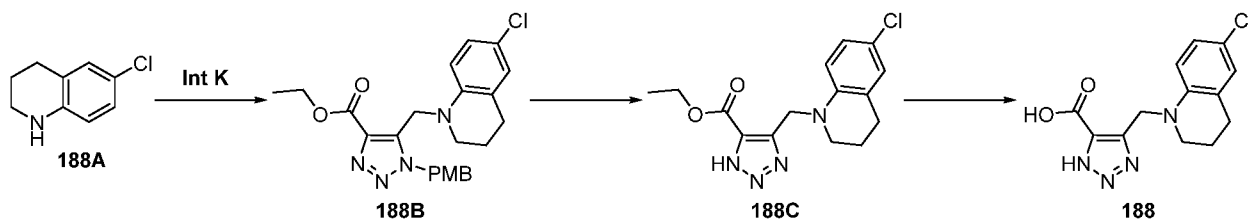
[001150] To a solution of 6-chloronaphthalen-2-amine (**82C**) (1.00 g, 4.69 mmol) and Et₃N (1.18 g, 11.73 mmol) in THF (10 mL) was dropped neat AcCl (439 mg, 5.63 mmol) at room temperature. The mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate (160 mL), washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (tetrahydrofuran in petroleum ether, from 0% to 80% v/v) to afford Compound **187A**. MS (ESI) *m/z*: 220 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 2.10 (s, 3H), 7.43-7.47 (m, 1H), 7.59-7.62 (m, 1H), 7.83-7.86 (m, 2H), 7.94 (s, 1H), 8.32 (s, 1H), 10.20 (s, 1H).

[001151] Compounds **187B**, **187C**, **187D**, and **187** were synthesized by employing the procedures described for Compounds **182B**, **178A**, **1**, and **8F** using Compounds **187A**, **187B**, **187C**, and **187D** in lieu of Compounds **182A**, **82C**, **1E**, and **8E**. Compound **187B**: LC-MS (ESI) *m/z*: 206 [M+H]⁺; ¹H-NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 1.22 (t, *J* = 7.6 Hz, 3H), 3.08-3.15 (m, 2H), 5.99 (t, *J* = 5.2 Hz, 1H), 6.70 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.55-7.60 (m, 2H), 7.70 (s, 1H). Compound **187C**: LC-MS (ESI) *m/z*: 479 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 0.96 (t, *J* = 7.2 Hz, 3H), 1.46 (t, *J* = 7.2 Hz, 3H), 3.18 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 4.73 (s, 2H), 5.53 (s, 2H), 6.68-6.71 (m, 2H), 6.85-6.89 (m, 2H), 7.00 (s, 1H), 7.14-7.18 (m, 1H), 7.33-7.36 (m, 1H), 7.50-7.54 (m, 2H), 7.71 (s, 1H). Compound **187D**: LC-MS (ESI) *m/z*: 359 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 1.24 (t, *J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 3.68 (q, *J* = 7.2 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 5.13 (s, 2H), 7.28-7.46 (m, 2H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.68-7.77 (m, 3H). Compound **187**: LC-MS (ESI) *m/z*: 331 [M+H]⁺; ¹H-NMR (CD₃OD, 400 MHz): δ (ppm) 1.25 (t,

$J = 7.2$ Hz, 3H), 3.69 (q, $J = 7.2$ Hz, 2H), 4.96 (s, 2H), 7.05 (d, $J = 2.4$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 1H), 7.28 (d, $J = 8.8$ Hz, 1H), 7.55-7.62 (m, 3H).

[001152] Example 188

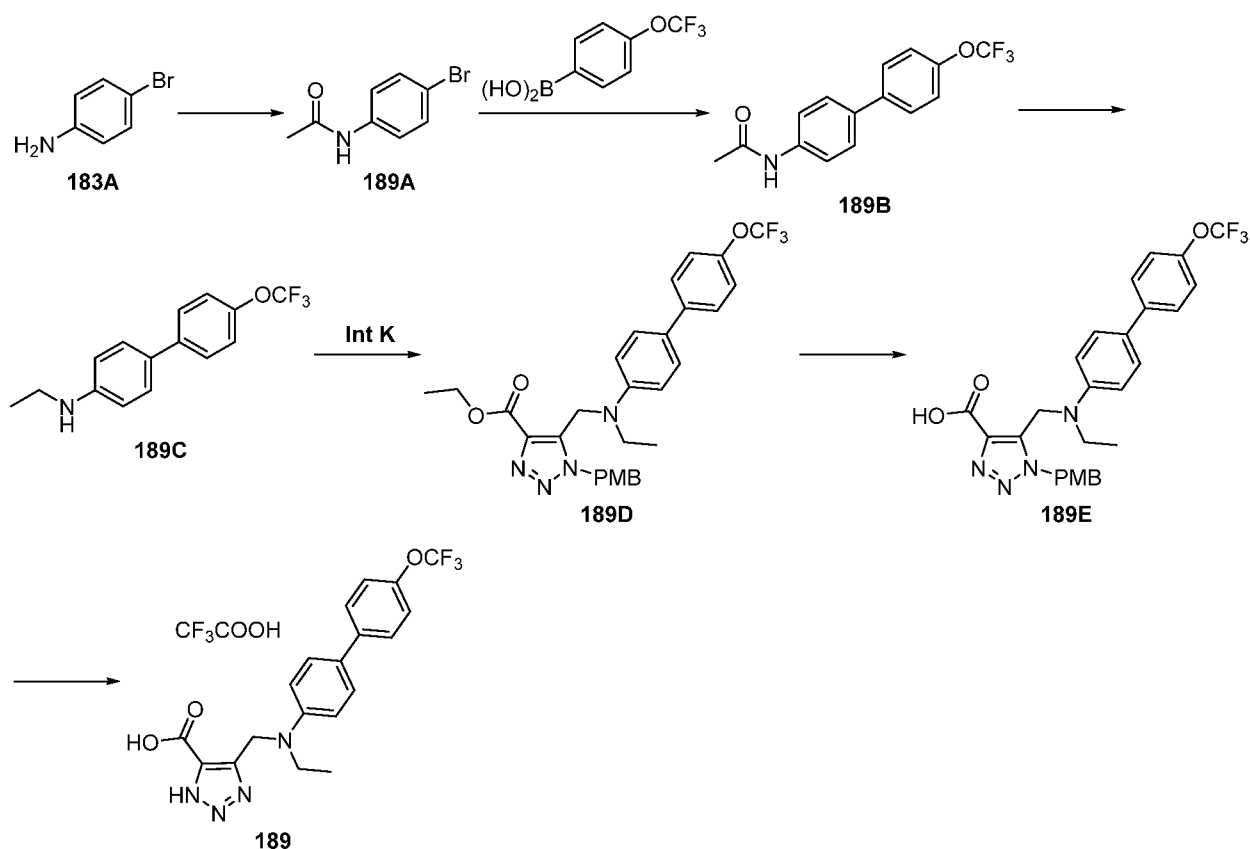
[001153] Synthesis of 4-((6-chloro-3,4-dihydroquinolin-1(2H)-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid (188)



[001154] Compounds **188B**, **188C**, and **188** were synthesized by employing the procedures described for Compounds **178A**, **1**, and **8F** using Compounds **188A**, **188B**, and **188C** in lieu of Compounds **82C**, **1E**, and **8E**. Compound **188B**: LC-MS (ESI) m/z : 441 $[M+H]^+$. Compound **188C**: LC-MS (ESI) m/z : 321 $[M+H]^+$. Compound **188**: LC-MS (ESI) m/z : 293 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): δ (ppm) 1.87-1.88 (m, 2H), 2.67-2.68 (m, 2H), 3.34-3.41 (m, 2H), 4.73 (m, 2H), 6.54 (brs, 1H), 6.87-6.91 (m, 2H).

[001155] Example 189

[001156] Synthesis of 4-((ethyl(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (189)

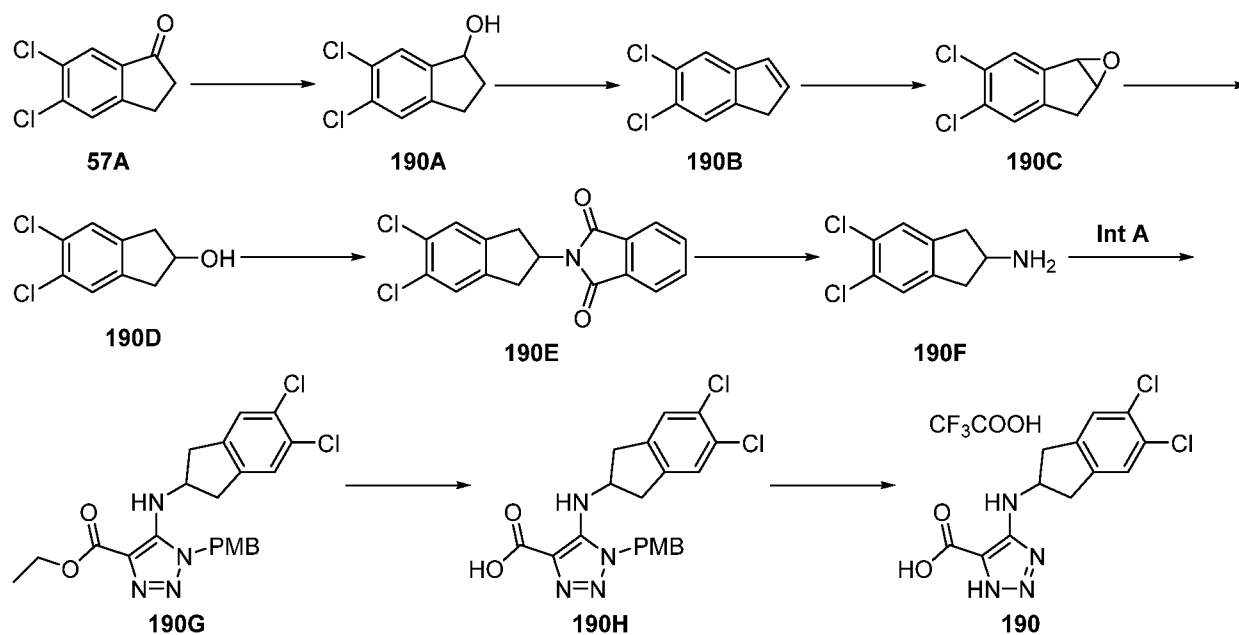


[001157] Compounds **189A**, **189B**, **189C**, **189D**, **189E**, and **189** were synthesized by employing the procedures described for Compounds **185A**, **4B**, **185B**, **178A**, **8F**, and **1** using Compounds **183A**, (4-(trifluoromethoxy)phenyl)boronic acid, **189A** with K_2CO_3 as base and as 1,4-dioxane/ H_2O solvent, **189B**, **189C**, **189D**, and **189E** in lieu of Compounds **69A**, (4-bromophenyl)boronic acid, **4A** with Na_2CO_3 as base and as toluene/ $EtOH/H_2O$ solvent, **185A**, **82C**, **8E**, and **1E**. Compound **189A**: LC-MS (ESI) m/z : 214 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.18 (s, 3H), 7.24 (s, 1H), 7.39-7.45 (m, 4H). Compound **189B**: LC-MS (ESI) m/z : 296 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.21 (s, 3H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.37 (s, 1H), 7.52 (d, $J = 8.1$ Hz, 2H), 7.56-7.61 (m, 4H). Compound **189C**: LC-MS (ESI) m/z : 282 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.30 (t, $J = 7.2$ Hz, 3H), 3.21 (q, $J = 7.2$ Hz, 2H), 3.69 (s, 1H), 6.68 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H). Compound **189D**: LC-MS (ESI) m/z : 555 $[M+H]^+$. Compound **189E**: LC-MS (ESI) m/z : 527 $[M+H]^+$. Compound **189**: LC-MS (ESI) m/z : 407 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.13 (t, $J = 7.2$ Hz, 3H), 3.57 (q, $J = 7.2$ Hz, 2H), 4.87 (s, 2H),

6.88 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H).

[001158] Example 190

[001159] Synthesis of 4-((5,6-dichloro-2,3-dihydro-1H-inden-2-yl)amino)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (190)



[001160] Compound **190A** was synthesized by employing the procedure described for Compound **57C** using Compound **57A** and EtOH as solvent in lieu of Compound **57B** and MeOH as solvent, LC-MS (ESI) m/z : 185 $[M-OH]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.93-2.00 (m, 1H), 2.49-2.57 (m, 1H), 2.75-2.83 (m, 1H), 2.98-3.05 (m, 1H), 5.21 (t, $J = 6.0$ Hz, 1H), 7.34 (s, 1H), 7.48 (s, 1H).

[001161] To a mixture of Compound **190A** (4.3 g, 21.3 mmol) in toluene (100 mL) was added $MgSO_4$ (5.11 g, 42.6 mmol) and p -TsOH (366 mg, 2.13 mmol). The mixture was heated at reflux for 2 hours. After cooled down to room temperature, the mixture was filtered, diluted with water (50 mL), and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 , concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 5% v/v) to give Compound **190B**. LC-MS (ESI) m/z : 185 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.39-3.40 (m, 2H), 6.62 (d, $J = 8.8$ Hz, 1H), 6.80 (d, $J = 8.8$ Hz, 1H), 7.46 (s, 1H), 7.53 (s, 1H).

