

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

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
06 May 2021 (06.05.2021)



(10) International Publication Number
WO 2021/083209 A1

(51) International Patent Classification:

C07D 309/04 (2006.01)	C07D 205/04 (2006.01)
C07D 319/12 (2006.01)	C07D 275/02 (2006.01)
C07D 309/10 (2006.01)	C07D 207/06 (2006.01)
C07D 309/08 (2006.01)	C07D 401/04 (2006.01)
C07C 317/14 (2006.01)	C07D 295/08 (2006.01)
C07D 307/10 (2006.01)	A61K 31/10 (2006.01)
C07D 309/12 (2006.01)	A61P 3/00 (2006.01)
C07D 211/46 (2006.01)	A61P 9/00 (2006.01)
C07D 309/06 (2006.01)	A61P 29/00 (2006.01)

(21) International Application Number:

PCT/CN2020/124381

(22) International Filing Date:

28 October 2020 (28.10.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/CN2019/113957

29 October 2019 (29.10.2019) CN

PCT/CN2020/087022

26 April 2020 (26.04.2020) CN

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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, IT, 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,

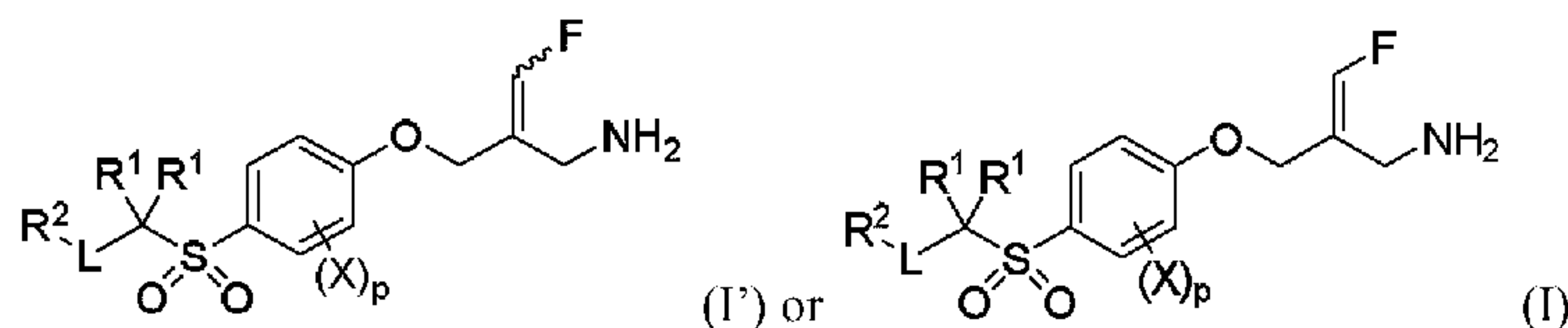
NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,
SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(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))

(54) Title: SSAO INHIBITORS AND USE THEREOF



(57) Abstract: Provided are a compound of formula (I') or (I), a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which modulates the activity of SSAO, a pharmaceutical composition comprising a compound of formula (I') or (I), and a method of treating or preventing a disease in which SSAO plays a role.

SSAO INHIBITORS AND USE THEREOF

BACKGROUND

[0001] Semicarbazide-sensitive amino oxidase/vascular adhesion protein-1 (SSAO/VAP-1) exists both as a membrane-bound isoform and a plasma soluble isoform. It is predominantly expressed in endothelial cell surface, vascular smooth muscle, and adipose cells. Both the membrane-bound VAP-1 protein and the soluble SSAO enzyme have amine oxidase enzymatic activity. SSAO catalyzes oxidative deamination of primary amines and produces aldehyde, hydrogen peroxide and ammonium. SSAO protein and activities are involved in leukocyte adhesion and migration from blood to tissue, which is often upregulated during inflammation.

[0002] SSAO/VAP-1 participates in many cellular processes including glucose disposition, inflammation responses and the associated pain, and leukocyte recruitment. High activity levels of this enzyme are associated with diabetes, atherosclerosis, stroke and complications thereof, chronic kidney disease, and Alzheimer's disease, among other disorders. SSAO/VAP-1 has also been implicated in the pathogenesis of liver diseases such as the fatty liver disease.

[0003] Nonalcoholic fatty liver disease (NAFLD) has shown an increasing prevalence, along with a global increase in diabetes and metabolic syndrome. NAFLD, a continuum of liver abnormalities from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), can be characterized as ectopic accumulation of lipid, progressive lobular inflammation, hepatocyte degeneration and fibrosis in liver. It has a variable course but can lead to cirrhosis, liver cancer and other liver related morbidities. Therefore, there is a need for treatments for NAFLD and/or NASH.

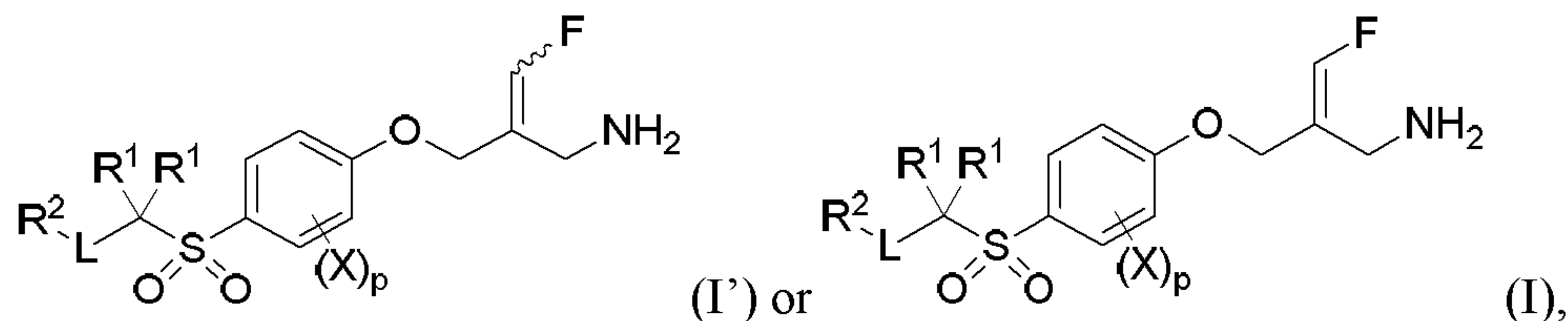
[0004] An SSAO/VAP-1 inhibitor is believed to be able to reduce liver inflammation and fibrosis, and thereby provide a treatment for liver diseases, in particular, NAFLD and/or NASH. In addition, since activation of SSAO/VAP-1 has been implicated in inflammation and the associated pain, inhibition of SSAO/VAP-1 may also be useful in treating pain, and in particular, pain associated with osteoarthritis.

[0005] Currently, there is no approved drugs for the treatment for NASH, while the standard of care for NASH including diet control and/or life style changes often lacks effect once liver cell injury and inflammation are evident. In addition, the current standard of care for pain is dominated by nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, which are not recommended for chronic use due to adverse effect and abuse. Thus, there is a need for

SSAO/VAP-1 inhibitors as therapeutic options for the treatment of chronic pain. The present application addresses the need.

SUMMARY

5 [0006] A first aspect of the application relates to a compound of Formula (I') or (I):



or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R¹, R², L, X, and p are as described in detail below.

10 [0007] Another aspect of the application relates to a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0008] Another aspect of the application relates to a method of treating a SSAO-mediated disorder. The method comprises administering to a subject in need of a treatment for a disease or disorder associated with modulation of SSAO a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

20 [0009] Another aspect of the application relates to a method of reducing liver inflammation. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

25 [0010] Another aspect of the application relates to a method of reducing neuroinflammation. The method comprises administering to a subject in need thereof a therapeutically effective

amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0011] Another aspect of the application relates to a method of reducing liver fibrosis. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0012] Another aspect of the application relates to a method of reducing lung fibrosis. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0013] Another aspect of the application relates to a method of treating liver diseases. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0014] Another aspect of the application relates to a method of treating nonalcoholic fatty liver disease (NAFLD). The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a

pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0015] Another aspect of the application relates to a method of treating nonalcoholic steatohepatitis (NASH). The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0016] Another aspect of the application relates to a method of treating cardiovascular diseases. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0017] Another aspect of the application relates to a method of treating atherosclerosis. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0018] Another aspect of the application relates to a method of treating stroke and complications thereof. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0019] Another aspect of the application relates to a method of treating myocardial infarction. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0020] Another aspect of the application relates to a method of treating chronic kidney diseases. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0021] Another aspect of the application relates to a method of treating autoimmune diseases. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0022] Another aspect of the application relates to a method of treating metabolic diseases. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0023] Another aspect of the application relates to a method of treating inflammation. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug,

stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

5 [0024] Another aspect of the application relates to a method of treating pain. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0025] Another aspect of the application relates to a method of treating pain associated with osteoarthritis. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0026] Another aspect of the application relates to a method of modulating (*e.g.*, inhibiting) SSAO. The method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier.

[0027] Another aspect of the application relates to a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier, for use in a method of treating a SSAO-mediated disorder or of modulating (*e.g.*, inhibiting) SSAO.

[0028] Another aspect of the application relates to use of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient, or carrier, in the manufacture of a medicament for treating a SSAO-mediated disorder or for modulating (*e.g.*, inhibiting) SSAO.

[0029] The present application further provides methods of treating a disease or disorder associated with modulation of SSAO including, but not limited to, liver diseases, nonalcoholic steatohepatitis (NASH), cardiovascular diseases, metabolic diseases, inflammation, and pain, comprising administering to a subject suffering from at least one of the diseases or disorders a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof.

[0030] The present application provides inhibitors of SSAO that are therapeutic agents in the treatment of diseases such as liver diseases, nonalcoholic steatohepatitis (NASH), cardiovascular diseases, metabolic diseases, inflammation, pain, and other disease associated with the modulation of SSAO.

[0031] The present application further provides compounds and compositions with an improved efficacy and safety profile relative to known SSAO inhibitors. The present application also provides agents with novel mechanisms of action toward SSAO in the treatment of various types of diseases including liver diseases, nonalcoholic steatohepatitis (NASH), cardiovascular diseases, metabolic diseases, inflammation, and pain. Ultimately the present application provides the medical community with a novel pharmacological strategy for the treatment of diseases and disorders associated with SSAO.

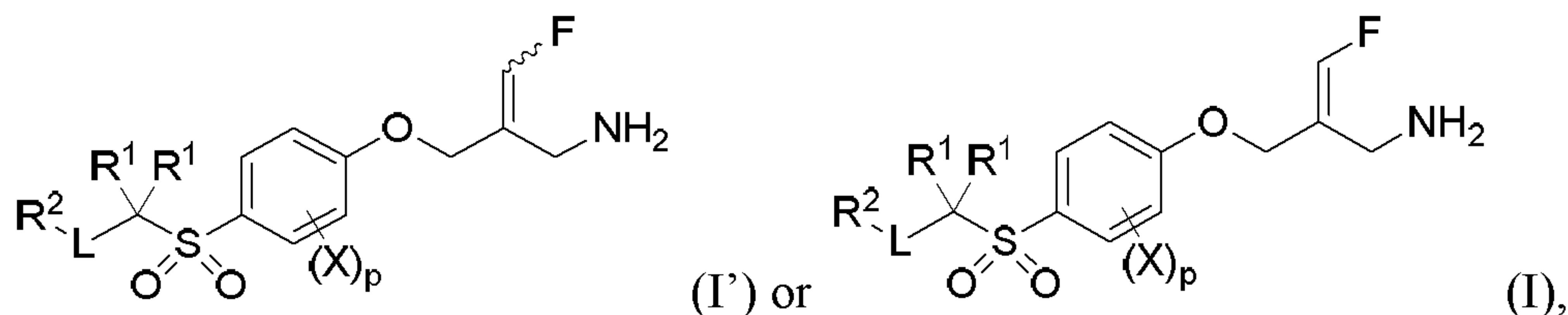
DETAILED DESCRIPTION

Compounds of the Application

[0032] The present application relates to compounds and compositions thereof that are capable of modulating the activity of semicarbazide-sensitive amino oxidase (SSAO). The application features methods of treating, preventing, or ameliorating a disease or disorder in which SSAO plays a role by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I') or (I), or a pharmaceutically acceptable salt, solvate,

prodrug, stereoisomer, or tautomer thereof. The compounds of the present application can be used in the treatment of a variety of SSAO-mediated diseases and disorders by inhibiting the activity of SSAO. Inhibition of SSAO provides treatment, prevention, or amelioration of diseases including, but not limited to, liver diseases, nonalcoholic steatohepatitis (NASH), cardiovascular diseases, metabolic diseases, inflammation, and pain.

[0033] In a first aspect of the application, a compound of Formula (I') or (I) is described:



or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

each X is independently Cl or F;

p is 0, 1, 2, or 3;

L is absent, -O-, (C₁-C₄) alkylene, substituted (C₁-C₄) alkylene, -O-(C₁-C₄) alkylene, substituted -O-(C₁-C₄) alkylene, (C₁-C₄) alkylene-O-, or substituted (C₁-C₄) alkylene-O-, wherein the substituted (C₁-C₄) alkylene, substituted -O-(C₁-C₄) alkylene, or substituted (C₁-C₄) alkylene-O- is substituted with one or more L¹;

each L¹ is independently (C₁-C₄) alkyl, F, or CF₃; or two L¹, together with the atom to which they are attached, form a 3- to 5-membered cycloalkyl ring;

each R¹ is independently H, F, methyl, ethyl, or CF₃;

R² is (C₁-C₄) alkyl substituted with one or more (C₁-C₄) alkoxy, (C₁-C₄) alkoxy, NR³C(O)R⁴, C(O)NR³R⁴, phenyl, (C₃-C₈) cycloalkyl, heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O, or heteroaryl comprising one or two 5- to 6-membered rings and 1 to 3 heteroatoms selected from N and O, wherein the phenyl, cycloalkyl, heterocyclyl, or heteroaryl is optionally substituted with one or more R⁵;

R³ is H, methyl, or ethyl;

R⁴ is (C₁-C₄) alkyl or (C₃-C₁₀) cycloalkyl optionally substituted with one or more R⁸; or R³ and R⁴, together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵;

each R^5 is independently (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy, cyano, oxo, $C(O)R^7$, $C(O)NR^7R^{7'}$, $NR^3C(O)R^7$, $NR^3S(O)_2R^4$, $S(O)_2R^4$, (C_1-C_4) alkyl substituted with one or more hydroxy or R^6 , (C_3-C_{10}) cycloalkyl optionally substituted with one or more hydroxy or R^6 , or heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 ; or two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated or 5- or 6-membered aromatic ring optionally comprising 1 or 2 heteroatoms selected from N and O;

each R^6 is independently $NR^3C(O)R^7$ or $C(O)NR^3R^7$;

each R^7 is independently

OH, (C_1-C_4) alkoxy, (C_1-C_6) alkyl optionally substituted with one or more (C_1-C_4) alkoxy, CF_3 , F, or (C_3-C_{10}) cycloalkyl,

(C_3-C_{10}) cycloalkyl optionally substituted with one or more R^8 , or

phenyl optionally substituted with one or more R^8 ;

each $R^{7'}$ is independently H, methyl, or ethyl; or

R^7 and $R^{7'}$, together with the atom to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 ; or

R^3 and R^7 , together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 ; and

each R^8 is independently (C_1-C_4) alkyl, (C_1-C_4) alkoxy, CF_3 , OH, or F.

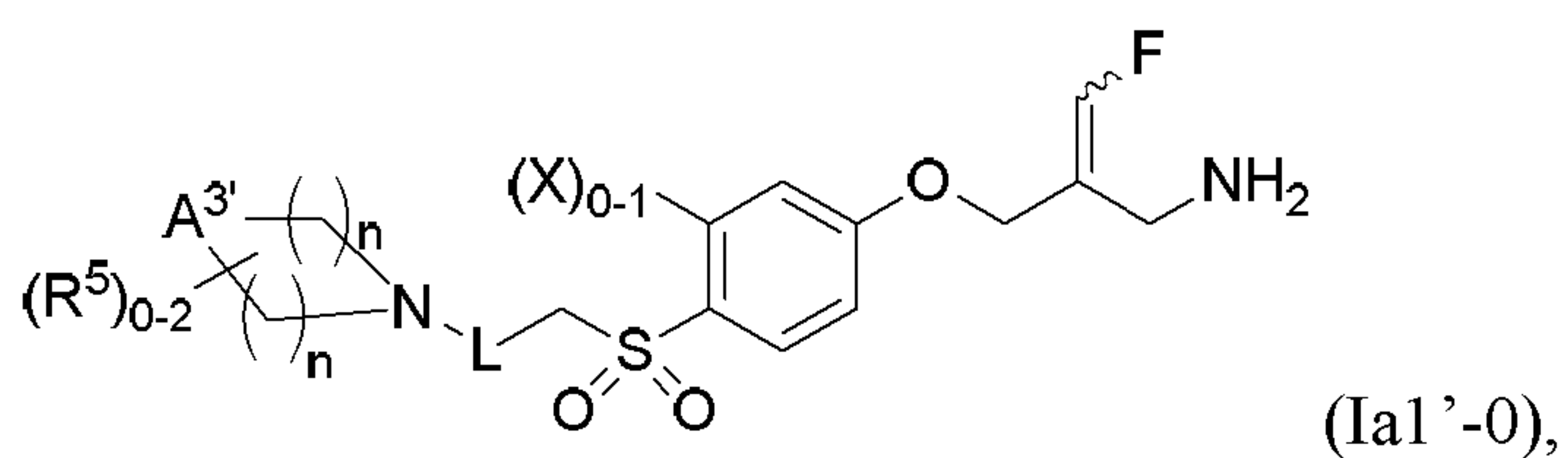
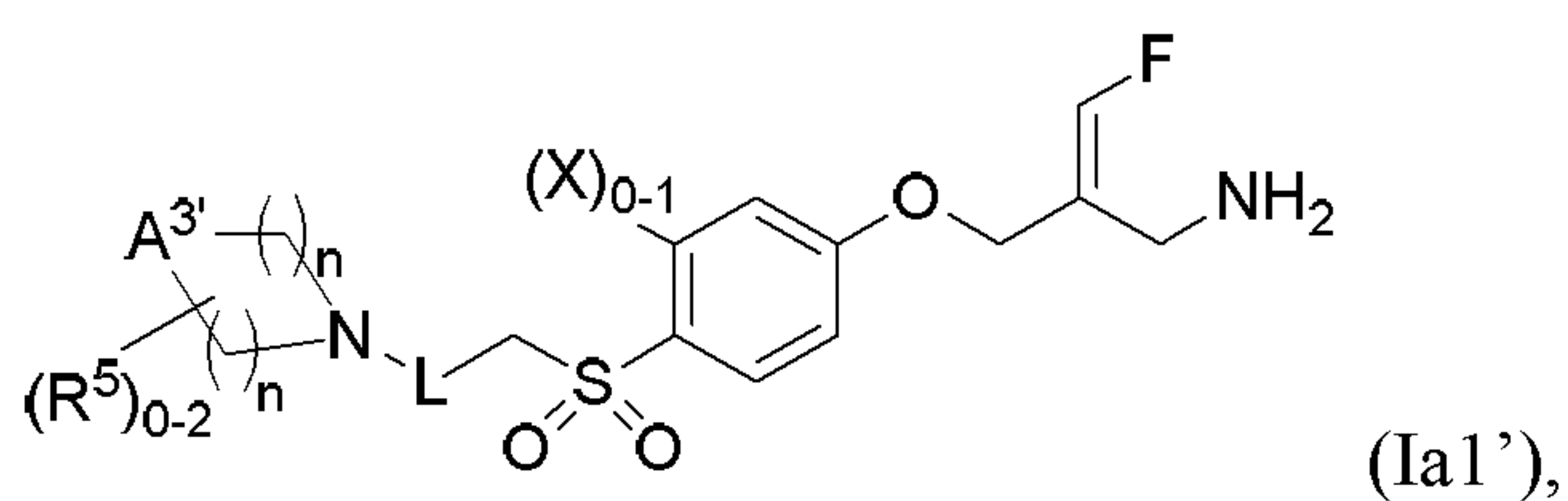
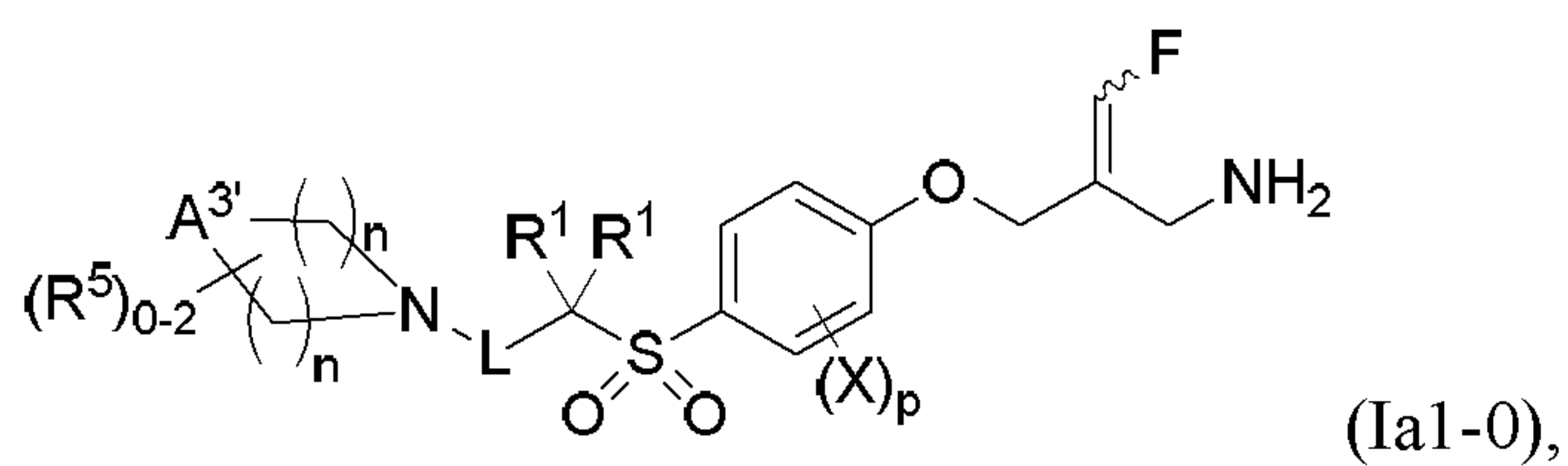
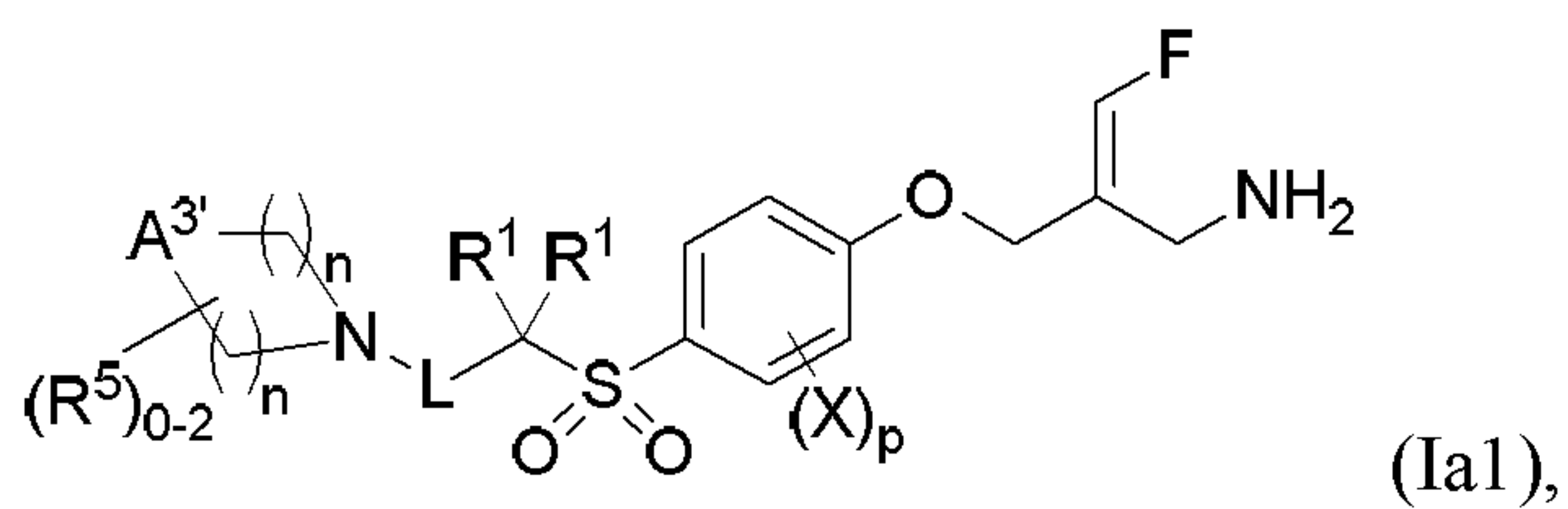
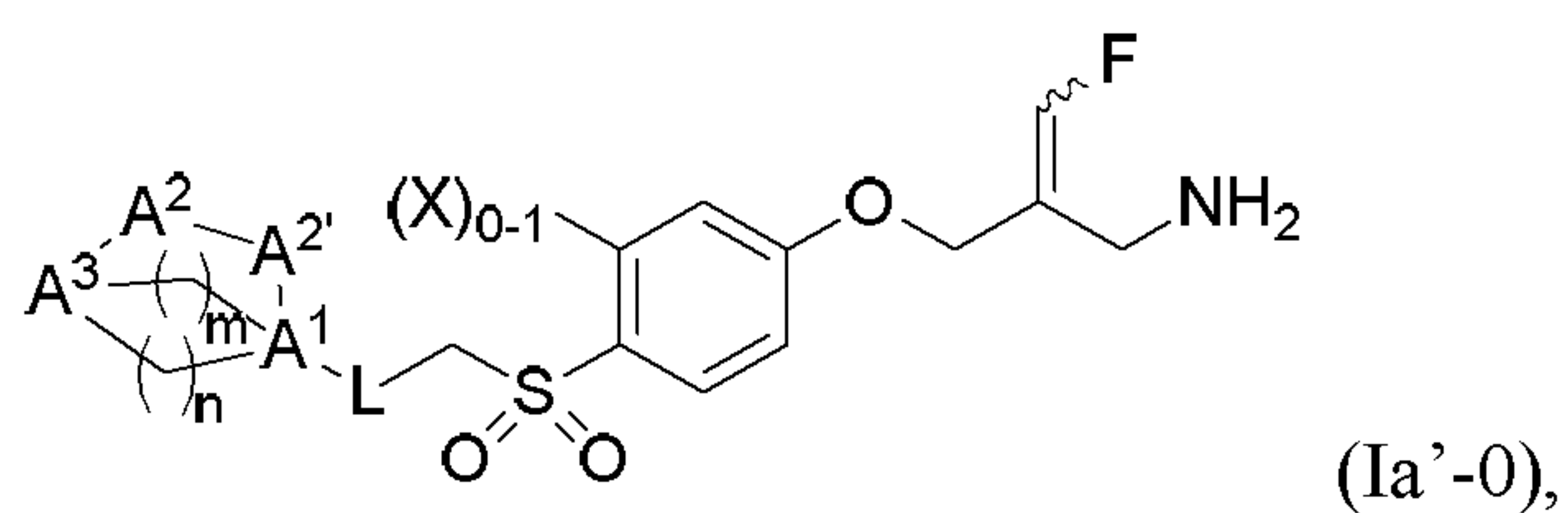
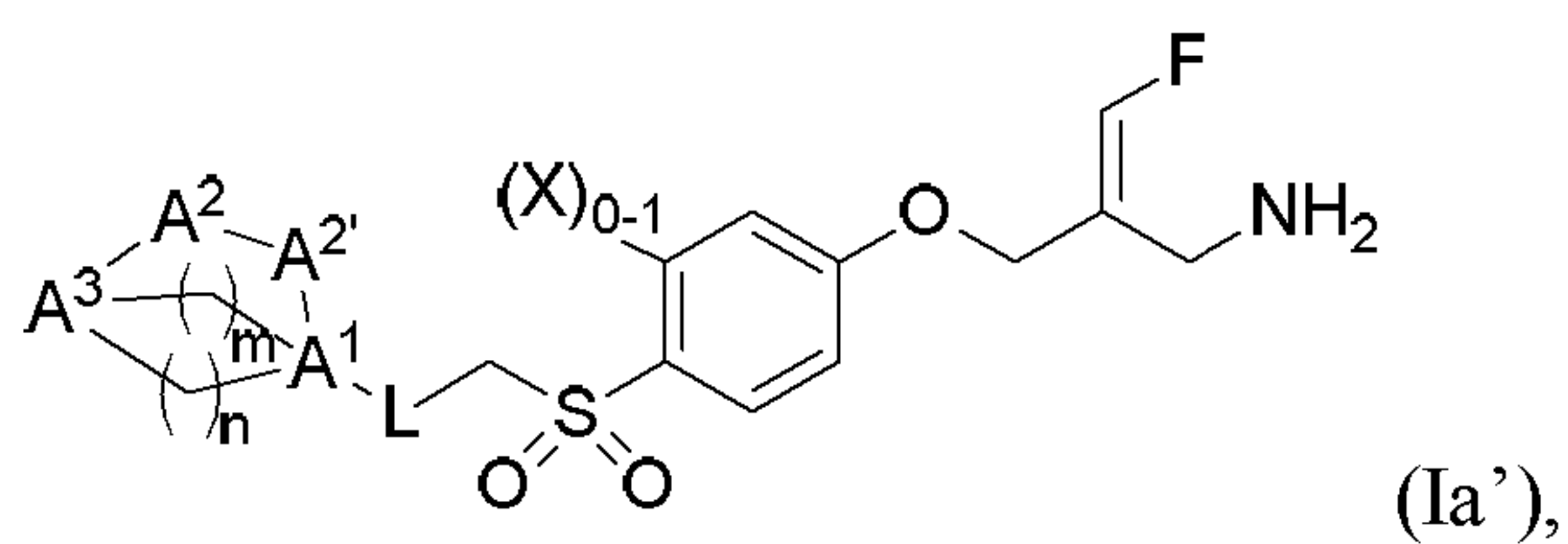
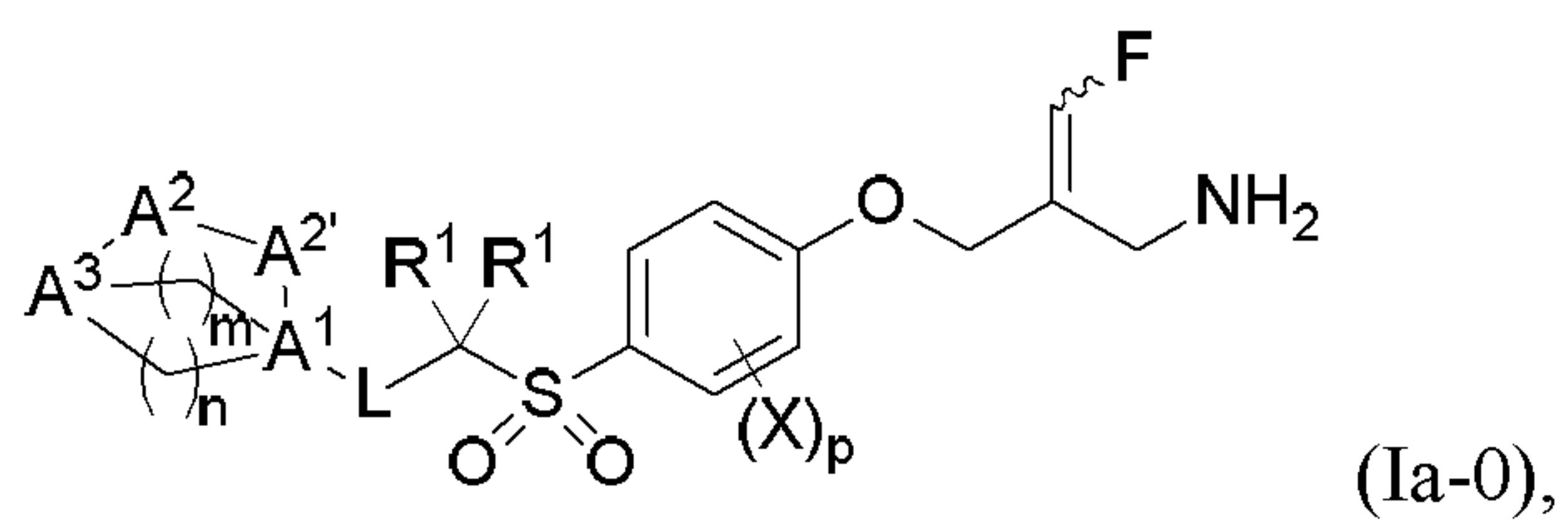
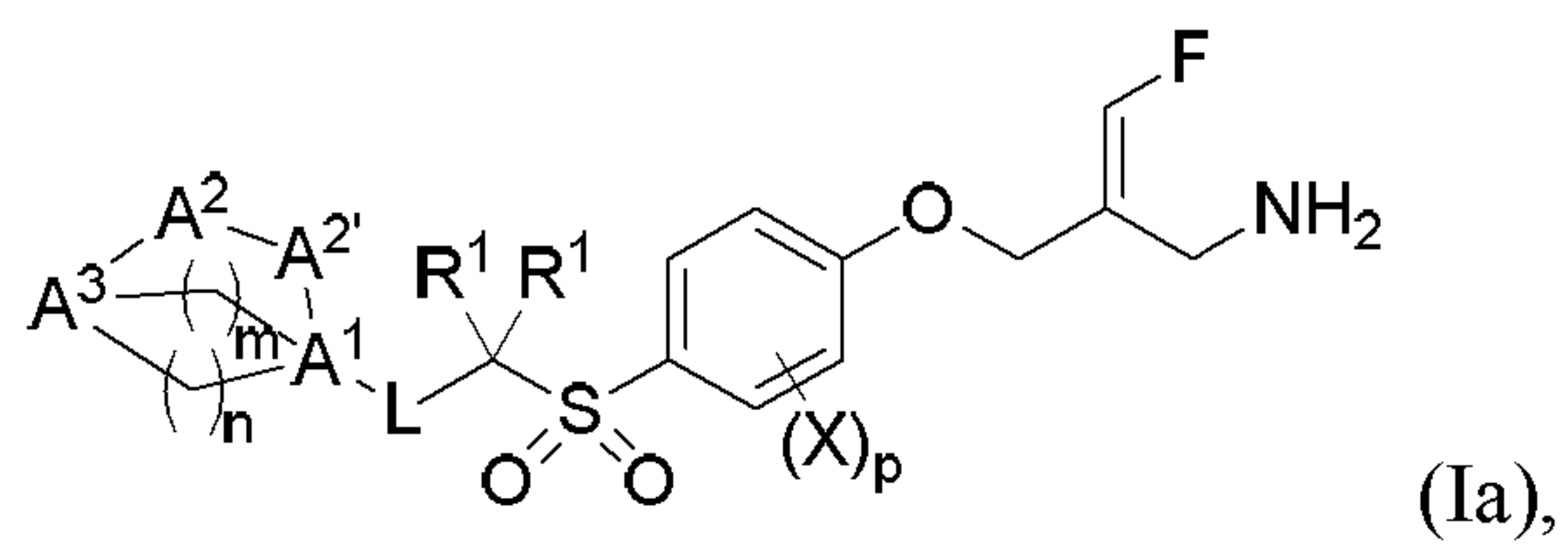
[0034] In some embodiments, in the compounds of Formula (I') or (I), each R^7 is independently