[001162] To a mixture of Compound **190B** (1.0 g, 5.43 mmol) in dichloromethane (60 mL) was added *m*-CPBA (1.40 g, 8.15 mmol) and NaHCO₃ (685 mg, 8.15 mmol). The resulting mixture was stirred at room temperature under nitrogen for 16 hours, quenched with water (100 mL), and extracted with dichloromethane (50 mL x 3). The combined organic layers was washed with water (200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to give Compound **190C**. LC-MS (ESI) *m/z*: 201 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.95 (dd, *J* = 18, 2.8 Hz, 1H), 3.18 (d, *J* = 18 Hz, 1H), 4.15 (t, *J* = 2.8 Hz, 1H), 4.22 (t, *J* = 2.8 Hz, 1H), 7.32 (s, 1H), 7.57 (s, 1H).

[001163] To a solution of Compound **190C** (400 mg, 2 mmol) in 1,4-dioxane (100 mL) was added InCl₃ (443 mg, 2 mmol) and stirred at 60 °C for 2 hours, followed by addition of NaCNBH₃ (378 mg, 6 mmol). The mixture was heated at reflux for 2 hours. After cooled down to room temperature, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to give Compound **190D**. LC-MS (ESI) *m/z*: 185 [M-OH]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.89 (dd, *J* = 18, 2.8 Hz, 2H), 3.17 (dd, *J* = 18, 2.8 Hz, 2H), 4.72-4.76 (m, 1H), 7.32 (s, 2H).

[001164] Compound **190E** was synthesized by employing the procedure described for Compound **90C** using O-phthalimide and Compound **190D** with DEAD in lieu of Intermediate **H** and Compound **90B** with DIAD, LC-MS (ESI) *m/z*: 332 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 3.15-3.22 (m, 2H), 3.53-3.59 (m, 2H), 5.13-5.22 (m, 1H), 7.32 (s, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H).

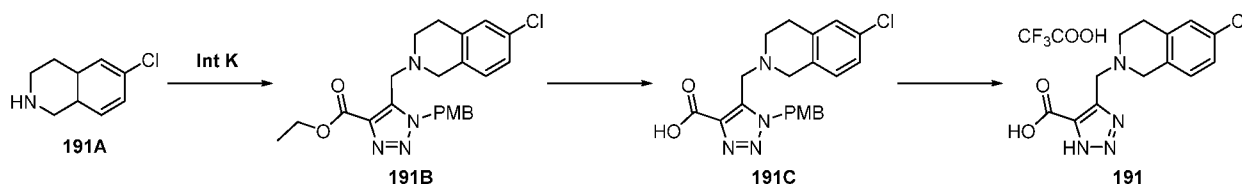
[001165] To a mixture of Compound **190E** (570 mg, 1.72 mmol) in methanol (50 mL) was added 85% N₂H₄ (5 mL), stirred at reflux for 16 hours, and concentrated under reduced pressure. The residue was purified with reverse phase chromatography using eluent (methanol in water (include 0.5% NH₄HCO₃), 80% v/v) to furnish Compound **190F**. LC-MS (ESI) *m/z*: 202 [M+H]⁺.

[001166] Compounds **190G**, **190H**, and **190** were synthesized by employing the procedures described for Compounds **6B**, **8F**, and **1** using Intermediate **A**, Compounds **190F** with *t*-BuONa as base and DMF as solvent, **190G**, and **190H** in lieu of Compounds **6A**, 1-

methylpiperazine with K_3PO_4 as base and toluene as solvent, **8E**, and **1E**. Compound **190G**: LC-MS (ESI) m/z : 461 $[M+H]^+$. Compound **190H**: LC-MS (ESI) m/z : 433 $[M+H]^+$. Compound **190**: LC-MS (ESI) m/z : 313 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 2.91-2.97 (m, 2H), 3.23-3.29 (m, 2H), 4.37 (s, 1H), 5.36 (s, 1H), 7.51 (s, 2H).

[001167] Example 191

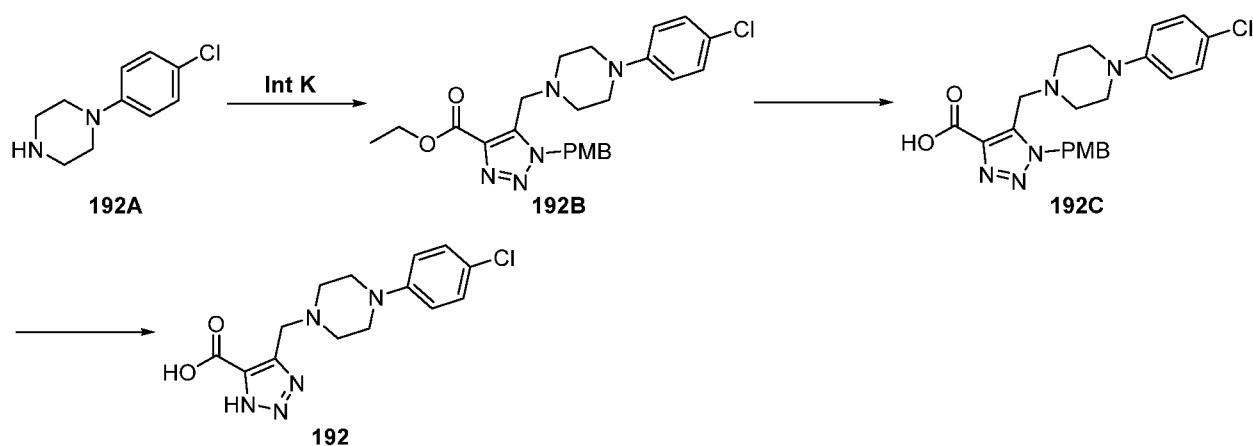
[001168] Synthesis of 4-((6-chloro-3,4-dihydroisoquinolin-2(1H)-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (191)



[001169] Compounds **191B**, **191C**, and **191** were synthesized by employing the procedures described for Compounds **178A**, **8F**, and **1** using Compounds **191A**, **191B**, and **191C** in lieu of Compounds **82C**, **8E**, and **1E**. Compound **191B**: LC-MS (ESI) m/z : 441 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.42 (t, $J = 7.2$ Hz, 3H), 2.67-2.70 (m, 2H), 2.82-2.85 (m, 2H), 3.50 (s, 2H), 3.77 (s, 3H), 3.91 (s, 2H), 4.45 (q, $J = 7.2$ Hz, 2H), 5.69 (s, 2H), 6.78-6.80 (m, 2H), 6.88-6.90 (m, 1H), 7.09-7.13 (m, 4H). Compound **191C**: LC-MS (ESI) m/z : 413 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 2.60-2.61 (m, 2H), 2.68-2.69 (m, 2H), 3.49 (s, 2H), 3.66 (s, 3H), 4.05 (s, 2H), 5.51 (s, 2H), 6.76 (d, $J = 8.6$ Hz, 2H), 6.97 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 4H). Compound **191**: LC-MS (ESI) m/z : 293 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.05-3.08 (m, 2H), 3.49 (s, 2H), 4.37 (s, 2H), 4.64 (s, 2H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

[001170] Example 192

[001171] Synthesis of 4-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid (192)

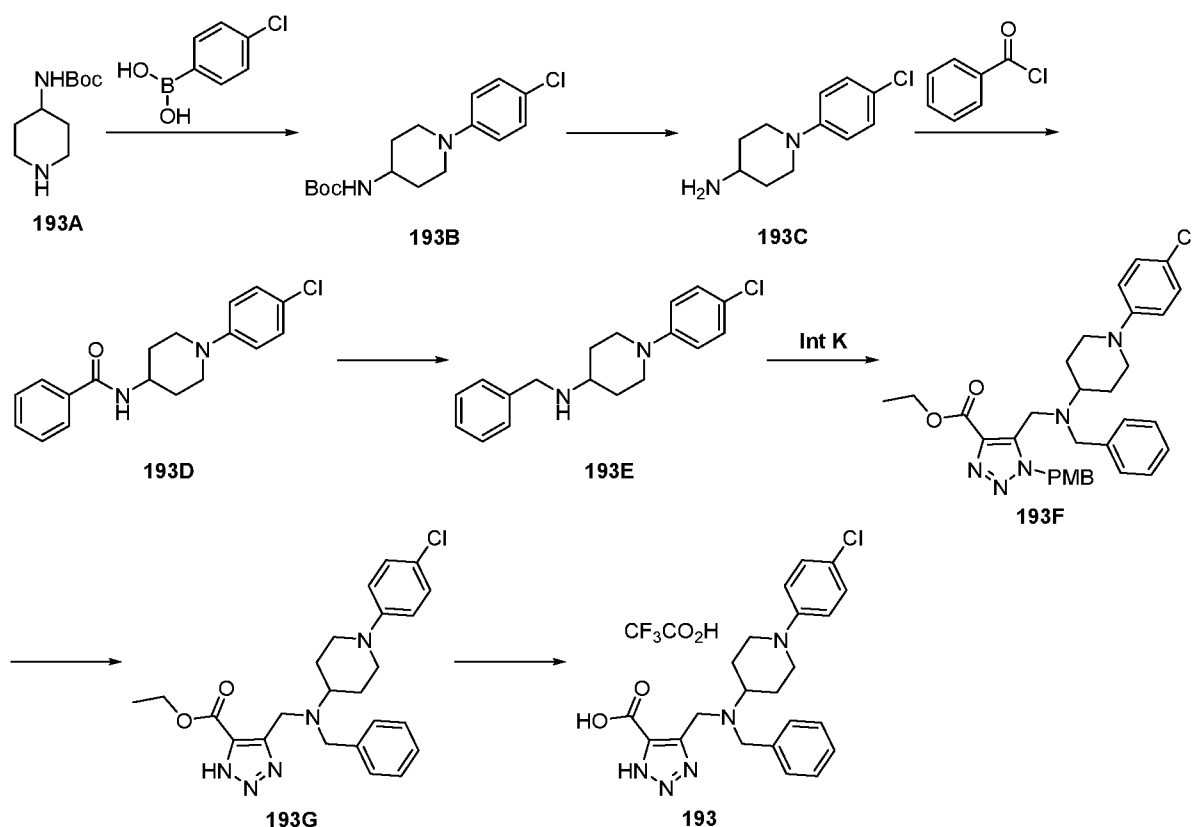


[001172] Compounds **192B**, **192C**, and **192** were synthesized by employing the procedures described for Compounds **178A**, **8F**, and **1** using Compounds **192A**, **192B**, and **192C** in lieu of Compounds **82C**, **8E**, and **1E**. Compound **192B**: LC-MS (m/z): 470 $[M+H]^+$.

Compound **192C**: LC-MS (m/z): 442 $[M+H]^+$. Compound **192**: LC-MS (m/z): 322 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 3.36-3.82 (m, 8H), 4.78 (s, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H).

[001173] **Example 193**

[001174] **Synthesis of 4-((benzyl(1-(4-chlorophenyl)piperidin-4-yl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (193)**



[001175] Compounds **193B** and **193C** were synthesized by employing the procedures described for Compounds **70B** and **175E** using (4-chlorophenyl)boronic acid, Compounds **193A** with pyridine as base, and **192B** in lieu of (4-(trifluoromethoxy)phenyl)boronic acid, Compounds **70A** with K_3PO_4 as base, and **175D**. Compound **193B**: LC-MS (ESI) m/z : 311 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.46 (s, 9H), 1.49-1.55 (m, 2H), 2.03-2.07 (m, 2H), 2.79-2.86 (m, 2H), 3.54-3.61 (m, 3H), 4.48-4.49 (m, 1H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 8.8$ Hz, 2H). Compound **193C**: LC-MS (ESI) m/z : 211 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.47-1.55 (m, 4H), 1.90-1.94 (m, 2H), 2.74-2.80 (m, 3H), 3.58-3.62 (m, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.19 (d, $J = 8.8$ Hz, 2H).

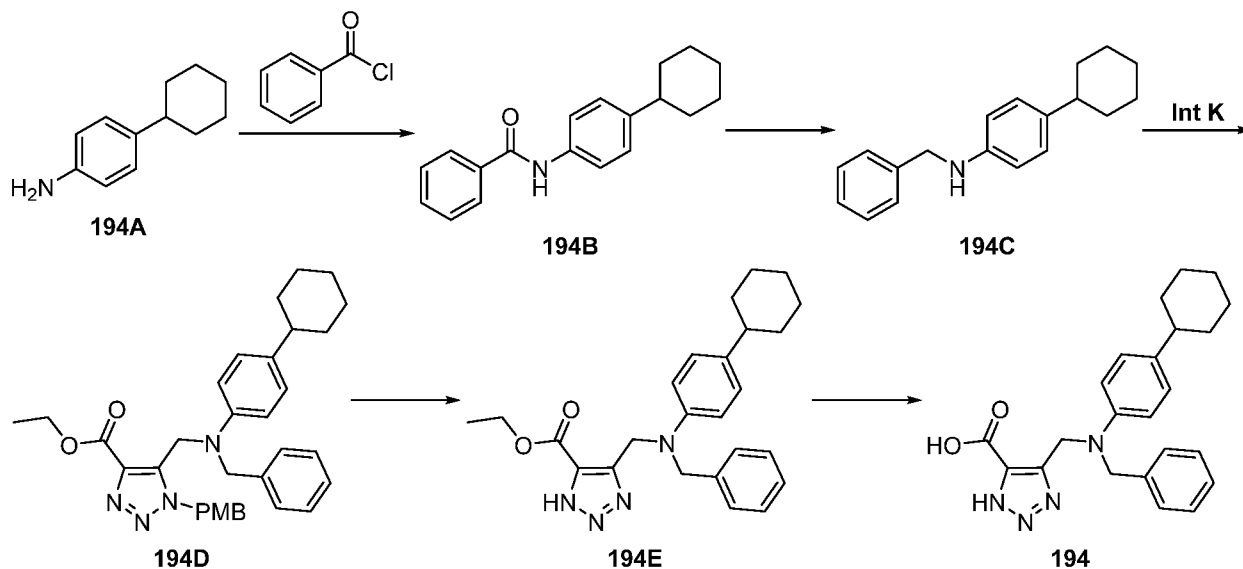
[001176] A mixture of Compound **193C** (278 mg, 1.32 mmol), benzoyl chloride (228 mg, 1.62 mmol), DMAP (36 mg, 0.294 mmol) and triethylamine (297 mg, 2.94 mmol) in dichloromethane (30 mL) was stirred at room temperature for 4 hours. The mixture was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 , concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 20% v/v) to give compound **193D**. LC-MS (ESI) m/z : 315 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz): δ (ppm) 1.73-1.83 (m, 2H), 2.03-2.06 (m, 2H), 2.83-2.89 (m, 2H), 3.71-3.75 (m, 2H), 4.03-4.07 (m, 1H),

6.96-7.01 (m, 2H), 7.20 (d, $J = 8.8$ Hz, 2H), 7.44-7.48 (m, 2H), 7.51-7.56 (m, 1H), 7.83 (m, $J = 7.6$ Hz, 2H).

[001177] Compounds **193E**, **193F**, **193G**, and **193** were synthesized by employing the procedures described for Compounds **182B**, **178A**, **1**, and **8F** using Compounds **193D**, **193E**, **193F**, and **192G** in lieu of Compounds **182A**, **82C**, **1E**, and **8E**. Compound **193E**: LC-MS (ESI) m/z : 301 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.59-1.62 (m, 2H), 2.02-2.05 (m, 2H), 2.69-2.78 (m, 3H), 3.59-3.63 (m, 2H), 3.88 (s, 2H), 6.85 (d, $J = 9.2$ Hz, 2H), 7.17-7.20 (m, 2H), 7.28-7.39 (m, 5H). Compound **193F**: LC-MS (ESI) m/z : 574 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.24 (t, $J = 7.2$ Hz, 3H), 1.71-1.81 (m, 2H), 1.94-1.97 (m, 2H), 2.64-2.70 (m, 2H), 2.84-2.90 (m, 1H), 3.65-3.68 (m, 2H), 3.78 (s, 3H), 3.80 (s, 2H), 4.05 (s, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 5.76 (s, 2H), 6.80-6.85 (m, 4H), 7.14-7.27 (m, 9H). Compound **193G**: LC-MS (ESI) m/z : 454 $[M+H]^+$. Compound **193**: LC-MS (ESI) m/z : 426 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 2.07-2.17 (m, 2H), 2.26-2.29 (m, 2H), 2.75-2.81 (m, 2H), 3.61-3.67 (m, 1H), 3.85-3.89 (m, 2H), 4.57 (s, 2H), 4.78 (s, 2H), 6.98 (d, $J = 9.2$ Hz, 2H), 7.20-7.24 (m, 2H), 7.41-7.52 (m, 5H).

[001178] Example 194

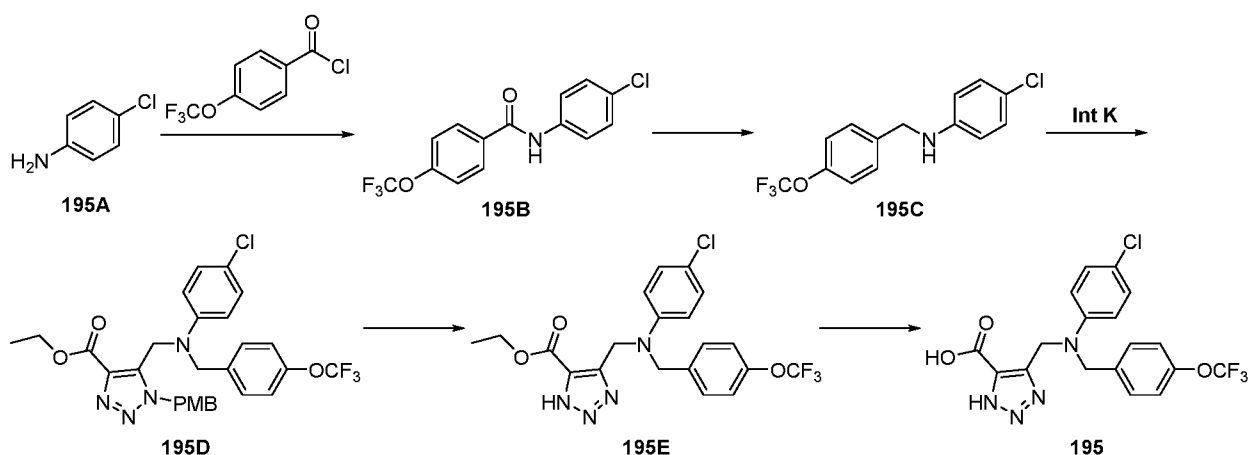
[001179] Synthesis of 4-((benzyl(4-cyclohexylphenyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid (194)



[001180] Compounds **194B**, **194C**, **194D**, **194E**, and **194** were synthesized by employing the procedures described for Compounds **193D**, **182B**, **178A**, **1**, and **2** using Compounds **194A** with THF as solvent and without DMAP, **194B**, **194C**, **194D**, and **194E** in lieu of Compounds **193C** with THF as solvent and with DMAP, **182A**, **82C**, **1E**, and **1**. Compound **194B**: LC-MS (ESI) m/z : 280 $[M+H]^+$. Compound **194C**: LC-MS (ESI) m/z : 266 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.16-1.38 (m, 5H), 1.69-1.84 (m, 5H), 2.36-2.37 (m, 1H), 3.90 (s, 1H), 4.30 (s, 2H), 6.58 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H), 7.26-7.38 (m, 5H). Compound **194D**: LC-MS (ESI) m/z : 539 $[M+H]^+$. Compound **194E**: LC-MS (ESI) m/z : 419 $[M+H]^+$. Compound **194**: LC-MS (ESI) m/z : 391 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 400 MHz): 1.17-1.27 (m, 5H), 1.63-1.71 (m, 5H), 2.28-2.30 (m, 1H), 4.68 (s, 2H), 4.89 (s, 2H), 6.58 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 8.0$ Hz, 2H), 7.21-7.32 (m, 5H), 13.45 (brs, 1H), 15.38 (brs, 1H).

[001181] Example 195

[001182] Synthesis of 4-(((4-chlorophenyl)(4-(trifluoromethoxy)benzyl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid (195)

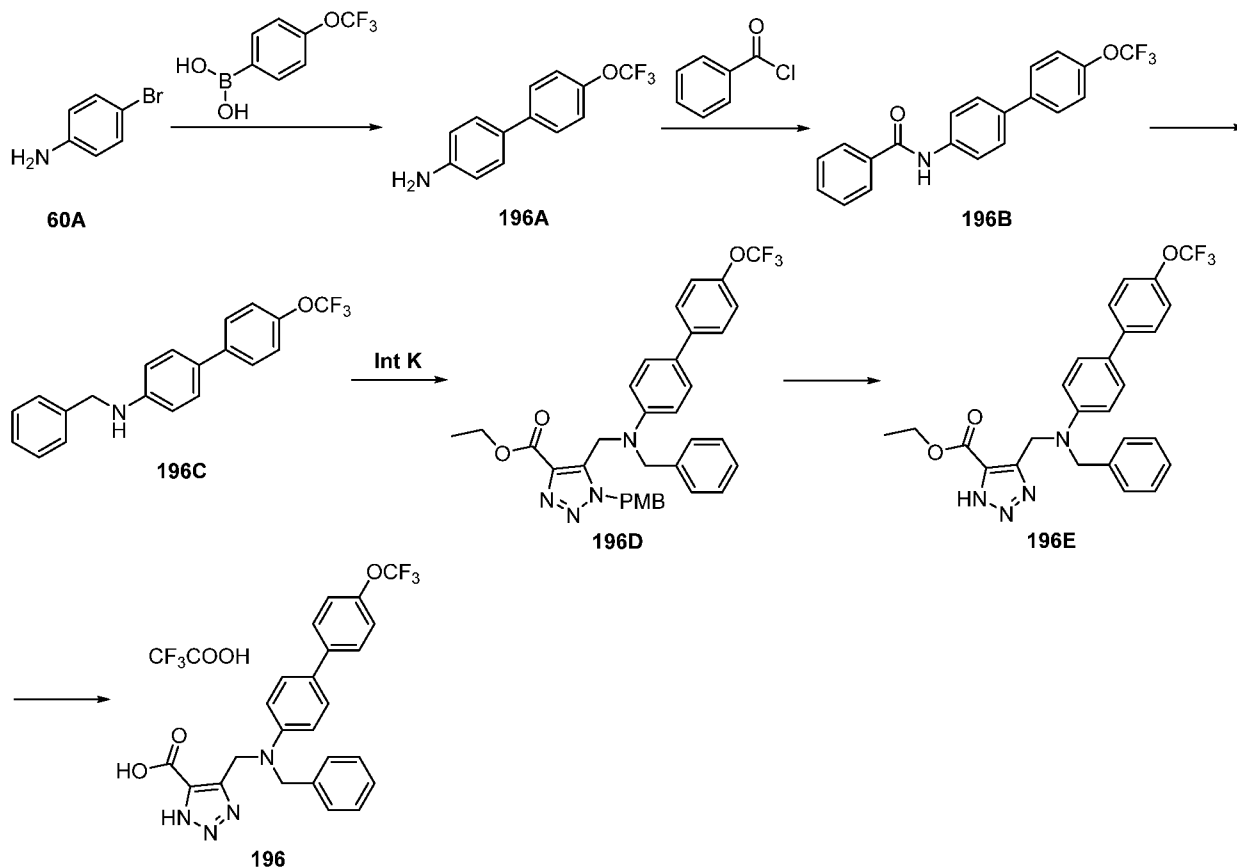


[001183] Compounds **195B**, **195C**, **195D**, **195E**, and **195** were synthesized by employing the procedures described for Compounds **193D**, **182B**, **178A**, **1**, and **8F** using 4-(trifluoromethoxy)benzoyl chloride, Compounds **195A** without DMAP, **195B** with $\text{BH}_3 \cdot \text{Me}_2\text{S}$ as reducing agent, **195C**, **195D**, and **195E** in lieu of benzoyl chloride, Compounds **193C** with DMAP, **182A** with $\text{BH}_3 \cdot \text{THF}$ as reducing agent, **82C**, **1E**, and **8E**. Compound **195B**: LC-MS (ESI) m/z : 316 $[M+H]^+$. Compound **195C**: $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 4.11 (s, 1H), 4.33 (s, 2H), 6.52-6.56 (m, 2H), 7.11-7.14 (m, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H). Compound **195D**: LC-MS (ESI) m/z : 575 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): 1.27 (t, $J = 7.2$ Hz, 3H), 3.79 (s, 3H), 4.30 (q, $J = 7.2$ Hz, 2H), 4.72 (s, 2H), 4.81 (s, 2H), 5.78 (s, 2H),

6.72-6.74 (m, 2H), 6.82-6.85 (m, 2H), 7.10-7.12 (m, 4H), 7.21-7.24 (m, 4H). Compound **195E**: LC-MS (ESI) m/z : 455 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): 1.35 (t, $J = 7.2$ Hz, 3H), 4.42 (q, $J = 7.2$ Hz, 2H), 4.70 (s, 2H), 4.94 (s, 2H), 6.69 (d, $J = 8.6$ Hz, 2H), 7.12-7.17 (m, 4H), 7.26 (m, 2H). Compound **195**: LC-MS (ESI) m/z : 427 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): 4.74 (s, 2H), 4.93 (s, 2H), 6.65 (d, $J = 8.7$ Hz, 2H), 7.10 (d, $J = 8.9$ Hz, 2H), 7.28-7.35 (m, 4H).