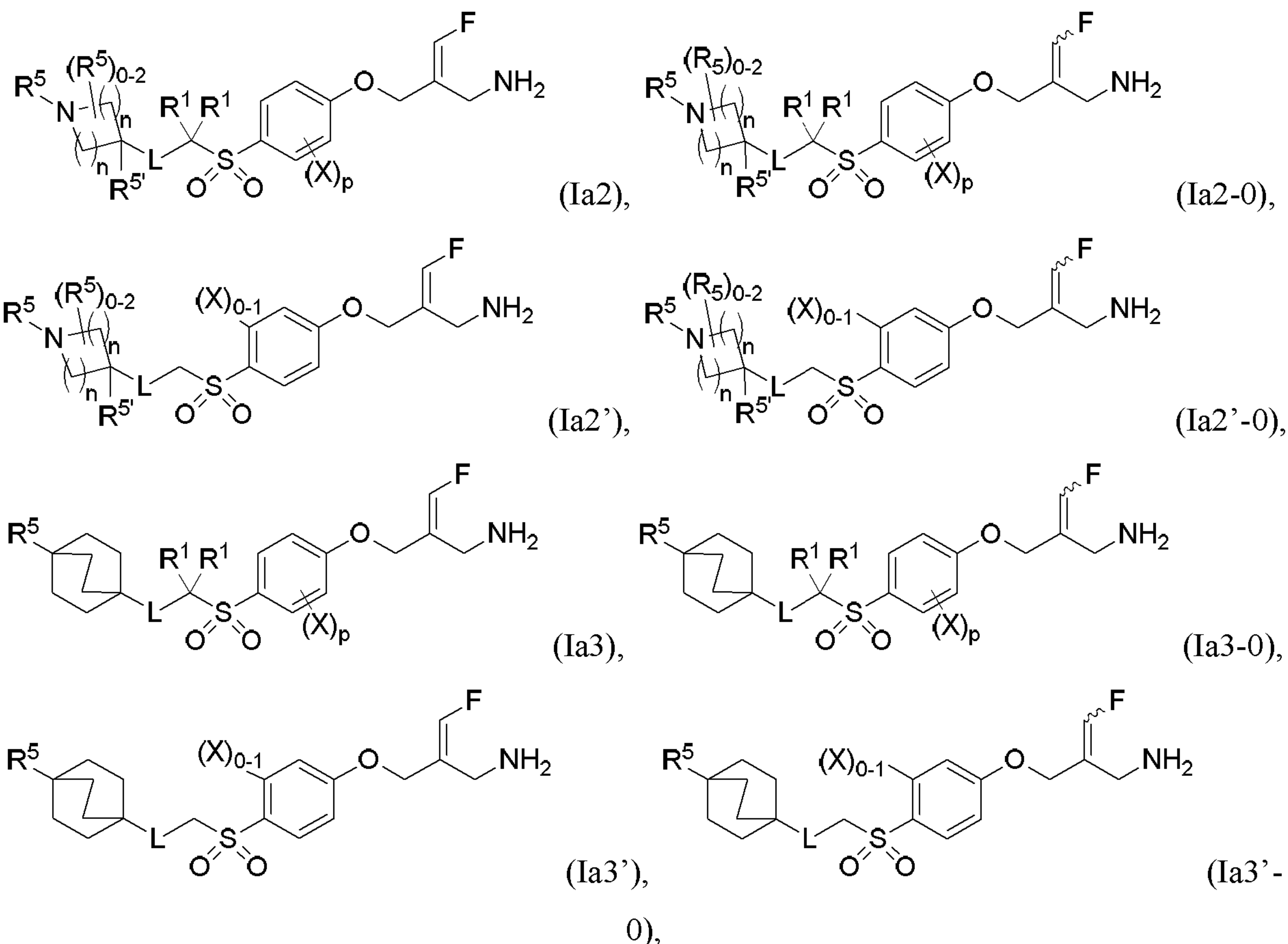
(C_1-C_4) alkoxy, (C_1-C_6) alkyl optionally substituted with one or more (C_1-C_4) alkoxy, CF_3 , F, or (C_3-C_{10}) cycloalkyl,

(C_3-C_{10}) cycloalkyl optionally substituted with one or more R^8 , or

phenyl optionally substituted with one or more R^8 .