[001184] Example 196

[001185] Synthesis of 4-((benzyl(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)amino)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (196**)**

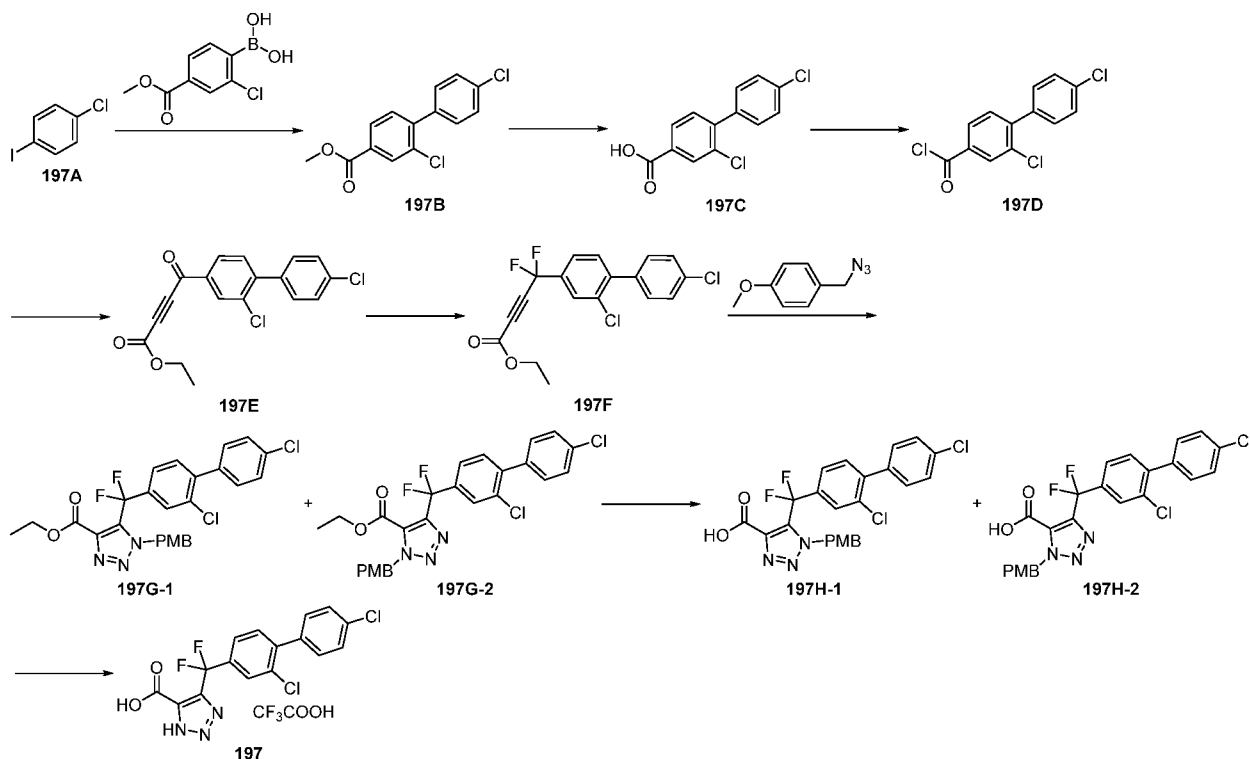


[001186] Compounds **166A**, **166B**, **166C**, **166D**, **166E**, and **196** were synthesized by employing the procedures described for Compounds **8B**, **193D**, **182B**, **178A**, **1**, and **8F** using 4-(trifluoromethoxy)phenylboronic acid, Compounds **60A** with K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **166A** without DMAP, **166B**, **166C**, **166D**, and **166E** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** with Cs_2CO_3 as base and toluene as solvent, **193C** with DMAP, **182A**, **82C**, **1E**, and **8E**. Compound **166A**: LC-MS (ESI) m/z : 254 $[M+H]^+$. Compound **166B**: LC-MS (ESI) m/z : 358 $[M+H]^+$. Compound **166C**: LC-MS (ESI) m/z : 344

$[M+H]^+$; $^1\text{H-NMR}$: (CDCl_3 , 400 MHz): δ (ppm) 4.19 (s, 1H), 4.38 (s, 2H), 6.69-6.71 (m, 2H), 7.21-7.27 (m, 3H), 7.29-7.40 (m, 6H), 7.50-7.52 (m, 2H). Compound **196D**: LC-MS (ESI) m/z : 617 $[M+H]^+$. Compound **196E**: LC-MS (ESI) m/z : 497 $[M+H]^+$. Compound **196**: LC-MS (ESI) m/z : 469 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 4.54 (s, 2H), 4.86 (s, 2H), 6.94-6.96 (m, 2H), 7.08-7.27 (m, 7H), 7.30-7.32 (m, 4H).

[001187] Example 197

[001188] Synthesis of 4-((2,4'-dichloro-[1,1'-biphenyl]-4-yl)difluoromethyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (197**)**

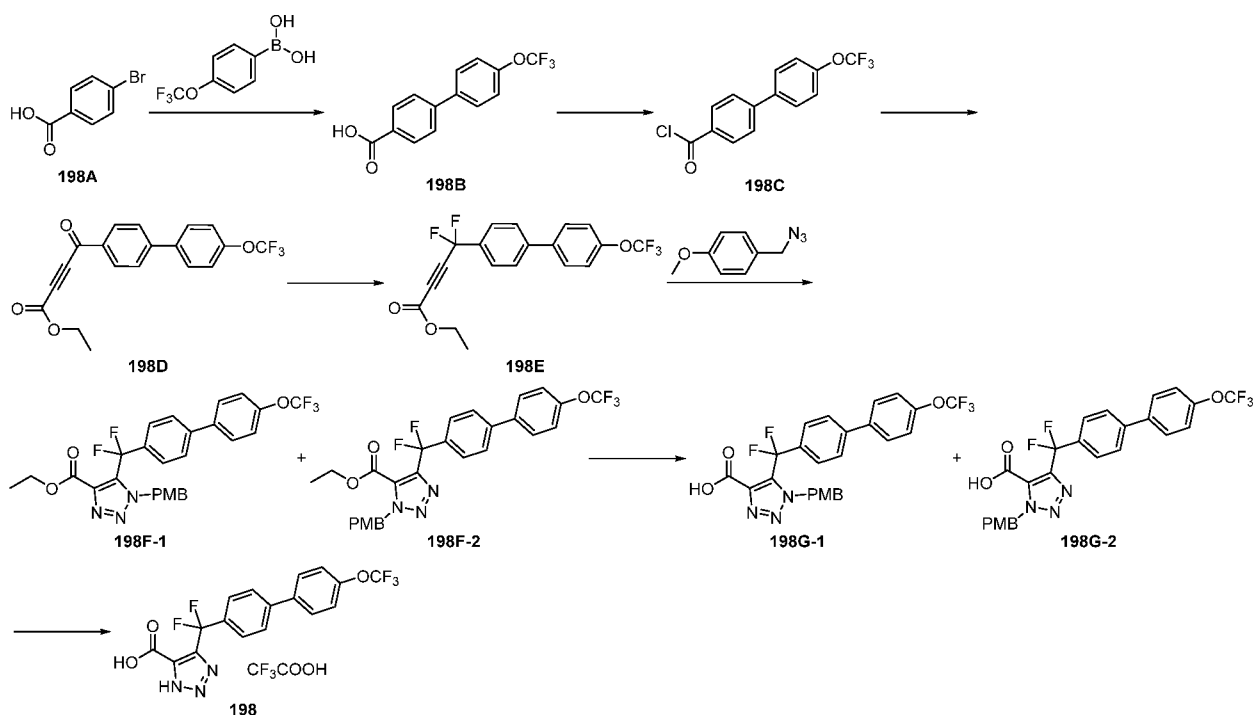


[001189] Compounds **197B**, **197C**, **197D**, **197E**, **197F**, Mixtures of **197G-1** and **197G-2**, **197H-1** and **197H-2**, and **197** were synthesized by employing the procedures described for Compounds **8B**, **8F**, **166B**, **166C**, **166D**, Mixtures of **166E-1** and **166E-2**, **8F**, and **1** using (2-chloro-4-(methoxycarbonyl)phenyl)boronic acid, Compounds **197A** with Na_2CO_3 as base and 1,4-dioxane/MeCN/ H_2O as solvent, **197B**, **197C**, **197D**, **197E**, **197F**, Mixtures of **197G-1** and **197G-2**, and **197H-1** and **197H-2** in lieu of (3,4-dichlorophenyl)boronic acid, Compounds **8A** with Cs_2CO_3 as base and DME/ H_2O as solvent, **8E**, **166A**, **166B**, **166C**, **166D**, **8E**, and **1E**. Compound **197B**: LC-MS (ESI) m/z : 281 $[M+H]^+$. Compound **197C**: LC-MS (ESI) m/z : 267 $[M+H]^+$. Compound **197E**: LC-MS (ESI) m/z : 347 $[M+H]^+$. Compound **197F**: LC-MS (ESI)

m/z: non-ionizable compound under routine conditions used. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.35 (t, $J = 7.1$ Hz, 3H), 4.31 (q, $J = 7.2$ Hz, 2H), 7.34–7.40 (m, 2H), 7.41–7.45 (m, 3H), 7.58–7.62 (m, 1H), 7.76 (d, $J = 1.4$ Hz, 1H). Mixtures of **197G-1** and **197G-2**: LC-MS (ESI) m/z: 532 $[\text{M}+\text{H}]^+$. Mixtures of **197H-1** and **197H-2**: LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. Compound **197**: LC-MS (ESI) m/z: 384 $[\text{M}+\text{H}]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 7.49 – 7.59 (m, 6H), 7.75 (s, 1H).

[001190] Example 198

[001191] Synthesis of 4-(difluoro(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)methyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (**198**)

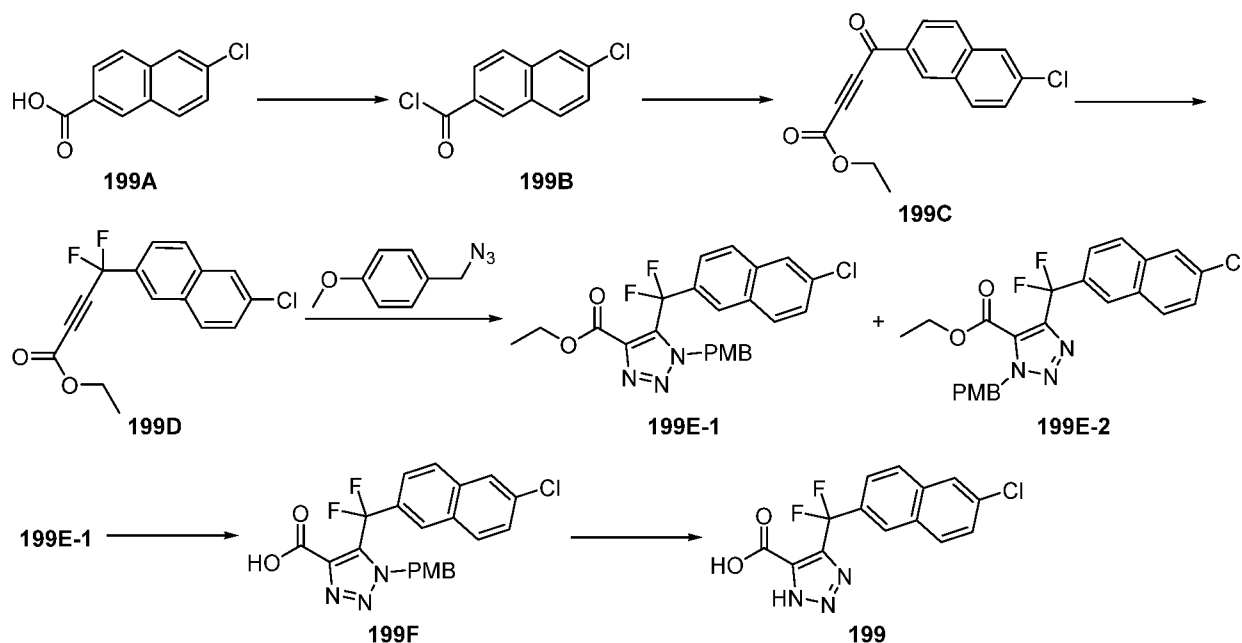


[001192] Compounds **198B**, **198C**, **198D**, **198E**, Mixtures of **198F-1** and **198F-2**, **198G-1** and **198G-2**, and **198** were synthesized by employing the procedures described for Compounds **4B**, **166B**, **166C**, **166D**, Mixtures of **166E-1** and **166E-2**, **8F**, and **1** using (4-(trifluoromethoxy)phenyl)boronic acid, Compounds **198A** with K_2CO_3 as base and 1,4-dioxane/ H_2O as solvent, **198B**, **198C**, **198D**, **198E**, Mixtures of **198F-1** and **198F-2**, and **198G-1** and **198G-2** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** with Na_2CO_3 as base and toluene/ $\text{EtOH}/\text{H}_2\text{O}$ as solvent, **166A**, **166B**, **166C**, **166D**, **8E**, and **1E**. Compound **198B**: LC-MS (ESI) m/z: 281 $[\text{M}-\text{H}]^-$. Compound **198D**: LC-MS (ESI) m/z: 363 $[\text{M}+\text{H}]^+$. Compound **198E**: LC-MS (ESI) m/z: non-ionizable compound under routine conditions used. Mixtures of **198F-1** and

198F-2: LC-MS (ESI) m/z : 548 $[M+H]^+$. Mixtures of **198G-1** and **198G-2**: LC-MS (ESI) m/z : 1061 $[2M+Na]^+$. Compound **198**: LC-MS (ESI) m/z : 400 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 7.47 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.77 (d, $J = 8.0$ Hz, 2H), 7.82 (d, $J = 8.4$ Hz, 2H).

[001193] Example 199

[001194] Synthesis of 4-((6-chloronaphthalen-2-yl)difluoromethyl)-1H-1,2,3-triazole-5-carboxylic acid (199)

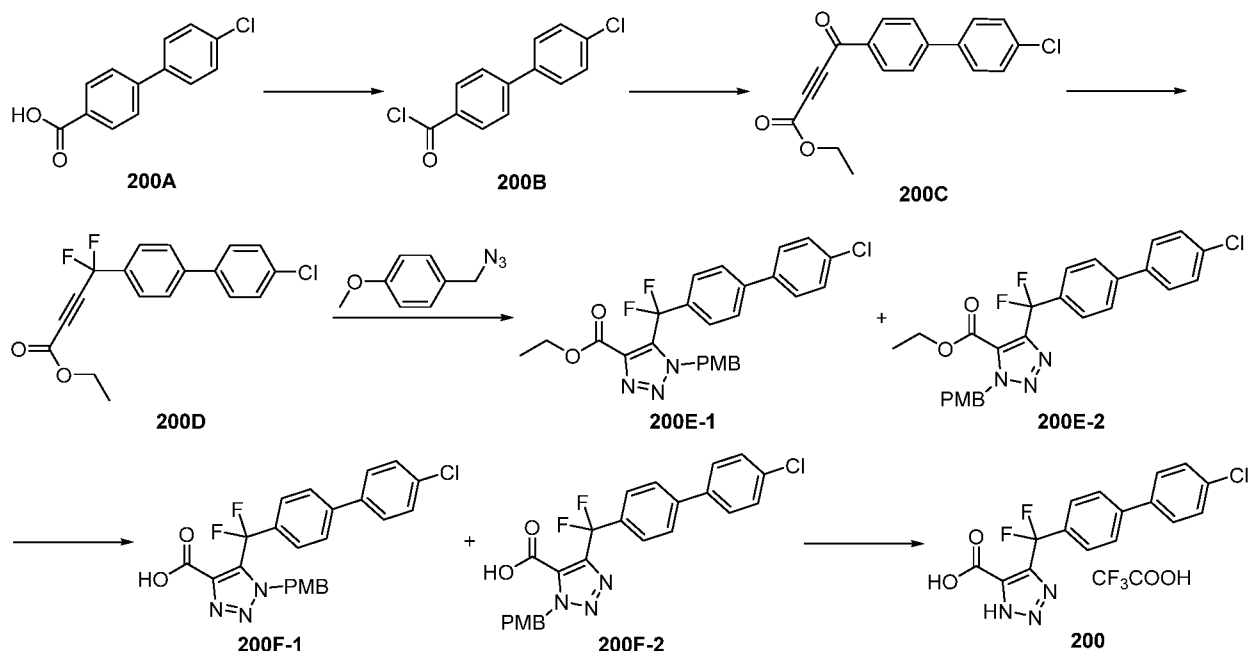


[001195] Compounds **199B**, **199C**, **199D**, **199E-1** and **199E-2**, **199F**, and **199** were synthesized by employing the procedures described for Compounds **166B**, **166C**, **166D**, Mixtures of **166E-1** and **166E-2**, **8F**, and **1** using Compounds **199A**, **199B**, **199C**, **199D**, **199E-1**, and **199F** in lieu of Compounds **166A**, **166B**, **166C**, **166D**, **8E**, and **1E**. Compound **199C**: LC-MS (ESI) m/z : 287 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.40 (t, $J = 7.2$ Hz, 3H), 4.39 (q, $J = 6.8$ Hz, 2H), 7.55 (dd, $J = 2, 8.8$ Hz, 1H), 7.84 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 2$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 8.12 (dd, $J = 2, 8.8$ Hz, 1H), 8.66 (s, 1H). Compound **199D**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.32 (t, $J = 7.2$ Hz, 3H), 4.30 (q, $J = 7.6$ Hz, 2H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.86 (d, $J = 6.8$ Hz, 1H), 7.87-7.89 (m, 3H), 8.14 (s, 1H). Compound **199E-1**: LC-MS (ESI) m/z : 472 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.18 (t, $J = 6.8$ Hz, 3H), 3.58 (s, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 5.73 (s, 2H), 6.60 (dd, $J = 2, 6.4$ Hz, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 7.25-7.26 (m,

1H), 7.44 (dd, $J = 2.$, 8.4 Hz, 1H), 7.48-7.50 (m, 2H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.80 (d, $J = 2.0$ Hz, 1H). Compound **199E-2**: LC-MS (ESI) m/z : 472 $[M+H]^+$; ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.26 (t, $J = 7.2$ Hz, 3H), 3.78 (s, 3H), 4.25 (q, $J = 7.2$ Hz, 2H), 5.82 (s, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.48 (dd, $J = 2.$, 8.4 Hz, 1H), 7.68 (dd, $J = 2.$, 8.4 Hz, 1H), 7.79-7.86 (m, 3H), 8.02 (s, 1H). Compound **199F**: LC-MS (ESI) m/z : 466 $[M+Na]^+$. Compound **199**: LC-MS (ESI) m/z : 324 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.61 (dd, $J = 2.8.$, 8.0 Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 8.15 (d, $J = 2.8$ Hz, 2H).

[001196] Example 200

[001197] Synthesis of 4-((4'-chloro-[1,1'-biphenyl]-4-yl)difluoromethyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (200)

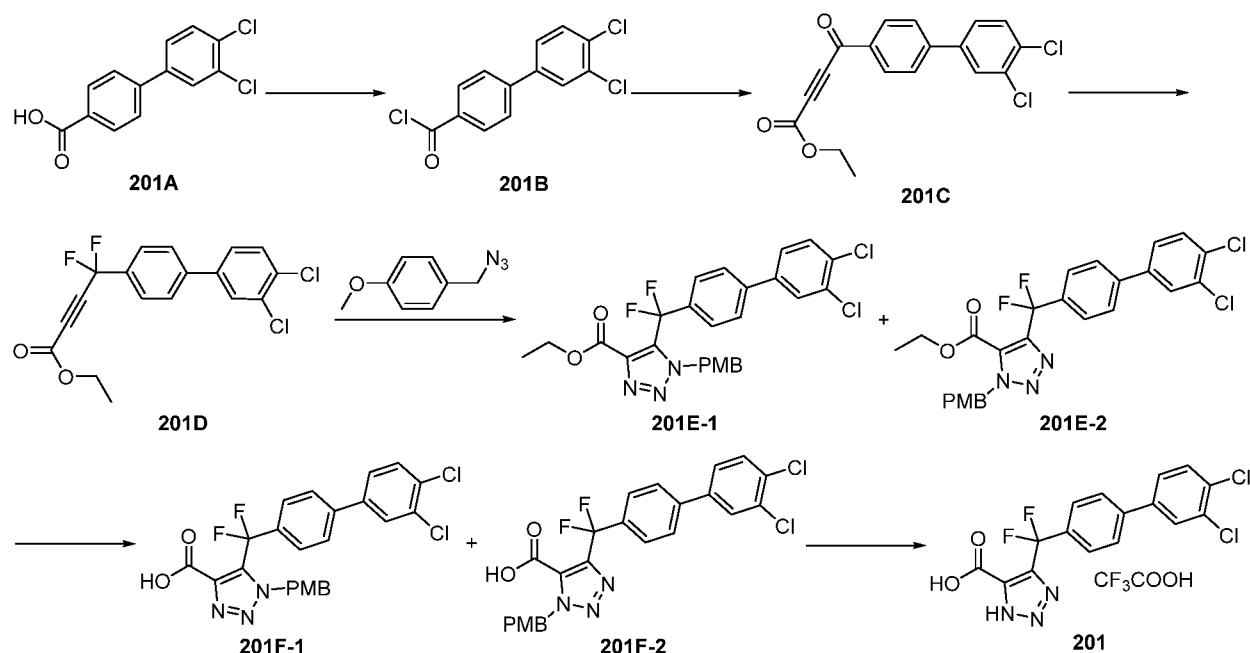


[001198] Compounds **200B**, **200C**, **200D**, Mixtures of **200E-1** and **200E-2**, **200F-1** and **200F-2**, and **200** were synthesized by employing the procedures described for Compounds **166B**, **166C**, **166D**, Mixtures of **166E-1** and **166E-2**, **8F**, and **1** using Compounds **200A**, **200B**, **200C**, **200D**, Mixtures of **200E-1** and **200E-2**, and **200F-1** and **200F-2** in lieu of Compounds **166A**, **166B**, **166C**, **166D**, **8E**, and **1E**. Compound **200C**: LC-MS (ESI) m/z : 313 $[M+H]^+$. Compound **200D**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Mixtures of **200E-1** and **200E-2**: LC-MS (ESI) m/z : 498 $[M+H]^+$. Mixtures of **200E-1** and **200E-2**: LC-MS (ESI) m/z : 961 $[2M+Na]^+$. Compound **200**: LC-MS (ESI) m/z : 350 $[M+H]^+$; ^1H -NMR ($DMSO-$

d_6 , 400 MHz): δ (ppm) 7.53 (d, $J = 8.0$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.72 (d, $J = 8.4$ Hz, 2H), 7.77 (d, $J = 8.4$ Hz, 2H).

[001199] Example 201

[001200] Synthesis of 4-((3',4'-dichloro-[1,1'-biphenyl]-4-yl)difluoromethyl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (201**)**



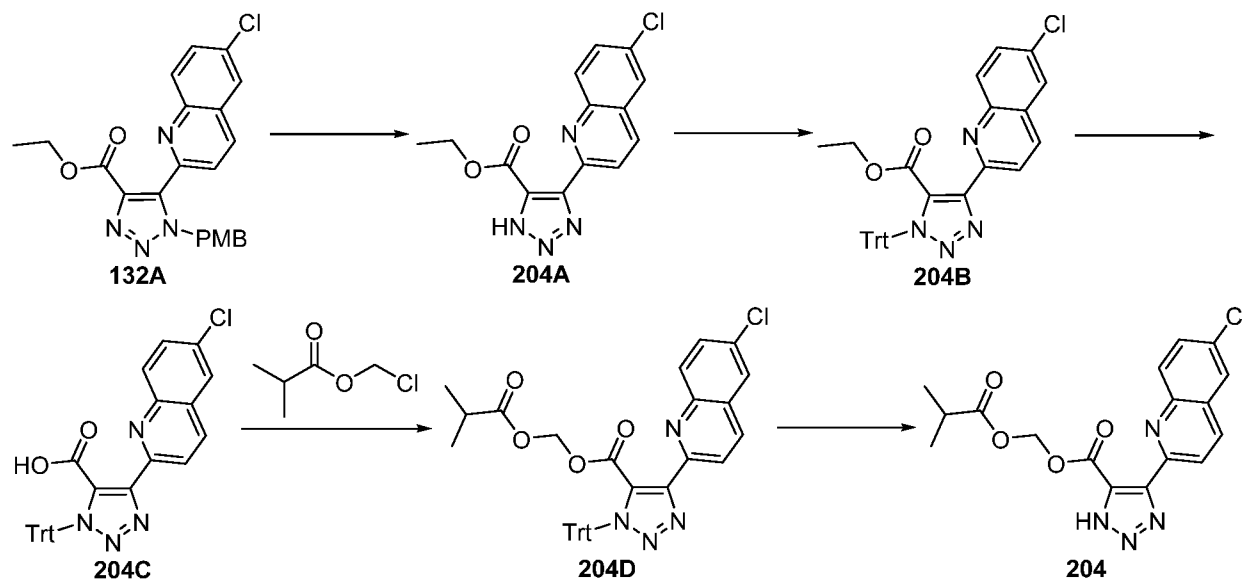
[001201] Compounds **201B**, **201C**, **201D**, Mixtures of **201E-1** and **201E-2**, **201F-1** and **201F-2**, and **201** were synthesized by employing the procedures described for Compounds **166B**, **166C**, **166D**, Mixtures of **166E-1** and **166E-2**, **8F**, and **1** using Compounds **201A**, **201B**, **201C**, **201D**, Mixtures of **201E-1** and **201E-2**, and **201F-1** and **201F-2** in lieu of Compounds **166A**, **166B**, **166C**, **166D**, **8E**, and **1E**. Compound **201B**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **201C**: LC-MS (ESI) m/z : 347 $[M+H]^+$. Compound **201D**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used, ^1H -NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.35 (t, $J = 7.1$ Hz, 3H), 4.31 (q, $J = 7.1$ Hz, 2H), 7.42 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.50 – 7.58 (m, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.68 (d, $J = 2.1$ Hz, 1H), 7.74 (d, $J = 8.4$ Hz, 2H). Mixtures of **201E-1** and **201E-2**: LC-MS (ESI) m/z : 532 $[M+H]^+$. Mixtures of **201E-1** and **201E-2**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **201**: LC-MS (ESI) m/z : 384 $[M+H]^+$; ^1H -NMR ($DMSO-d_6$, 400 MHz): δ (ppm) 7.62 (d, $J = 8.2$ Hz, 2H), 7.71 – 7.78 (m, 2H), 7.85 (d, $J = 8.2$ Hz, 2H), 8.01 (d, $J = 1.6$ Hz, 1H), 13.53 (s, 1H), 15.98 (s, 1H).