[0035] In some embodiments, the compounds of Formula (I') or (I) have the structure of Formula (Ia), (Ia-0), (Ia'), (Ia'-0), (Ia1), (Ia1-0), (Ia1'), (Ia1'-0), (Ia2), (Ia2-0), (Ia2'), (Ia2'-0), (Ia3), (Ia3-0), (Ia3'), or (Ia3'-0):





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or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

A^1 is N or $CR^{5'}$;

$R^{5'}$ is H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy, or cyano;

10 A^2 and $A^{2'}$ are each independently absent, CH_2 , CHR^5 , $C(R^5)_2$, NH, NR^5 , or O, provided that at least one of A^2 and $A^{2'}$ is not absent and that $A^2-A^{2'}$ is not O-O, O-NH, O- NR^5 , NH-O, NH-NH, NH- NR^5 , NR^5 -O, NR^5 -NH, or NR^5 - NR^5 ;

A^3 is CH_2 , CHR^5 , $C(R^5)_2$, NH, NR^5 , or O when m is 0, or CH or CR^5 when m is 1 or 2, provided that A^2-A^3 is not O-O, O-NH, O- NR^5 , NH-O, NH-NH, NH- NR^5 , NR^5 -O, NR^5 -NH, or NR^5 - NR^5 ;

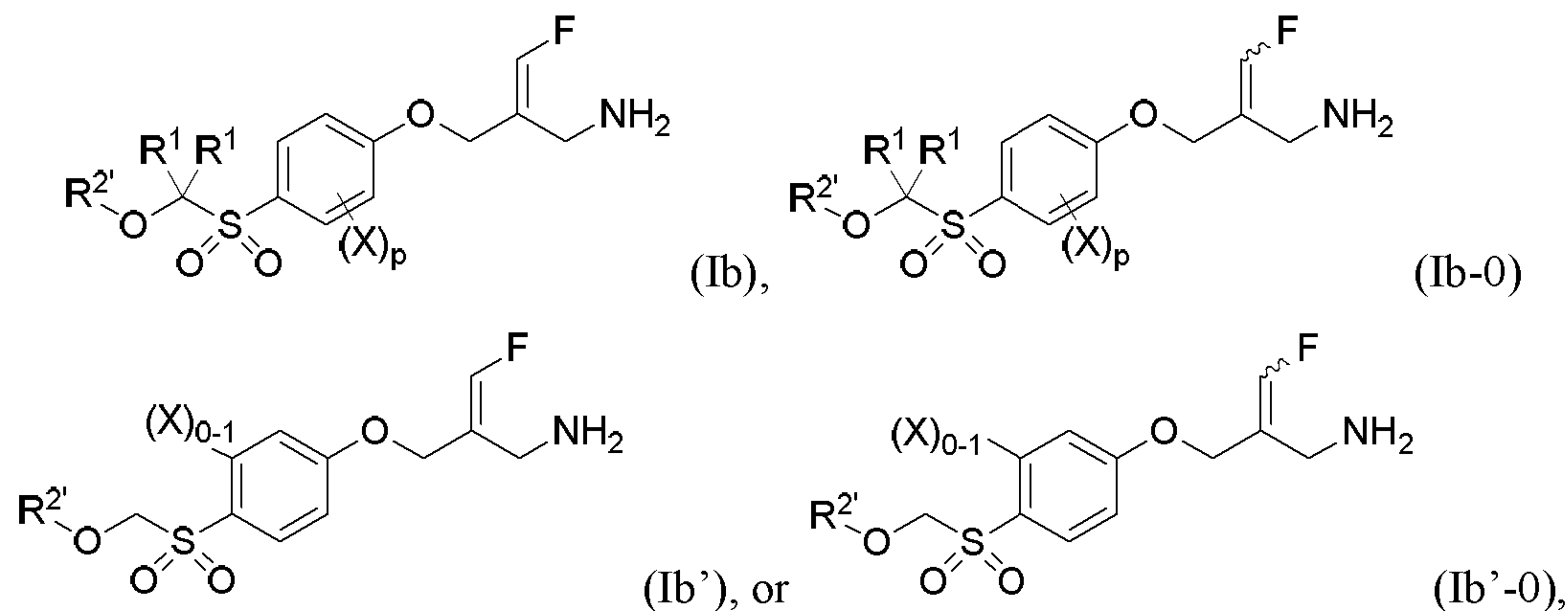
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$A^{3'}$ is CH_2 , CHR^5 , $C(R^5)_2$, NH, NR^5 , or O;

m is 0, 1, or 2; and

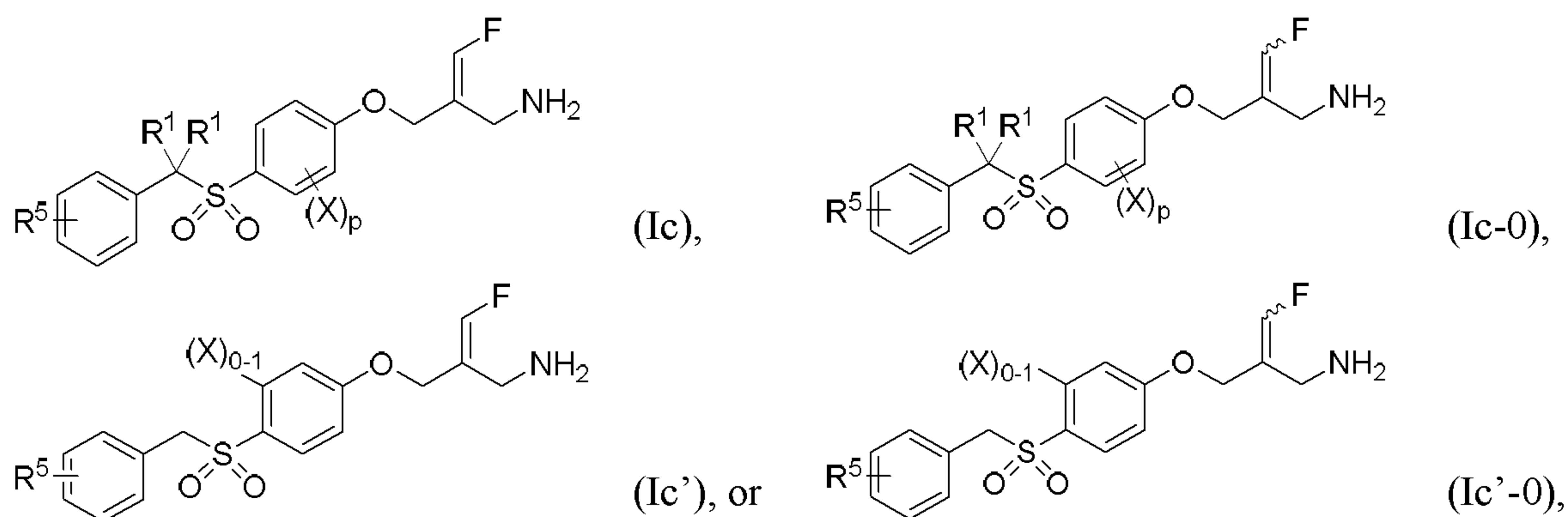
n is 1 or 2.

[0036] In some embodiments, the compounds of Formula (I') or (I) have the structure of Formula (Ib), (Ib-0), (Ib'), or (Ib'-0):



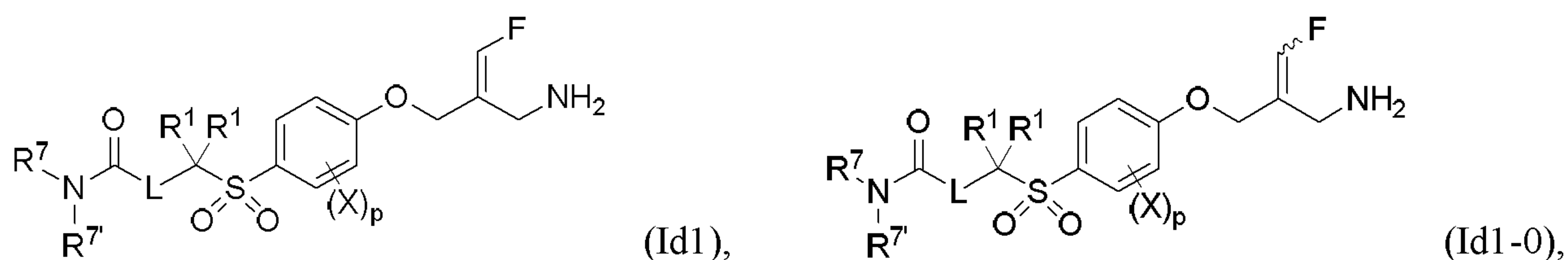
5 and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein $\text{R}^{2'}$ is (C_1-C_4) alkyl substituted with one or more (C_1-C_4) alkoxy, (C_1-C_4) alkoxy, $\text{NR}^3\text{C}(\text{O})\text{R}^4$, $\text{C}(\text{O})\text{NR}^3\text{R}^4$, or heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O, wherein the heterocyclyl is optionally substituted with one or more R^5 .

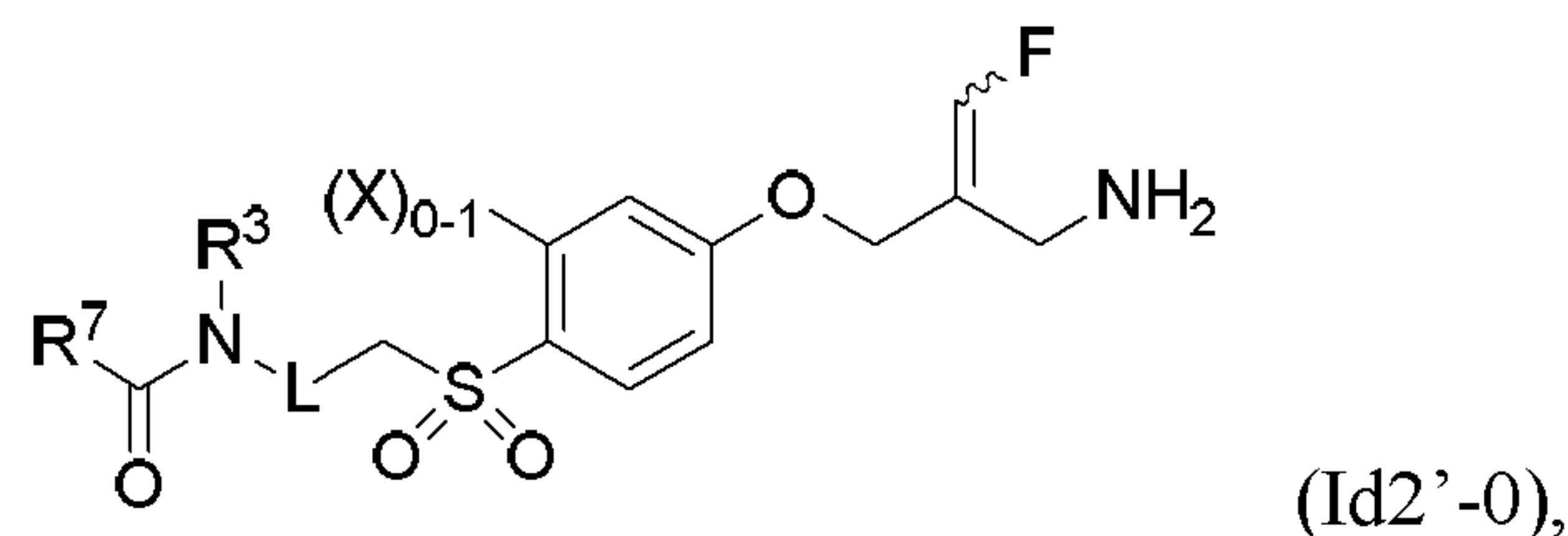
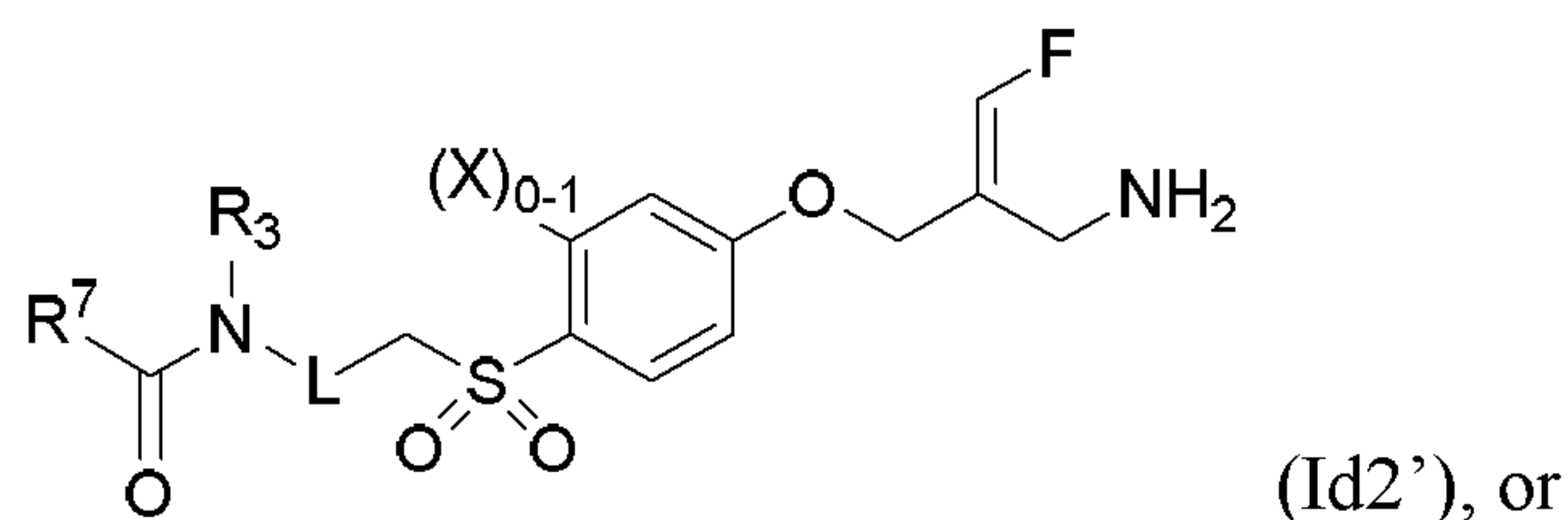
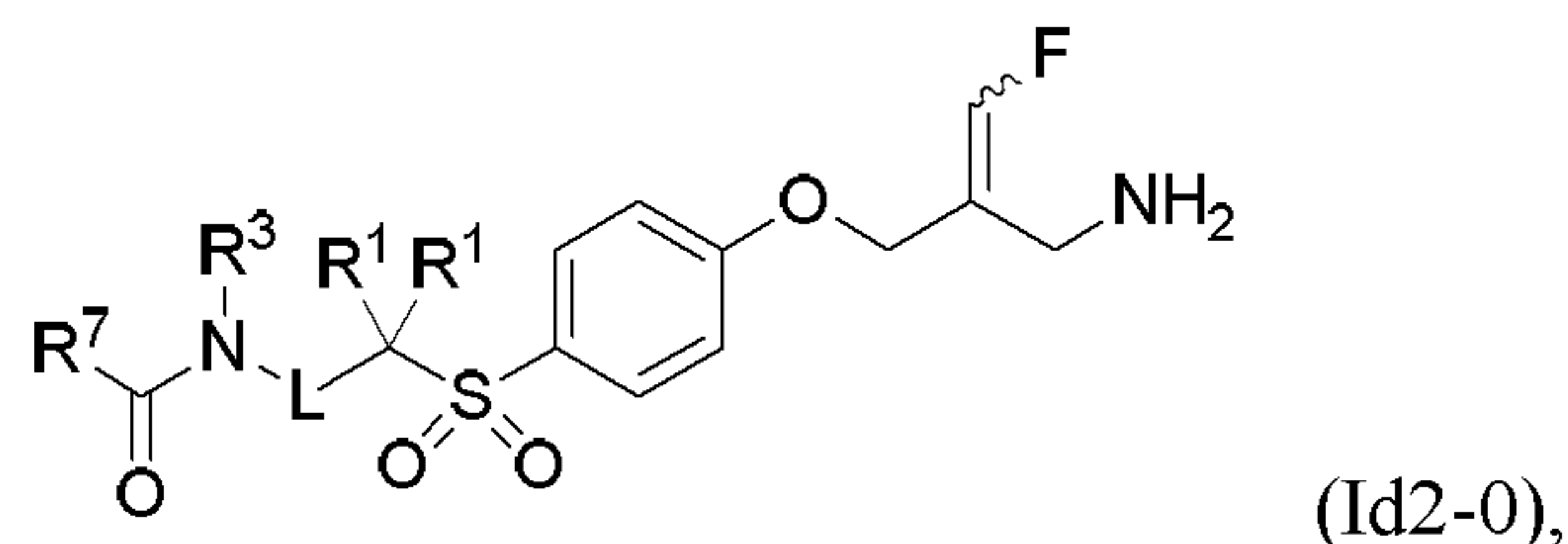
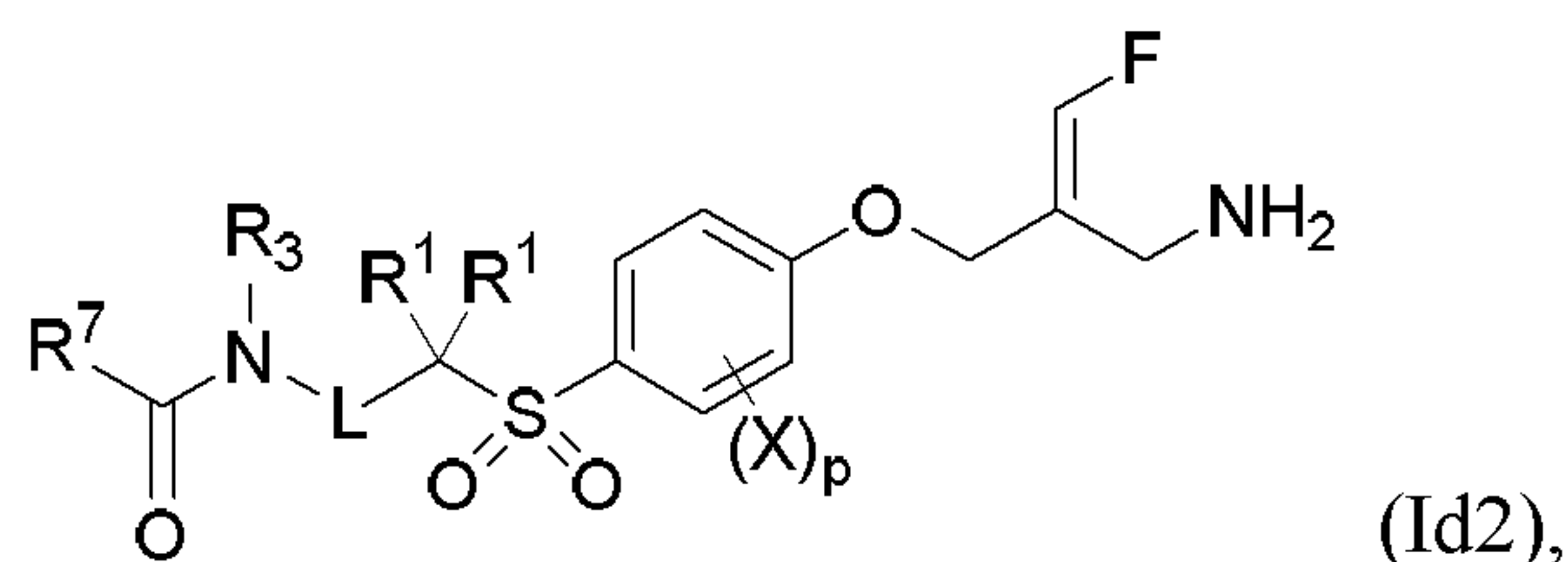
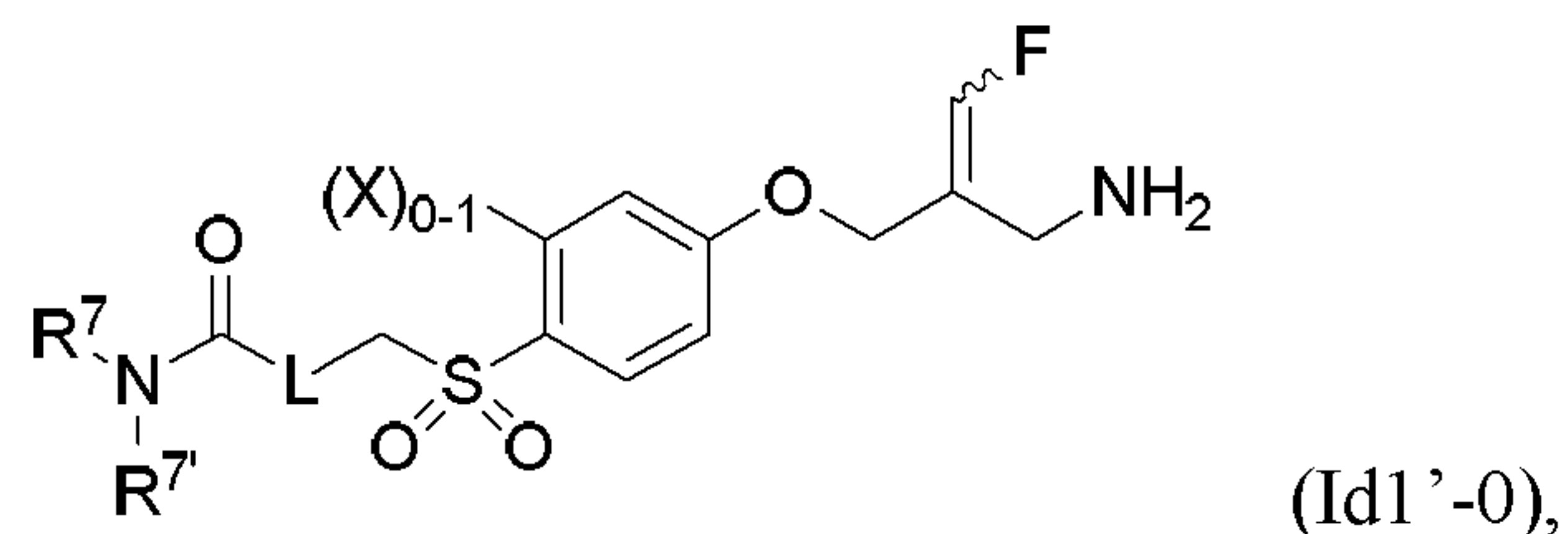
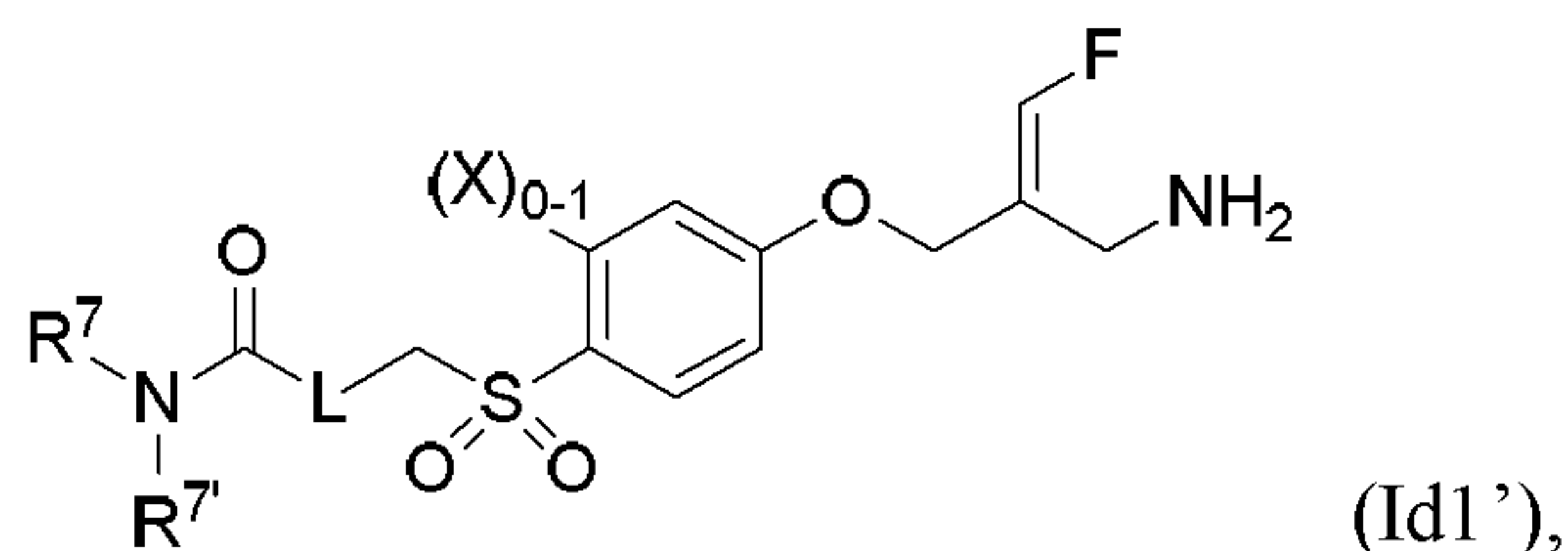
10 [0037] In some embodiments, the compounds of Formula (I') or (I) have the structure of Formula (Ic), (Ic-0), (Ic'), or (Ic'-0):



and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0038] In some embodiments, the compounds of Formula (I') or (I) have the structure of Formula (Id1), (Id1-0), (Id1'), (Id1'-0), (Id2), (Id2-0), (Id2'), or (Id2'-0):





and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

[0039] For the formulae above, where applicable:

[0040] In some embodiments, L is absent, -O-, (C₁-C₄) alkylene, substituted (C₁-C₄) alkylene, (C₁-C₄) alkylene-O-, or substituted (C₁-C₄) alkylene-O-.

5 [0041] In some embodiments, L is absent, -O-, (C₁-C₂) alkylene, substituted (C₁-C₂) alkylene, (C₁-C₂) alkylene-O-, or substituted (C₁-C₂) alkylene-O-.

[0042] In some embodiments, L is absent or -O-.

[0043] In some embodiments, L is absent.

[0044] In some embodiments, L is -O-.

10 [0045] In some embodiments, L is (C₁-C₂) alkylene substituted with one or more L¹.

[0046] In some embodiments, L is (C₁-C₂) alkylene-O- or (C₁-C₂) alkylene-O- substituted with one or more L¹.

[0047] In some embodiments, each L¹ is independently (C₁-C₄) alkyl, F, or CF₃.

[0048] In some embodiments, each L¹ is independently methyl, ethyl, F, or CF₃.

15 [0049] In some embodiments, each L¹ is independently methyl or ethyl.

[0050] In some embodiments, two L¹, together with the atom to which they are attached, form a cyclopropyl, cyclobutyl, or cyclopentyl ring.

[0051] In some embodiments, two L¹, together with the atom to which they are attached, form a cyclopropyl ring.

[0052] In some embodiments, each R^1 is H.

[0053] In some embodiments, each R^1 is independently F, methyl, ethyl, or CF_3 .

[0054] In some embodiments, each R^1 is independently methyl or ethyl.

[0055] In some embodiments, each R^1 is independently methyl or CF_3 .

5 [0056] In some embodiments, R^2 is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl) substituted with one or more (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy).

[0057] In some embodiments, R^2 is methyl or ethyl substituted with methoxy or ethoxy.

10 [0058] In some embodiments, R^2 is (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy).

[0059] In some embodiments, R^2 is methoxy or ethoxy.