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[001207] Compounds **203B**, **203C**, **203D**, **203E**, and **203** were synthesized by employing the procedures described for Compounds **4B**, **27C**, **4B**, **1**, and **8F** using (4-chlorophenyl)boronic acid, Compounds **203A** with K_2CO_3 as base and 1,4-dioxane as solvent, **203B** with DMSO as solvent, **203C**, Intermediate **A** with 1,4-dioxane/ H_2O as solvent, **203D**, and **203E** in lieu of (4-bromophenyl)boronic acid, Compounds **4A** with Na_2CO_3 as base and toluene/ $EtOH/H_2O$ as solvent, **27B** with 1,4-dioxane as solvent, (4-bromophenyl)boronic acid, **4A** with toluene/ $EtOH/H_2O$ as solvent, **1E**, and **8E**. Compound **203B**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used; ^1H -NMR ($CDCl_3$, 400 MHz,): δ (ppm) 7.34-7.42 (m, 4H), 7.50-7.52 (m, 2H), 7.71-7.73 (m, 1H). Compound **203C**: LC-MS (ESI) m/z : non-ionizable compound under routine conditions used. Compound **203D**: LC-MS (ESI) m/z : 532 $[M+H]^+$. Compound **203E**: LC-MS (ESI) m/z : 412 $[M+H]^+$. Compound **203**: LC-MS (ESI) m/z : 384 $[M+H]^+$; ^1H -NMR (CD_3OD , 400 MHz,): δ (ppm) 7.47-7.57 (m, 5H), 8.12-8.14 (m, 1H), 8.21 (s, 1H).

[001208] **Example 204**

[001209] **Synthesis of (isobutyryloxy)methyl 4-(6-chloroquinolin-2-yl)-1H-1,2,3-triazole-5-carboxylate (204)**



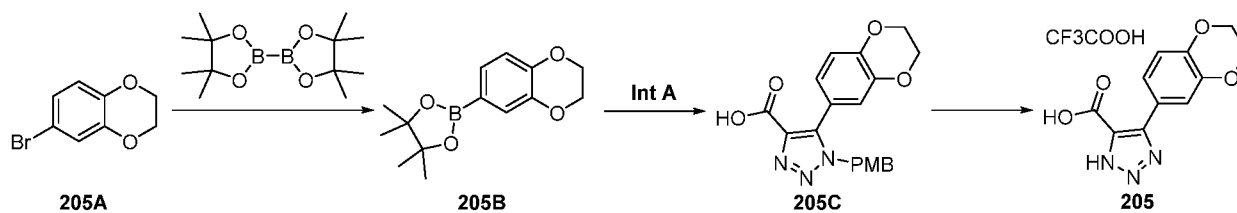
[001210] To a solution of Compound **132A** (474 mg, 1.12 mmol) in TFA (5 mL) was added thioanisole (139 mg, 1.12 mmol) and stirred at 60 °C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (50 mL)

and brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, from 10% to 40% v/v) to afford Compound **204A**. LC-MS (ESI) m/z : 303 $[M+H]^+$.

[001211] Compounds **204B**, **204C**, **204D**, and **204** were synthesized by employing the procedures described for Compounds **54A**, **8F**, **54C**, and **54** using Compounds **204A**, **204B**, chloromethyl isobutyrate, **204C** at room temperature, and **204D** in lieu of Compounds **33**, **8E**, chloromethyl pivalate, **54B** at 50 °C, and **54C**. Compound **204B**: LC-MS (ESI) m/z : 545 $[M+H]^+$. Compound **204C**: LC-MS (ESI) m/z : 517 $[M+H]^+$. Compound **204D**: LC-MS (ESI) m/z : 617 $[M+H]^+$. Compound **204**: LC-MS (ESI) m/z : 375 $[M+H]^+$; $^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ (ppm) 1.11 (d, J = 6.8 Hz, 6H), 2.51-2.61 (m, 1H), 5.97 (s, 2H), 7.76-7.81 (m, 1H), 8.04-8.16 (m, 3H), 8.38-8.42 (m, 1H).

[001212] **Reference Example 205**

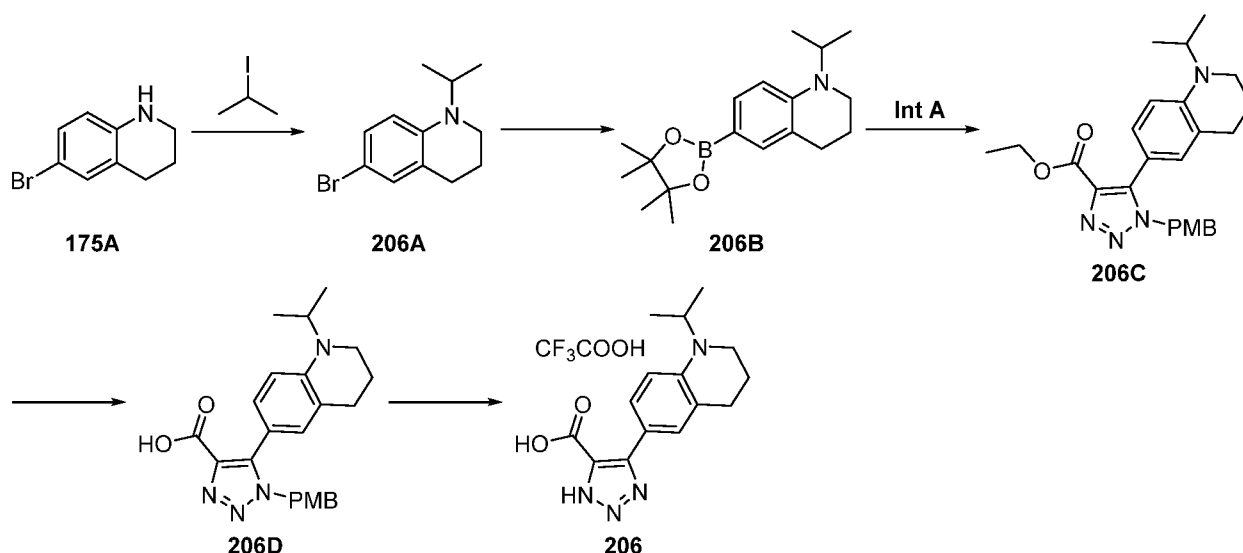
[001213] **Synthesis of 4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (205)**



[001214] Compounds **205B**, **205C**, and **205** were synthesized by employing the procedures described for Compounds **27C**, **4B**, and **1** using Compounds **205A**, Intermediate A, **205B** with K_2CO_3 as base and 1,4-dioxane as solvent, and **205C** in lieu of Compounds **27B**, **4A**, (4-bromophenyl)boronic acid with Na_2CO_3 as base and toluene/EtOH/ H_2O as solvent, and **1E**. Compound **205B**: LC-MS: (ESI) m/z : 263 $[M+H]^+$; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ (ppm) 1.33 (s, 12H), 4.24-4.29 (m, 4H), 6.87 (d, J = 8.0 Hz, 1H), 7.27-7.33 (m, 2H). Compound **205C**: LC-MS (ESI) m/z : 368 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 3.69 (s, 3H), 4.26-4.30 (m, 4H), 5.36 (s, 2H), 6.78-6.84 (m, 3H), 6.88-6.95 (m, 4H), 12.82 (s, 1H). Compound **205**: LC-MS (ESI) m/z : 248 $[M+H]^+$; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 4.23 (s, 4H), 6.81 (d, J = 8.4 Hz, 1H), 7.74-7.76 (m, 1H), 7.96 (s, 1H).

[001215] **Example 206**

[001216] **Synthesis of 4-(1-isopropyl-1,2,3,4-tetrahydroquinolin-6-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (206)**

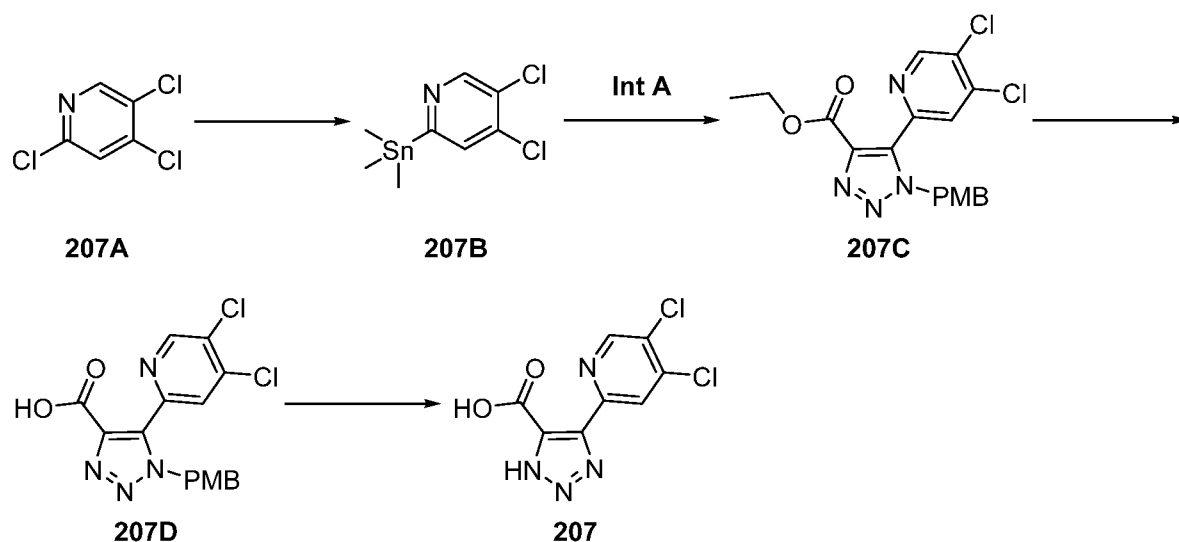


[001217] To a solution of 6-bromo-1,2,3,4-tetrahydroquinoline **175A** (1.4 g, 6.6 mmol) in DMF (30 mL) was added Cs_2CO_3 (3.8 g, 11.7 mmol) and 2-iodopropane (7.5 g, 17.6 mmol). The mixture was stirred at 55 °C for 16 hours. After cooled down to room temperature, the mixture was diluted with water (200 mL) and extracted with ethyl acetate in petroleum ether (15% v/v) (200 mL x 3). The combined organic phase was washed with brine (150 mL x 4), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (petroleum ether) to furnish Compound **206A**. LC-MS (ESI) m/z : 254 $[\text{M}+\text{H}]^+$.

[001218] Compound **206B** was synthesized by employing the procedure described for Compound **27C** using Compound **206A** in lieu of Compound **27B**, LC-MS (ESI) m/z : 302 $[\text{M}+\text{H}]^+$.

[001219] A mixture of Intermediate A (575 mg, 1.69 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (387 mg, 0.55 mmol), Compound **206B** (450 mg, 1.49 mmol), and Na_2CO_3 (473 mg, 4.46 mmol) in water (5 mL) and 1,4-dioxane (20 mL) was heated to 90 °C for 16 hours. The mixture was cooled down to room temperature, diluted with water (100 mL), and extracted with ethyl acetate (100 mL x 2). The combined organic phases were dried over anhydrous sodium sulfate, concentrated, and purified with preparative HPLC to afford Compound **206C**. LC-MS (ESI) m/z : 435 $[\text{M}+\text{H}]^+$.

[001220] Compounds **206D** and **206** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **206C** and **206D** in lieu of Compounds **8E** and **1E**. Compound **206D**: LC-MS (ESI) m/z : 407 $[\text{M}+\text{H}]^+$. Compound **206**: LC-MS (ESI) m/z : 287 $[\text{M}+\text{H}]^+$; ^1H -NMR ($\text{DMSO}-d_6$, 400 MHz): δ (ppm) 1.26 (s, 3H), 1.28 (s, 3H), 1.98-2.04 (m, 2H), 2.84 (s, 2H), 3.39 (s, 2H), 4.21 (s, 1H), 7.05 (s, 1H), 7.59 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 1H).

[001221] Example 207**[001222] Synthesis of 4-(4,5-dichloropyridin-2-yl)-1H-1,2,3-triazole-5-carboxylic acid (207)**

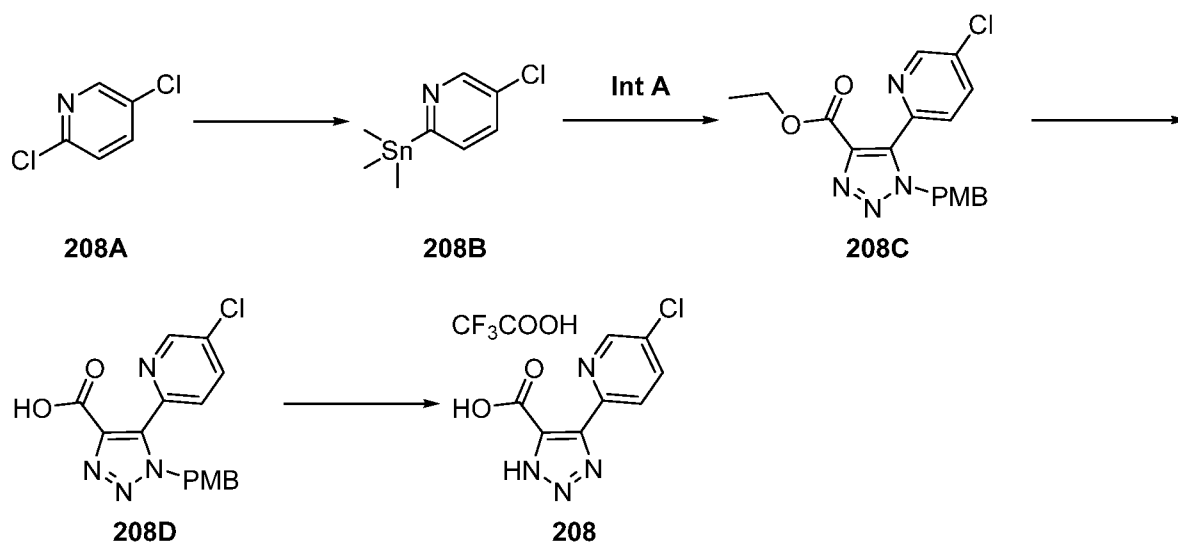
[001223] A mixture of 2,4,5-trichloropyridine **207A** (600 mg, 3.28 mmol), 1,1,1,2,2,2-hexamethyldistannane (1.18 g, 3.61 mmol), and tetrakis(triphenylphosphine)palladium (379 mg, 0.328 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen, and then heated at 100 °C under nitrogen for 3 hours. The reaction mixture was concentrated to give a crude Compound **207B**, which was used directly for next step without purification. LC-MS (ESI) m/z : 312 $[M+H]^+$.