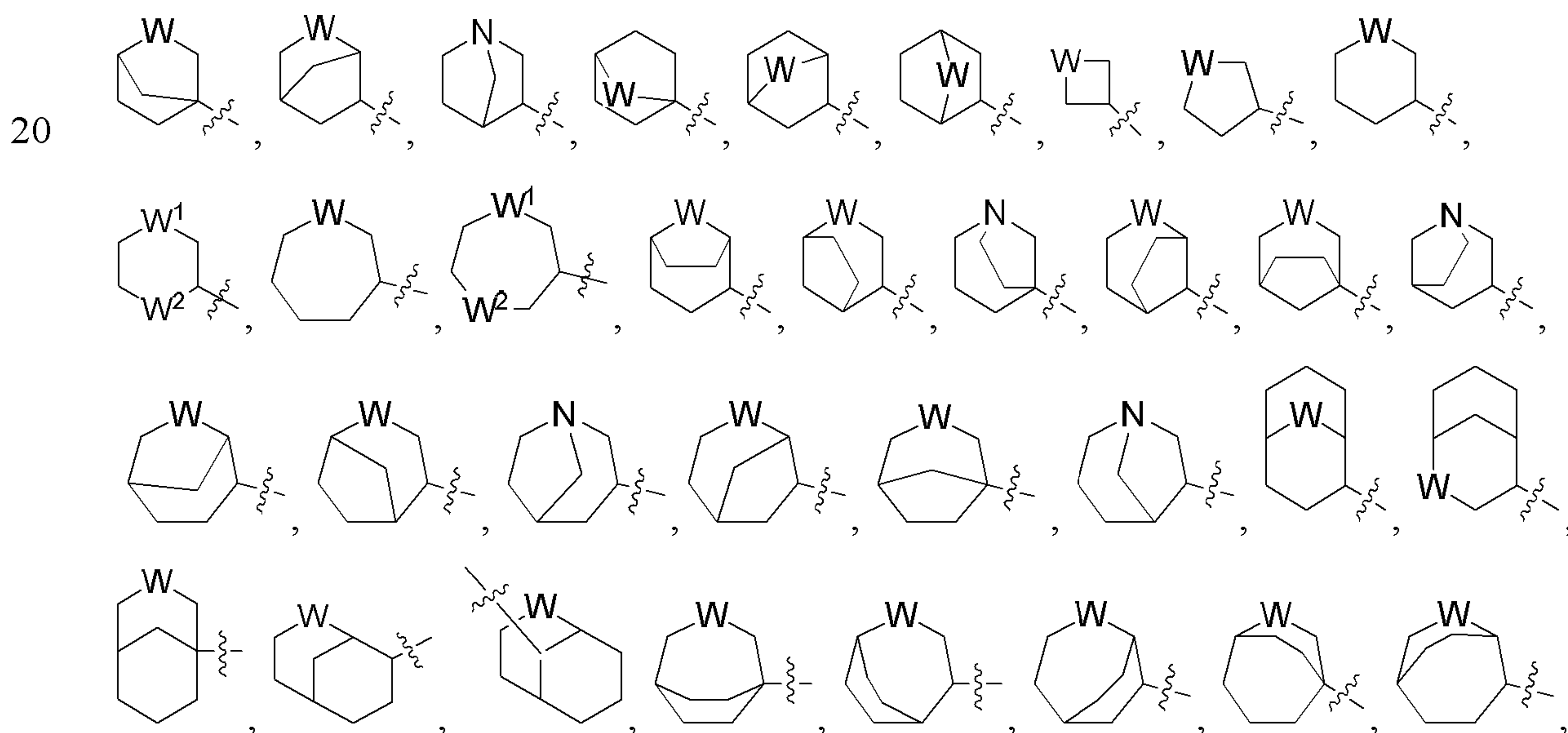
[0060] In some embodiments, R^2 is $NR^3C(O)R^4$ or $C(O)NR^3R^4$.

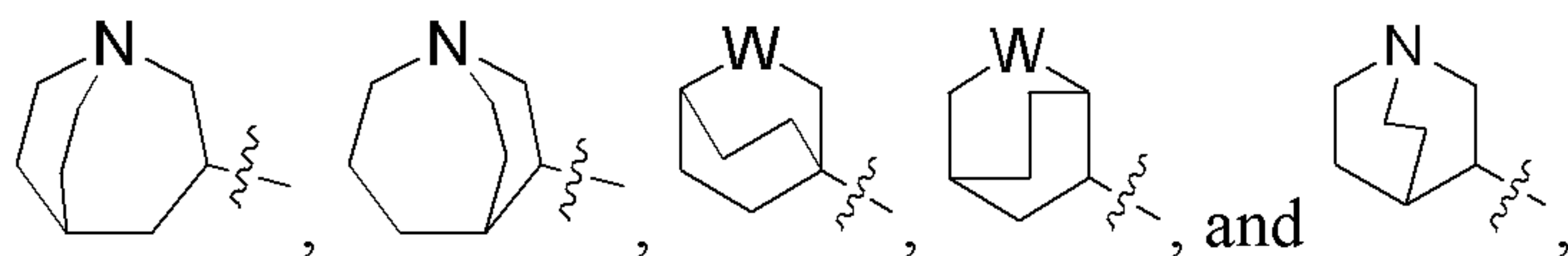
[0061] In some embodiments, R^2 is phenyl optionally substituted with one or more R^5 .

15 [0062] In some embodiments, R^2 is (C_3-C_8) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, or spiro-, bridged-, or fused cycloalkyl) optionally substituted with one or more R^5 .

[0063] In some embodiments, R^2 is heterocyclyl (*e.g.*, spiro-, bridged-, or fused-heterocyclyl) optionally substituted with one or more R^5 .

[0064] In some embodiments, R^2 is a heterocyclyl selected from:





wherein W, W¹ and W² are each independently CH₂, CHR⁵, C(R⁵)₂, O, S, NH, or NR⁵, each optionally substituted with one or more R⁵.

[0065] In some embodiments, R² is heteroaryl optionally substituted with one or more R⁵.

5 [0066] In some embodiments, R^{2'} is (C₁–C₄) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl) substituted with one or more (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy).

[0067] In some embodiments, R^{2'} is methyl or ethyl substituted with methoxy or ethoxy.

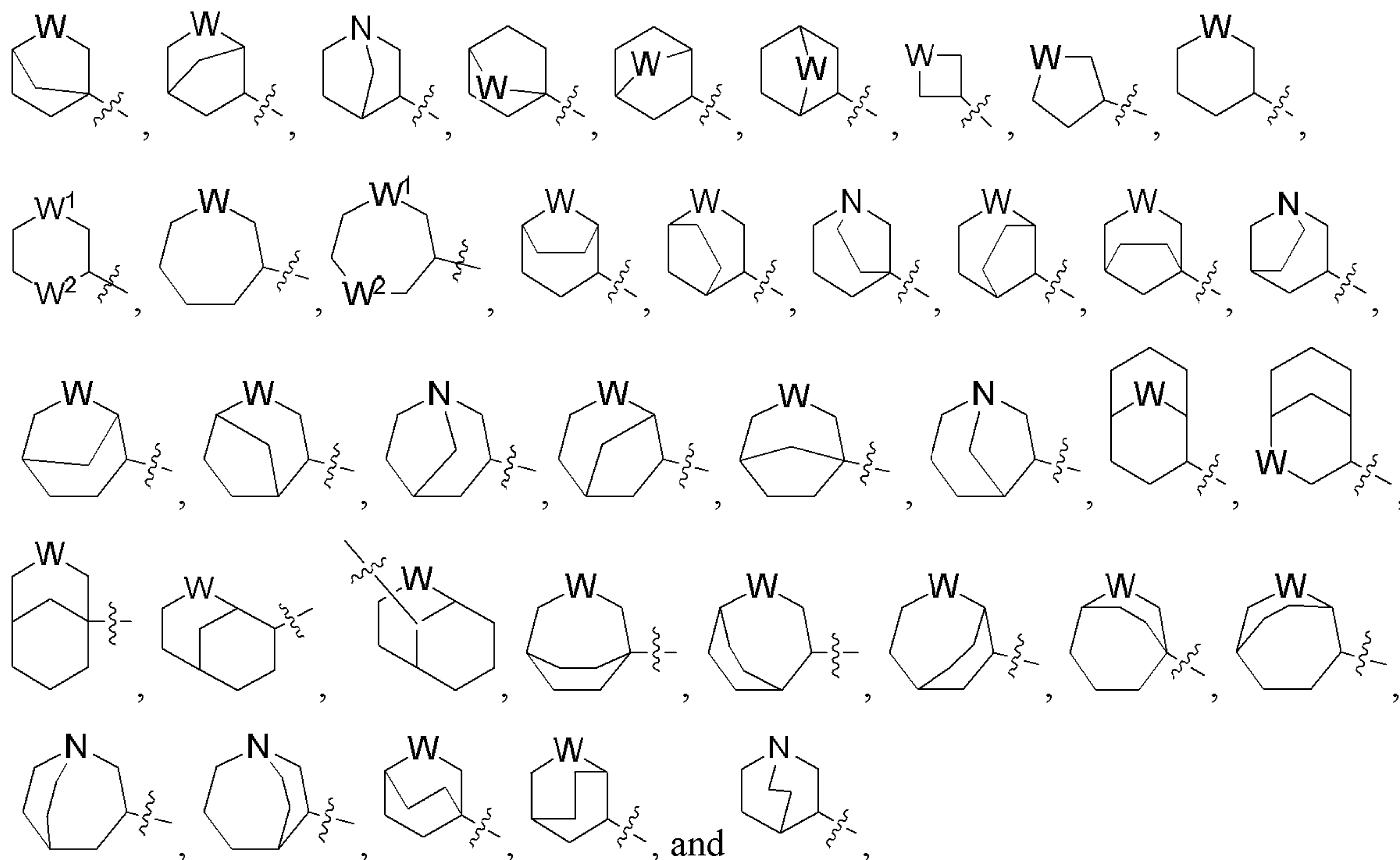
10 [0068] In some embodiments, R^{2'} is (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy).

[0069] In some embodiments, R^{2'} is methoxy or ethoxy.

[0070] In some embodiments, R^{2'} is NR³C(O)R⁴ or C(O)NR³R⁴.

[0071] In some embodiments, R^{2'} is heterocyclyl (*e.g.*, spiro-, bridged-, or fused-heterocyclyl) optionally substituted with one or more R⁵.

15 [0072] In some embodiments, R^{2'} is a heterocyclyl selected from:



20

wherein W, W¹ and W² are each independently CH₂, CHR⁵, C(R⁵)₂, O, S, NH, or NR⁵, each optionally substituted with one or more R⁵.

[0073] In some embodiments, R³ is H,

[0074] In some embodiments, R³ is methyl or ethyl.

5 [0075] In some embodiments, R⁴ is methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl.

[0076] In some embodiments, R⁴ is methyl or ethyl.

[0077] In some embodiments, R⁴ is (C₃–C₁₀) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, or spiro-, bridged-, or fused cycloalkyl)
10 optionally substituted with one or more R⁸. In some embodiments, R⁴ is (C₃–C₆) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or spiro-, bridged-, or fused cycloalkyl) optionally substituted with one or more R⁸. In some embodiments, R⁴ is cyclopropyl or cyclobutyl optionally substituted with one or more R⁸.

[0078] In some embodiments, R³ and R⁴, together with atom(s) to which they are attached,
15 form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵. In some embodiments, each R⁵ is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

[0079] In some embodiments, R³ and R⁴, together with atom(s) to which they are attached,
20 form a 4- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵. In some embodiments, each R⁵ is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

[0080] In some embodiments, R³ and R⁴, together with atom(s) to which they are attached,
25 form a 3-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵. In some embodiments, each R⁵ is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

[0081] In some embodiments, R³ and R⁴, together with atom(s) to which they are attached,
form a 4-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵. In some embodiments, each R⁵ is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

30 [0082] In some embodiments, R³ and R⁴, together with atom(s) to which they are attached,
form a 5-membered ring optionally comprising one additional heteroatom selected from N and O

and optionally substituted with one or more R^5 . In some embodiments, each R^5 is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

[0083] In some embodiments, R^3 and R^4 , together with atom(s) to which they are attached, form a 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^5 . In some embodiments, each R^5 is independently selected from methyl, ethyl, cyclopentyl, and phenyl.

[0084] In some embodiments, at least one R^5 is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl), (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), hydroxy, cyano, oxo, $C(O)R^7$, $C(O)NR^7R^7$, $NR^3C(O)R^7$, $NR^3S(O)_2R^4$, $S(O)_2R^4$, or (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl)) substituted with one or more hydroxy or R^6 .

[0085] In some embodiments, at least one R^5 is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl), (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), hydroxy, cyano, oxo, or (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl)) substituted with one or more hydroxy or R^6 .

[0086] In some embodiments, at least one R^5 is methyl, methoxy, hydroxy, or cyano.

[0087] In some embodiments, at least one R^5 is $C(O)R^7$, $C(O)NR^7R^7$, $NR^3C(O)R^7$, $NR^3S(O)_2R^4$, or $S(O)_2R^4$.

[0088] In some embodiments, at least one R^5 is $C(O)R^7$, $C(O)NR^7R^7$, or $NR^3C(O)R^7$.

[0089] In some embodiments, at least one R^5 is (C_3-C_{10}) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, or spiro-, bridged-, or fused cycloalkyl) optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is (C_3-C_6) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or spiro-, bridged-, or fused cycloalkyl) optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is cyclopropyl or cyclobutyl optionally substituted with one or more hydroxy or R^6 .

[0090] In some embodiments, at least one R^5 is heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is heterocyclyl comprising one 3- to 6-membering ring and 1 to 3 heteroatoms selected from N and O and optionally

substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is heterocyclyl comprising one 3- to 6-membering ring and 1 to 2 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is heterocyclyl comprising one 3- to 6-membering ring and 1 heteroatom selected from N and O and optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is heterocyclyl comprising two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 . In some embodiments, at least one R^5 is heterocyclyl comprising two 3- to 6-membering rings and 1 to 2 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 .

10 [0091] In some embodiments, at least two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated or 5- or 6-membered aromatic ring optionally comprising 1 or 2 heteroatoms selected from N and O.

[0092] In some embodiments, at least two R^5 , together with the atom or atoms to which they are attached, form a phenyl ring.

15 [0093] In some embodiments, at least two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated ring optionally comprising 1 or 2 heteroatoms selected from N and O.

[0094] In some embodiments, at least one R^5 is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl), (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), hydroxy, cyano, oxo, or (C_1-C_4) alkyl substituted with one or more hydroxy or R^6 .

[0095] In some embodiments, $R^{5'}$ is H.

[0096] In some embodiments, $R^{5'}$ is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl), (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), hydroxy, or cyano.

[0097] In some embodiments, $R^{5'}$ is methyl, methoxy, hydroxy, or cyano.

[0098] In some embodiments, at least one R^6 is $NR^3C(O)R^7$.

[0099] In some embodiments, at least one R^6 is $C(O)NR^3R^7$.

[00100] In some embodiments, each R^7 is independently
 30 (C_1-C_4) alkoxy, (C_1-C_6) alkyl optionally substituted with one or more (C_1-C_4) alkoxy, CF_3 , F, or (C_3-C_{10}) cycloalkyl,

(C₃–C₁₀) cycloalkyl optionally substituted with one or more R⁸, or
phenyl optionally substituted with one or more R⁸.