[001224] To a solution of the crude Compound **207B** in DMA (5 mL) was added Intermediate **A** (1.11 g, 3.28 mmol) and tetrakis(triphenylphosphine)palladium (379 mg, 0.328 mmol) and degassed with nitrogen, and then heated in a microwave reactor at 140 °C for 1 hour. The reaction mixture was quenched with a saturated KF solution (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and purified with flash column chromatography on silica gel (ethyl acetate in petroleum ether, 30% v/v) to afford Compound **207C**. LC-MS (ESI) m/z : 407 $[M+H]^+$.

[001225] Compounds **207D** and **207** were synthesized by employing the procedures described for Compounds **8F** and **1** using Compounds **207C** and **207D** in lieu of Compounds **8E** and **1E**. Compound **207D**: LC-MS (ESI) m/z : 379 $[M+H]^+$. Compound **207**: LC-MS (ESI) m/z : 259 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 8.49 (s, 1H), 8.98 (s, 1H).

[001226] Example 208

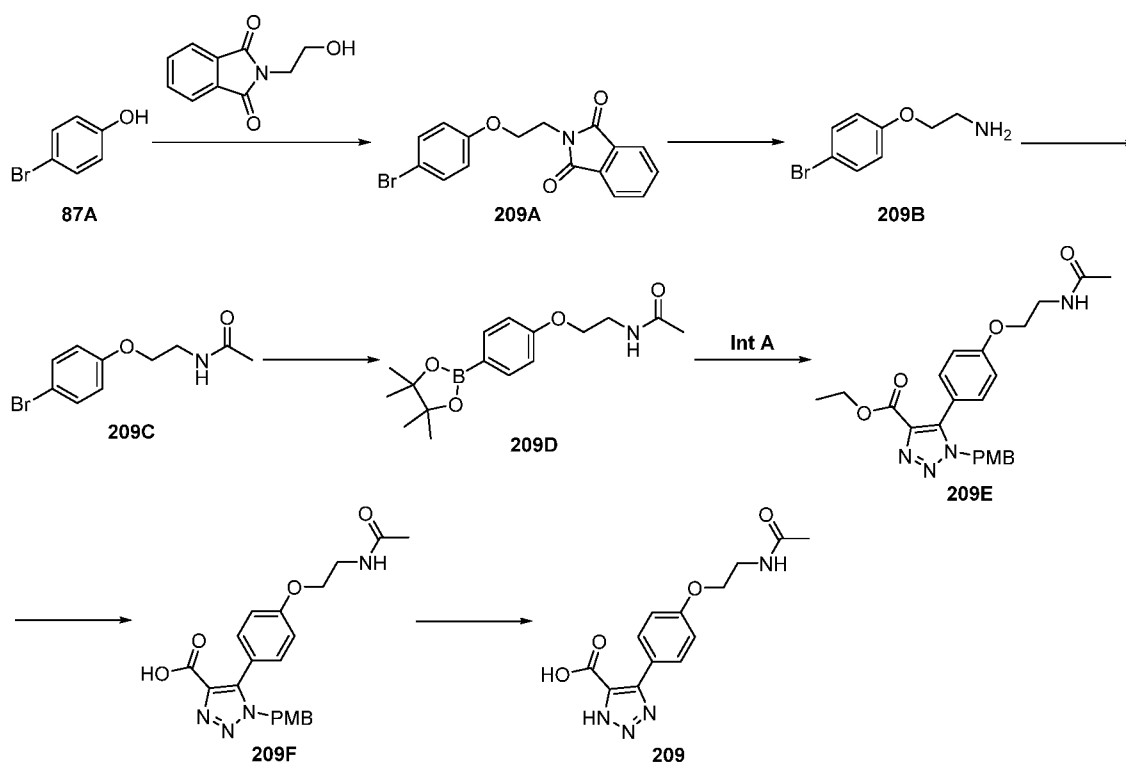
[001227] Synthesis of 4-(5-chloropyridin-2-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (208)



[001228] Compounds **208B**, **208C**, **208D**, and **208** were synthesized by employing the procedures described for Compounds **207B**, **207C**, **8F**, and **1** using Compounds **208A**, **208B** with 1,4-dioxane as solvent, **208C**, and **208D** in lieu of Compounds **207A**, **207B** with DMA as solvent, **8E**, and **1E**. Compound **208C**: LC-MS (ESI) m/z : 373 $[M+H]^+$. Compound **208D**: LC-MS (ESI) m/z : 345 $[M+H]^+$. Compound **208**: LC-MS (ESI) m/z : 225 $[M+H]^+$; $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz): δ (ppm) 8.22-8.32 (m, 2H), 8.87 (s, 1H).

[001229] Example 209

[001230] Synthesis of 4-(4-(2-acetamidoethoxy)phenyl)-1H-1,2,3-triazole-5-carboxylic acid (209)



[001231] Compounds **209A** and **209B** were synthesized by employing the procedures described for Compounds **90C** and **190F** using 2-(2-hydroxyethyl)isoindoline-1,3-dione, Compounds **87A** with DEAD as coupling reagent, and **209A** with EtOH as solvent in lieu of Compounds **90B**, Intermediate **H** with DIAD as coupling reagent, and **190E** with MeOH/H₂O as solvent. Compound **209A**: LC-MS (ESI) *m/z*: 346 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 4.07-4.13 (m, 2H), 4.18-4.21 (m, 2H), 6.73-6.76 (m, 2H), 7.31-7.34 (m, 2H), 7.72-7.74 (m, 2H), 7.85-7.87 (m, 2H). Compound **209B**: LC-MS (ESI) *m/z*: 216 [M+H]⁺.

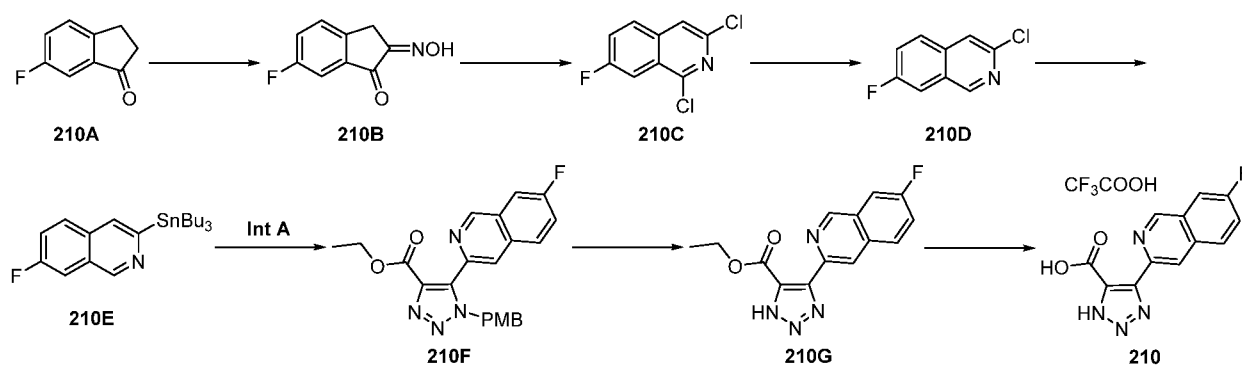
[001232] To a solution of Compound **209B** (541 mg, 2.65 mmol) in dichloromethane (20 mL) was added Et₃N (802 mg, 7.95 mmol) and acetic anhydride (541 mg, 5.3 mmol) and stirred at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL), washed with diluted HCl solution (1N, 30 mL) and saturated NaHCO₃ solution (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give Compound **209C**. LC-MS (ESI) *m/z*: 258 [M+H]⁺; ¹H-NMR (CDCl₃, 400 MHz): δ (ppm) 2.04 (s, 3H), 3.65 (t, *J* = 4.8 Hz, 2H), 4.00 (t, *J* = 4.8 Hz, 2H), 5.97 (b, 1H), 6.75-6.79 (m, 2H), 7.35-7.39 (m, 2H).

[001233] Compounds **209D**, **209E**, **209F**, and **209** were synthesized by employing the procedures described for Compounds **27C**, **4B**, **8F**, and **1** using Compounds **209C**, Intermediate

A, **209D** with K_2CO_3 as base and 1,4-dioxane as solvent, **209E**, and **209F** in lieu of Compounds **27B**, **4A**, (4-bromophenyl)boronic acid with Na_2CO_3 as base and toluene/EtOH/ H_2O as solvent, **8E**, and **1E**. Compound **209D**: LC-MS (ESI) m/z : 306 $[M+H]^+$. Compound **209E**: LC-MS (ESI) m/z : 439 $[M+H]^+$. Compound **209F**: LC-MS (ESI) m/z : 411 $[M+H]^+$. Compound **209**: LC-MS (ESI) m/z : 291 $[M+H]^+$; ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 1.83 (s, 3H), 3.42 (q, $J = 5.6$ Hz, 2H), 4.04 (t, $J = 5.7$ Hz, 2H), 7.04 (d, $J = 8.5$ Hz, 2H), 7.77 (s, 2H), 8.12 (s, 1H), 12.97 (s, 1H), 15.69 (s, 1H).

[001234] Example 210

[001235] Synthesis of 4-(7-fluoroisoquinolin-3-yl)-1H-1,2,3-triazole-5-carboxylic acid 2,2,2-trifluoroacetate (210)



[001236] To a solution of 6-fluoro-2,3-dihydro-1H-inden-1-one (**210A**) (3.0 g, 20 mmol) in ether (20 mL) was added a solution of HCl in 1,4-dioxane (4 M, 7.5 mL, 30 mmol), followed by dropping isopentyl nitrite (3.5 g, 30 mmol) at 0 °C. The mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure. The residue was washed with petroleum ether (50 mL) to afford Compound **210B**. LC-MS (ESI) m/z : 180 $[M+H]^+$. ^1H -NMR (DMSO- d_6 , 400 MHz): δ (ppm) 3.76 (s, 2H), 7.50 (s, 1H), 7.51-7.68 (m, 2H), 12.74 (s, 1H).

[001237] A mixture of Compound **210B** (2.5 g, 14 mmol) and PCl_5 (4.3 g, 21 mmol) in $POCl_3$ (20 mL) was stirred at 80 °C overnight. After cooled down to room temperature, the mixture was concentrated under reduced pressure to give a crude Compound **210C**. LC-MS (ESI) m/z : 216 $[M+H]^+$.

[001238] To a solution of Compound **210C** (3.0 g, 14 mmol) in acetic acid (10 mL) was added 55% aqueous HI solution (5 mL) and stirred at 100 °C for 16 hours. The mixture was concentrated under reduced pressure. The residue was diluted with saturated $NaHCO_3$ solution (100 mL), extracted with ethyl acetate (50 mL x 3), washed with water (50 mL) and brine (50

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 349

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 349

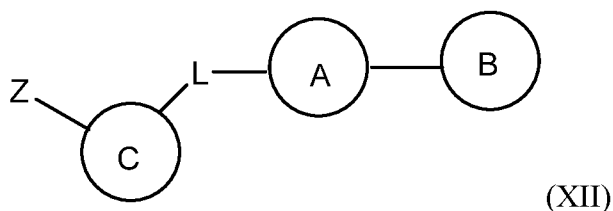
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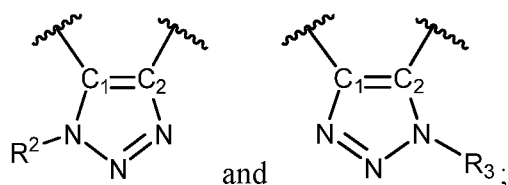
WE CLAIM:

1. A compound of Formula (XII):



wherein:

ring C is selected from:



wherein the wavy lines (~~~~) indicate the points of attachment of the C₁ carbon to Z,
and the C₂ carbon to L;

L is a CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;
Z is -C(=O)H or -CH₂OY;

Y is hydrogen or W;

W is methylene substituted with R⁴; -C(=O)R⁵; -C(=O)OR⁵; -C(=O)NR⁵R⁶; -C(=O)SR⁵;
-S(O)R⁵; -S(O)₂R⁵; -S(O)(OR⁵); -S(O)₂(OR⁵); -SO₂NR⁵R⁶; -P(=O)(OR⁷)₂;
-P(=O)(O⁻)₂; -P(=O)(OR⁷)(O⁻); or -P(=O)(X) wherein X is -O(C(R⁸)₂)_mO-;

R^L is hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, phenyl, or benzyl; wherein the C₁₋₄ alkyl is
optionally substituted with hydroxycarbonyl, alkoxycarbonyl,
hydroxycarbonylalkyl, or alkylcarbonyloxy; and the phenyl group alone or as a
part of the benzyl group is optionally substituted with one or two groups selected
from halo and haloalkoxy;

Ring A is cycloalkyl, C₈₋₁₁ spirocycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

Ring B is present or not present; wherein:

when Ring B is present, then Ring A is optionally substituted with 1 or 2 R^{A1} groups;

each R^{A1} is independently selected from halo, alkyl, alkoxy, cyano, nitro, hydroxy, hydroxyalkyl, haloalkyl, haloalkoxy, (cycloalkyl)alkyl, (cycloalkyl)alkoxy, and cycloalkyl;

when Ring B is not present, then Ring A is optionally substituted with 1, 2, or 3 R^{A2} groups;

Ring B, when present, is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each is optionally substituted with 1, 2, or 3 R^B groups;

each R^{A2} and R^B is independently halo; cyano; alkyl; hydroxyalkyl; alkylsulfonyl; aminosulfonyl; alkylaminosulfonyl; dialkylaminosulfonyl; haloalkyl; alkoxy; aminoalkoxy; alkylaminoalkoxy; dialkylaminoalkoxy; hydroxyalkoxy; haloalkoxy; alkylcarbonyl; alkoxyalkoxy; aminocarbonyl; alkylaminocarbonyl; dialkylaminocarbonyl; alkylcarbonylaminoalkoxy; cycloalkyl; (cycloalkyl)alkyl; cycloalkyloxy; (cycloalkyl)alkoxy wherein the cycloalkyl group is optionally substituted with hydroxyalkyl; cycloalkylcarbonyl; cycloalkylcarbonyloxy; heterocycloalkyl optionally substituted with one or two groups independently selected from halo, alkyl, and alkylcarbonyl; (5-6-membered heterocycloalkyl-one)alkyl; 5-6-membered heterocycloalkyl-one; (heterocycloalkyl)alkyl; heterocycloalkylcarbonyl; or 5-6-membered heteroaryl optionally substituted with one group selected from alkyl, hydroxyalkyl, (hydroxycycloalkyl)alkyl, alkoxyalkyl, and hydroxycycloalkyl;

each R^2 and R^3 is independently hydrogen, alkyl, phenyl, benzyl, or alkoxy-substituted benzyl; wherein the alkyl is optionally substituted with halo, alkoxy, haloalkoxy, alkylcarbonyloxy, cycloalkylcarbonyloxy, or heterocycloalkylcarbonyloxy optionally substituted with alkoxycarbonyl;

R^4 is alkylcarbonyloxy, phenylcarbonyloxy, cycloalkylcarbonyloxy, heterocycloalkylcarbonyloxy, aminocarbonyloxy, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxycarbonyloxy, $-N(R^{10})C(O)R^{11}$, $-N(R^{10})C(O)OR^{11}$, $-N(R^{10})C(O)NR^{12}R^{13}$, $-O-P(=O)(O^-)_2$, $-O-P(=O)(OR^7)(O^-)$, or $-O-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO^-$;

each R^8 is independently hydrogen, halo, $-CN$, $-OR^9$, $-C(=O)R^9$, $-C(=O)OR^9$, $-C(=O)N(R^9)_2$, $-N(R^9)_2$, $-SR^9$, $-S(O)R^9$, $-S(O)_2R^9$, $-OC(=O)R^9$,

-OC(=O)OR⁹, -OC(=O)(N(R⁹)₂), -N(R⁹)C(=O)R¹⁴, -N(R⁹)C(=O)OR¹⁴,
 -SO₂N(R⁹)₂, alkyl, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl;
 each R⁵, R⁶, R⁷, R⁹, R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ is independently hydrogen, alkyl,
 cycloalkyl, aryl, arylalkyl, heterocycloalkyl, or heteroaryl; and
 m is 1, 2, or 3; and
 provided:

- i. the compound represented by Formula (XII) is exclusive of:
 - a. 4-(phenylamino)-1H-1,2,3-triazole-5-carbaldehyde;
 - b. 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazole-5-carbaldehyde;
 - c. ethyl hydrogen (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate);
 - d. diethyl (((5-((5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-1H-1,2,3-triazol-4-yl)methoxy)methyl)phosphonate); and
 - e. 1-((4-(hydroxymethyl)-1H-1,2,3-triazol-5-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione;
- ii. when Z is -C(=O)H, L is NR^L, R^L is hydrogen, and Ring A is phenyl, then Ring B is present and/or the phenyl Ring A is substituted with 1, 2, or 3 R^{A2} groups;
- iii. when Z is -C(=O)H, L is CH₂, and Ring A is cyclopropyl, phenyl, indole, or thiophene, then Ring B is present;
- iv. when Z is -C(=O)H, L is CH₂-O, and Ring A is phenyl, then Ring B is present;
- v. when Z is -CH₂OY, Y is W, W is -P(=O)(OR⁷)₂ or -P(=O)(OR⁷)(O⁻), R⁷ is ethyl, L is CH₂, and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2}; and
- vi. when Z is -CH₂OY, Y is hydrogen, L is CH₂, and Ring A is pyrimidine-2,4-dione, then Ring B is present and/or the pyrimidine-2,4-dione Ring A is unsubstituted or substituted with 2 R^{A2}; and

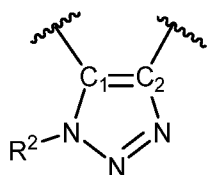
optionally a single stereoisomer or mixture of stereoisomers thereof and additionally optionally a pharmaceutically acceptable salt thereof.

2. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 1, wherein
L is a CF₂, O, S, S(=O), C(=O), CH₂-NR^L, CH₂-S, or Q-CH₂; wherein Q is O, NR^L, or S.
3. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 1, wherein
L is a CH₂, CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S;
and
Z is -CH₂OY.
4. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 1, wherein
L is a CF₂, O, NR^L, S, S(=O), C(=O), CH₂-Q, or Q-CH₂; wherein Q is O, NR^L, or S; and
Z is -CH₂OY.
5. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 1, wherein
L is a CF₂, O, S, S(=O), C(=O), CH₂-NR^L, CH₂-S, or Q-CH₂; wherein Q is O, NR^L, or S;
and
Z is -C(=O)H.
6. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-2, wherein Z is -C(=O)H.
7. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-2, wherein Z is -CH₂OY.
8. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-4 or 7, wherein Y is hydrogen.

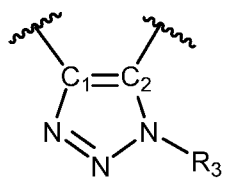
9. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-4 or 7, wherein Y is W.
10. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 9, wherein W is methylene substituted with R^4 ; $-C(=O)R^5$; $-C(=O)OR^5$; $-C(=O)NR^5R^6$; $-C(=O)SR^5$; $-S(O)R^5$; $-S(O)_2R^5$; $-S(O)(OR^5)$; $-S(O)_2(OR^5)$; or $-SO_2NR^5R^6$.
11. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of claim 9, wherein W is methylene substituted with R^4 ; $-P(=O)(OR^7)_2$; $-P(=O)(O^-)_2$; $-P(=O)(OR^7)(O^-)$; or $-P(=O)(X)$ wherein X is $-O(C(R^8)_2)_mO-$.
12. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1 or 3-11, wherein L is a CF_2 , O, NR^L , S, $S(=O)$, $C(=O)$, CH_2-O , or $O-CH_2$.
13. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1 or 3-11, wherein L is a CF_2 , O, S, $S(=O)$, $C(=O)$, CH_2-O , or $O-CH_2$.
14. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1 or 3-11, wherein L is O, NR^L , or S.
15. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1 or 3-11, wherein L is O, NH, or S.
16. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-15, wherein L is O or S.
17. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-16, wherein L is O.

18. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-17, wherein Ring A is C₃₋₇ cycloalkyl, 5-6 membered heterocycloalkyl, or phenyl.
19. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-18, wherein Ring A is C₃₋₇ cycloalkyl.
20. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-18, wherein Ring A is 5-6 membered heterocycloalkyl.
21. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-18, wherein Ring A is phenyl.
22. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-21, wherein Ring B is present.
23. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-22, wherein Ring B is 5-6 membered heterocycloalkyl, aryl, or heteroaryl.
24. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-23, wherein Ring B is 5-6 membered heterocycloalkyl.
25. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-23, wherein Ring B is phenyl.
26. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-23, wherein Ring B is heteroaryl.

27. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-26, wherein Ring B is independently substituted with 1 R^B group.
28. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-26, wherein Ring B is independently substituted with 2 R^B groups.
29. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-28, wherein R^B is independently halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{3-7} cycloalkoxy, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl.
30. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-29, wherein R^B is independently chloro, bromo, fluoro, methyl, trifluoromethyl, methoxy, isopropoxy, trifluoromethoxy, cyclopropoxy, cyclopentoxo, piperidinyl, piperidinylalkyl, or piperidinylcarbonyl.
31. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-30, wherein R^2 and R^3 are independently hydrogen.
32. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-31, wherein ring C is:



33. The compound, single stereoisomer or mixture of stereoisomers or pharmaceutically acceptable salt of any one of claims 1-31, wherein ring C is:



34. A compound selected from the group consisting of compounds 487, 488, 489, 490, 491, 492, 493-1, 493-2, 494, 495, 496, and 497, or a single stereoisomer or mixture of stereoisomers thereof and additionally optionally as a pharmaceutically acceptable salt thereof.
35. A pharmaceutical composition comprising a compound of any one of claims 1-34, optionally as a single stereoisomer, or mixtures of stereoisomers, and a pharmaceutically acceptable excipient.
36. A method of treating a disease or disorder associated with a defect in glyoxylate metabolism comprising administering to a patient suffering from such disease or disorder a compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35.
37. A method of treating a disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism comprising administering to a patient suffering from such disease or disorder a compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35.
38. The method of treating of claim 36 or 37, wherein the disease or disorder is characterized by high oxalate content in the urine.
39. The method of treating of claim 36 or 37, wherein the disease or disorder is characterized by a deficiency in the enzyme alanine : glyoxylate aminotransferase (AGT).

40. The method of treating of claim 36 or 37, wherein the disease or disorder is selected from the group consisting of: hyperoxaluria, genetic or environmental vitamin B6 deficiency, genetic or environmental abnormal calcium metabolism, abnormal collagen metabolism, abnormal function of oxalate transporters, and genetic kidney disease.
41. The method of treating of claim 40, wherein the hyperoxaluria is a primary hyperoxaluria (“PH”) or is a secondary hyperoxaluria.
42. The method of treating of claim 41, wherein the primary hyperoxaluria (“PH”) is selected from the group consisting of: Primary hyperoxaluria type 1 (“PH1”), Primary hyperoxaluria type 2 (“PH2”), and Primary hyperoxaluria type 3 (“PH3”).
43. The method of treating of claim 40, wherein the genetic or environmental abnormal calcium metabolism is hypercalciuria or hyperparathyroidism.
44. The method of treating of claim 40, wherein the genetic kidney disease is Hirschsprung’s disease.
45. The method of treating of claim 36 or 37, wherein the disease or disorder is an enteric hyperoxaluria.
46. The method of treating of claim 45, wherein the enteric hyperoxaluria is selected from the group consisting of: fat malabsorption, steatorrhea, inflammatory bowel disease (“IBD”), pancreatic insufficiency, biliary cirrhosis, short-bowel syndrome, bariatric surgery, jejunioileal bypass, Crohn’s disease, ulcerative colitis, cystic fibrosis, high blood pressure, diabetes, obesity, absence of the gastrointestinal tract-dwelling bacterium *Oxalobacter formigenes*, and ileal dysfunction.
47. The method of treating of claim 36 or 37, wherein the disease or disorder is a dietary hyperoxaluria.

48. The method of treating of claim 47, wherein the dietary hyperoxaluria is associated with and/or the result of one or more of a high oxalate diet, a high protein diet, a high oxalate precursor diet, and a low calcium diet.
49. The method of treating of claim 36 or 37, wherein the disease or disorder is an idiopathic hyperoxaluria.
50. The method of treating of claim 36 or 37, wherein the disease or disorder is a kidney disease.
51. The method of treating of claim 50, wherein the kidney disease is selected from the group consisting of: primary hyperoxaluria, dietary hyperoxaluria, kidney stones (nephrolithiasis), recurrent kidney stones, progressive kidney failure, nephrocalcinosis, urinary tract infections, end stage renal disease, chronic kidney disease (“CKD”), end-stage kidney disease (“ESKD”), hypertension, diabetes, urolithiasis, and systemic oxalosis.
52. The method of treating of claim 50, wherein the kidney disease is chronic kidney disease (“CKD”) or end-stage kidney disease (“ESKD”).
53. The method of treating of claim 36 or 37, wherein the disease or disorder is oxalate nephropathy or chronic calcium-oxalate nephropathy.
54. The method of treating of claim 36 or 37, wherein the disease or disorder is calcium oxalate (CaOx) stone disease, calcium oxalate (CaOx) nephrolithiasis, or renal failure.
55. A method of inhibiting the enzyme GO comprising administering to a patient suffering from such disease or disorder a compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35.

56. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35, for use as a medicament.
57. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35, for use in a method of treating a disease or disorder associated with a defect in glyoxylate metabolism.
58. The compound or pharmaceutically acceptable salt thereof for use or the pharmaceutical composition for use of claim 57, wherein the disease or disorder is primary hyperoxaluria.
59. The compound or pharmaceutically acceptable salt thereof of any one of claims 1-34 or the pharmaceutical composition of claim 35, for use in a method of treating a disease or disorder associated with the enzyme glycolate oxidase (GO) or alterations in oxalate metabolism.