[00101] In some embodiments, at least one R⁷ is (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), (C₁–C₆) alkyl (*e.g.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl) optionally substituted with one or more (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), CF₃, F, or (C₃–C₁₀) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl).

[00102] In some embodiments, at least one R⁷ is (C₁–C₆) alkyl (*e.g.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl) or (C₁–C₆) alkyl (*e.g.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl) substituted with one or more (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), CF₃, F, or (C₃–C₁₀) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, or spiro-, bridged-, or fused cycloalkyl).

[00103] In some embodiments, at least one R⁷ is (C₁–C₆) alkyl (*e.g.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl) or (C₁–C₆) alkyl (*e.g.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, pentyl, or hexyl) substituted with one or more (C₁–C₄) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy), CF₃, F, or (C₃–C₆) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or spiro-, bridged-, or fused cycloalkyl).

[00104] In some embodiments, at least one R⁷ is methyl or ethyl.

[00105] In some embodiments, at least one R⁷ is (C₃–C₁₀) cycloalkyl (*e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, or spiro-, bridged-, or fused cycloalkyl) optionally substituted with one or more R⁸.

[00106] In some embodiments, at least one R⁷ is phenyl optionally substituted with one or more R⁸.

[00107] In some embodiments, each R⁷ is H,

[00108] In some embodiments, at least one R⁷ is methyl or ethyl.

[00109] In some embodiments, R⁷ and R^{7'}, together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁸.

[00110] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 4- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

5 [00111] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 3- or 4-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00112] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 3-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

10 [00113] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 4-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00114] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 5-membered ring optionally comprising one additional heteroatom selected from N and O
15 and optionally substituted with one or more R^8 .

[00115] In some embodiments, R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00116] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached,
20 form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00117] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 4- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

25 [00118] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 3- or 4-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00119] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 3-membered ring optionally comprising one additional heteroatom selected from N and O
30 and optionally substituted with one or more R^8 .

[00120] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 4-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00121] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 5-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00122] In some embodiments, R^3 and R^7 , together with atom(s) to which they are attached, form a 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .

[00123] In some embodiments, at least one R^8 is (C_1-C_4) alkyl (*i.e.*, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl) or (C_1-C_4) alkoxy (*i.e.*, methoxy, ethoxy, propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, or *t*-butoxy).

[00124] In some embodiments, at least one R^8 is methyl or methoxy.

[00125] In some embodiments, at least one R^8 is CF_3 or F.

[00126] In some embodiments, p is 0.

[00127] In some embodiments, p is 1.

[00128] In some embodiments, X is F.

[00129] In some embodiments, X is Cl.

[00130] In some embodiments, m is 0.

[00131] In some embodiments, m is 1.

[00132] In some embodiments, m is 2.

[00133] In some embodiments, n is 1.

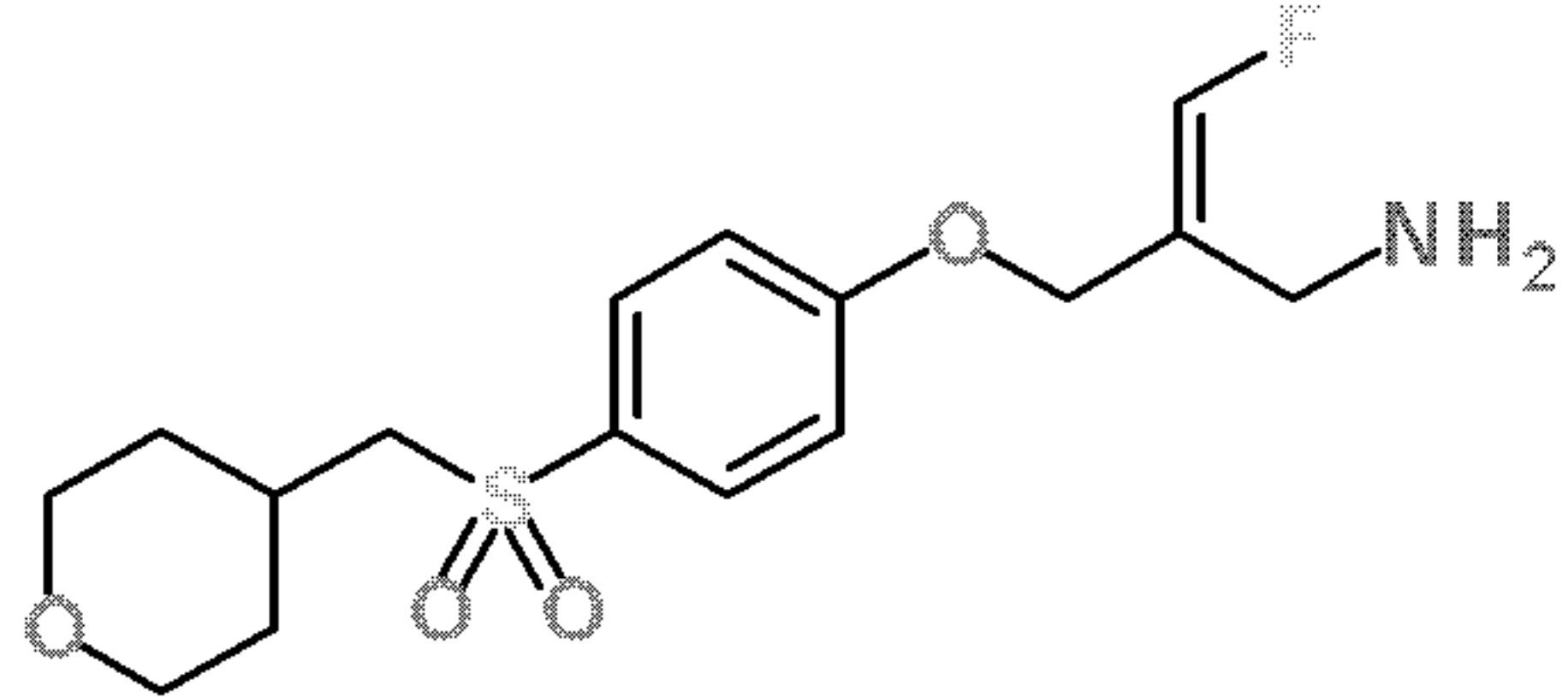
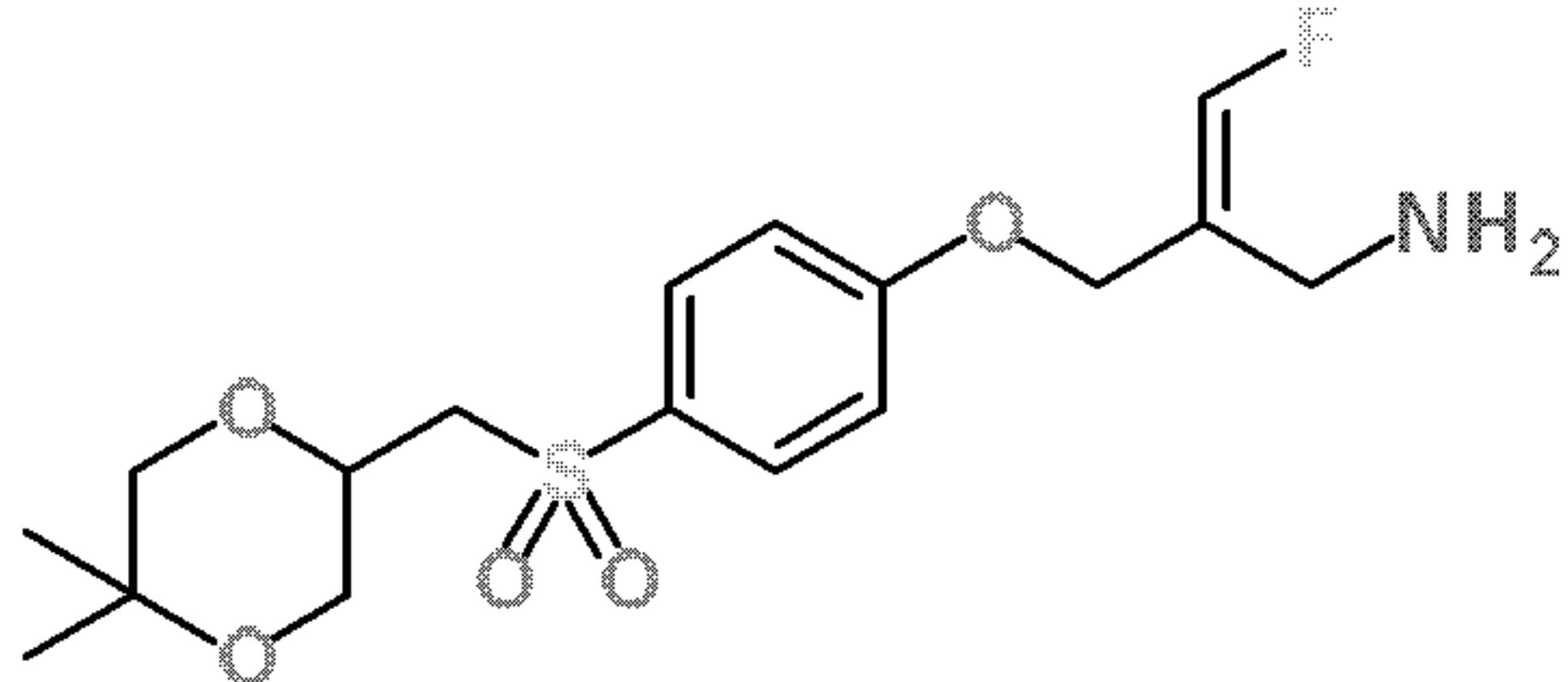
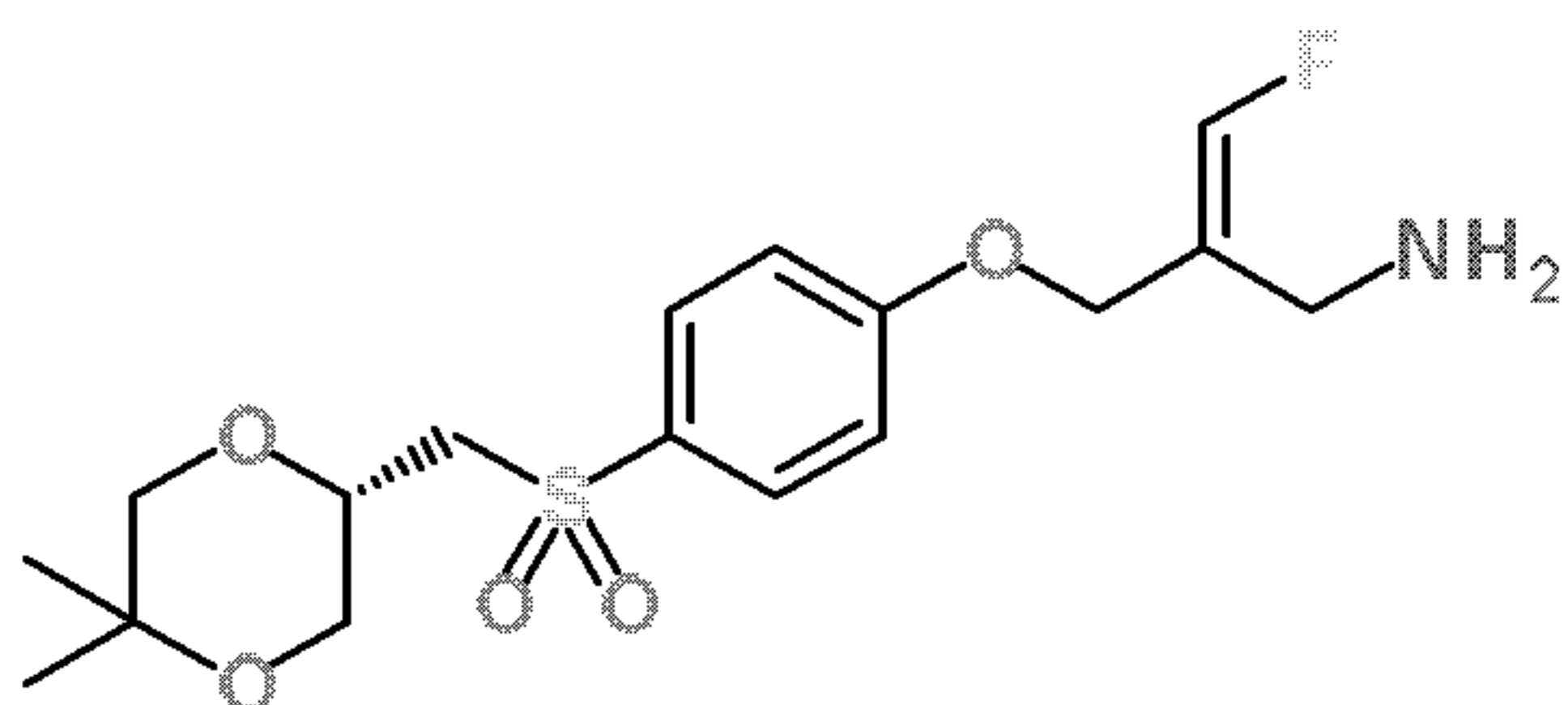
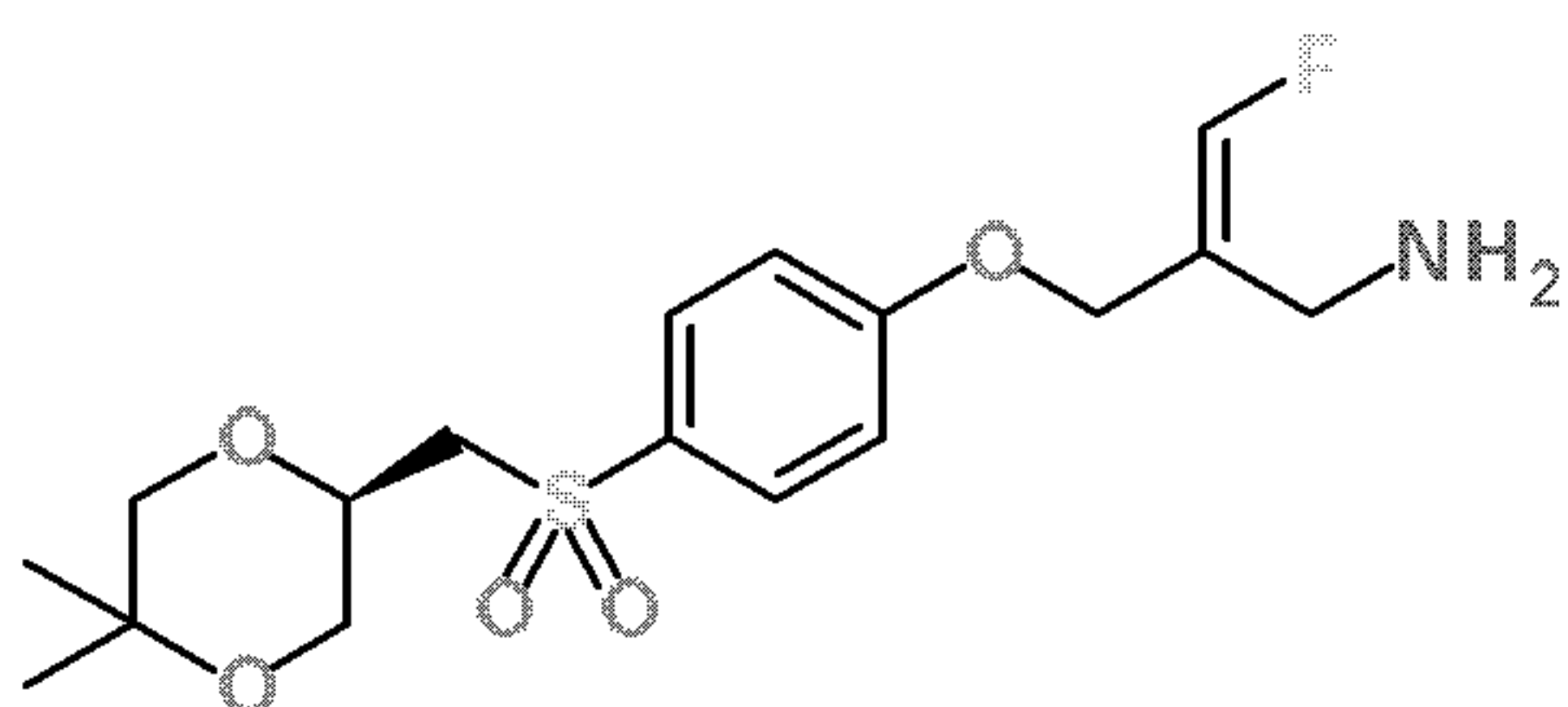
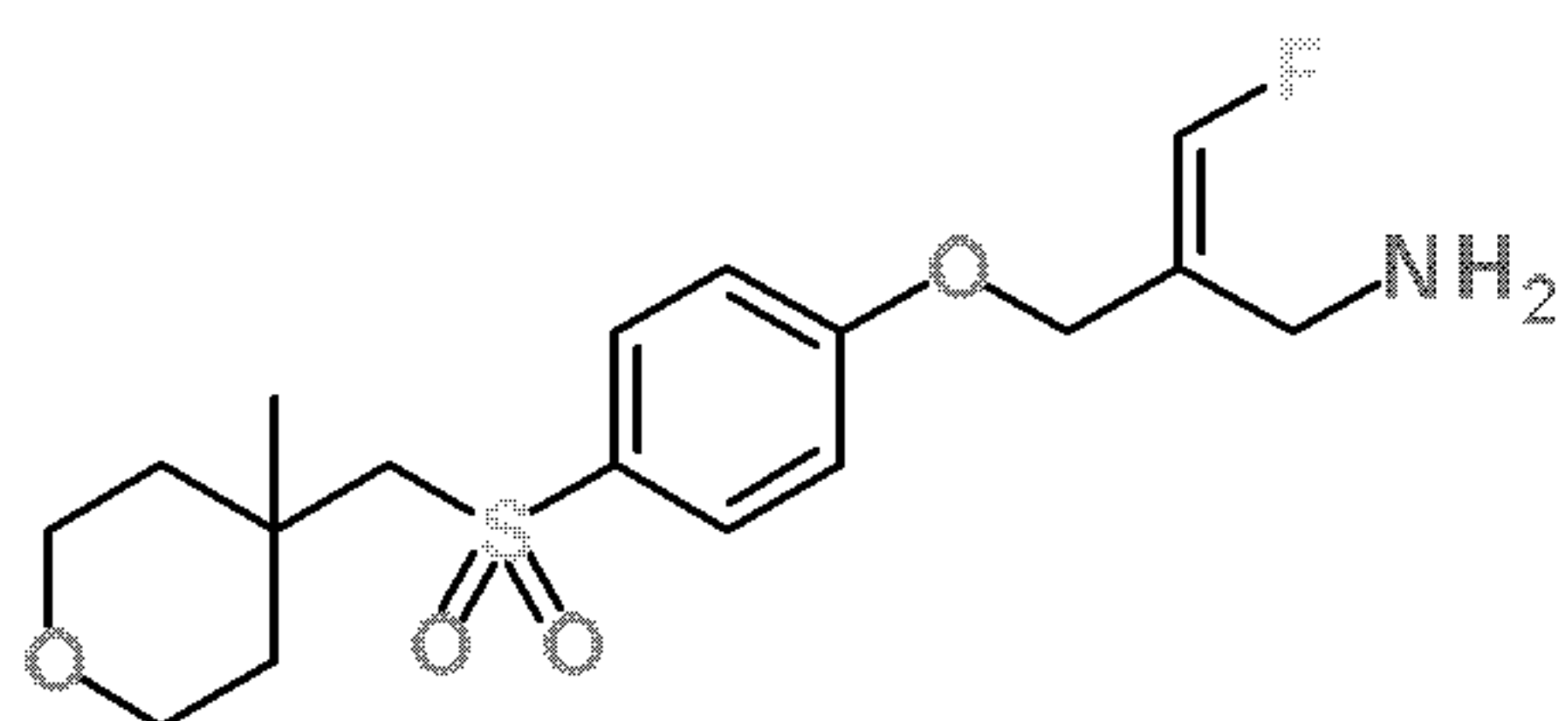
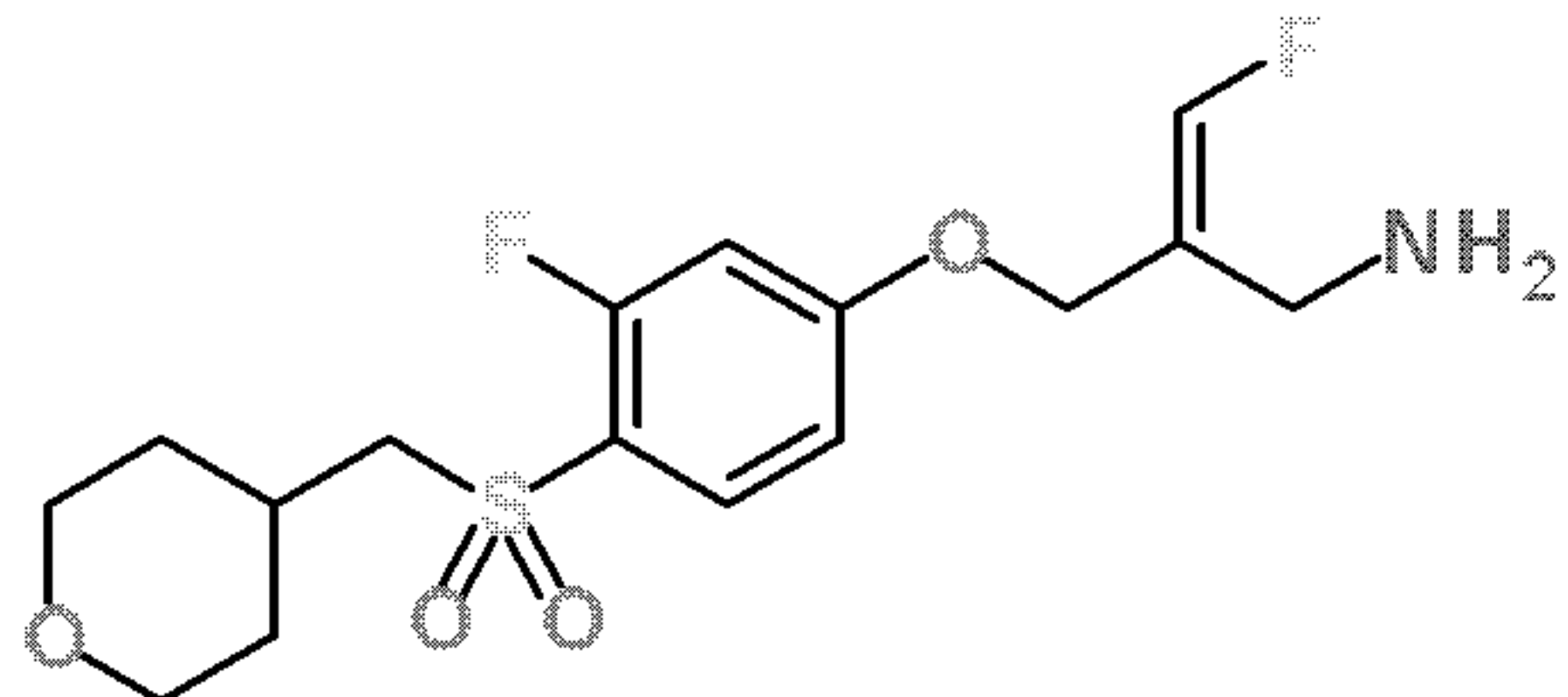
[00134] In some embodiments, n is 2.

[00135] Any of the moieties described herein for any one of $R^1, R^2, R^{2'}, R^3, R^4, R^5, R^{5'}, R^6, R^7, R^{7'}, R^8, A^1, A^2, A^{2'}, A^3, A^{3'}, X, L, L^1, m, n$, and p can be combined with any of the moieties described herein for one or more of the remainder of $R^1, R^2, R^{2'}, R^3, R^4, R^5, R^{5'}, R^6, R^7, R^{7'}, R^8, A^1, A^2, A^{2'}, A^3, A^{3'}, X, L, L^1, m, n$, and p .

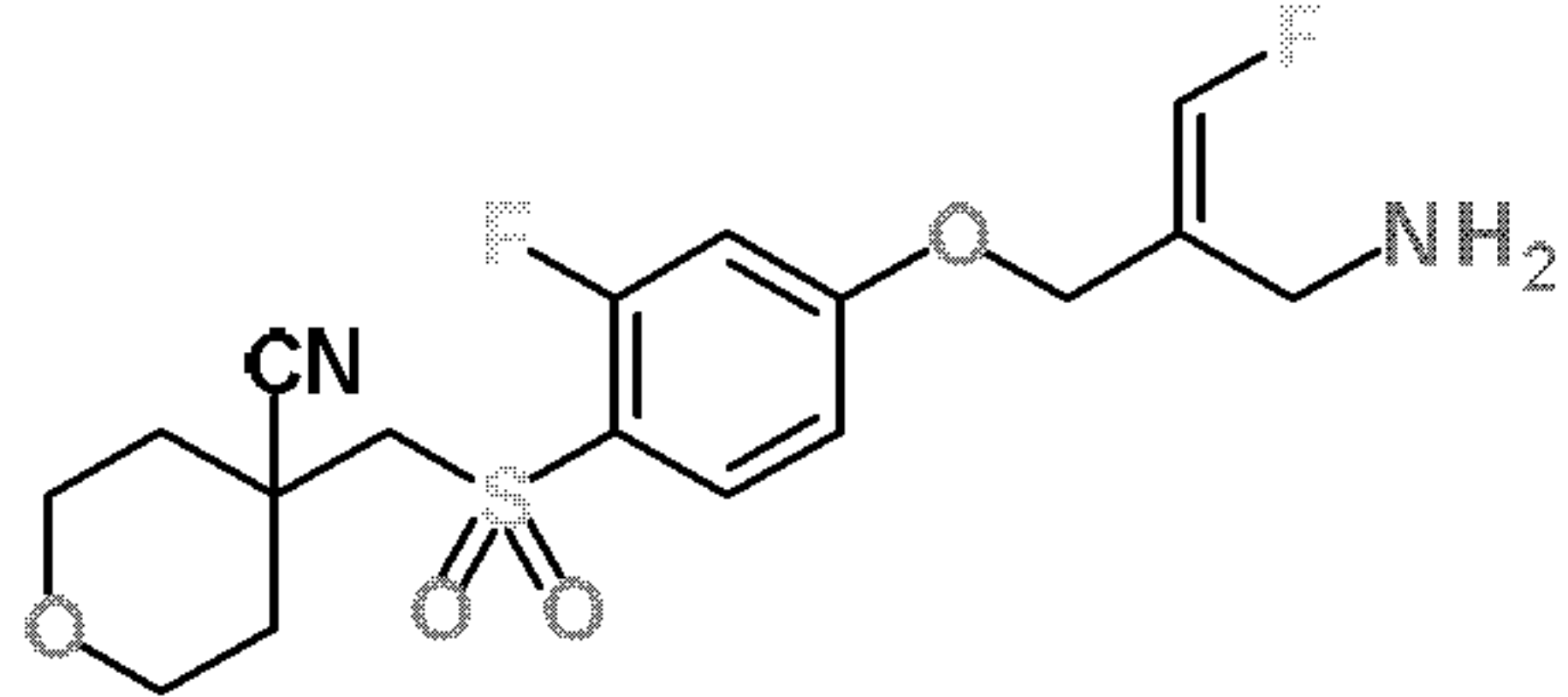
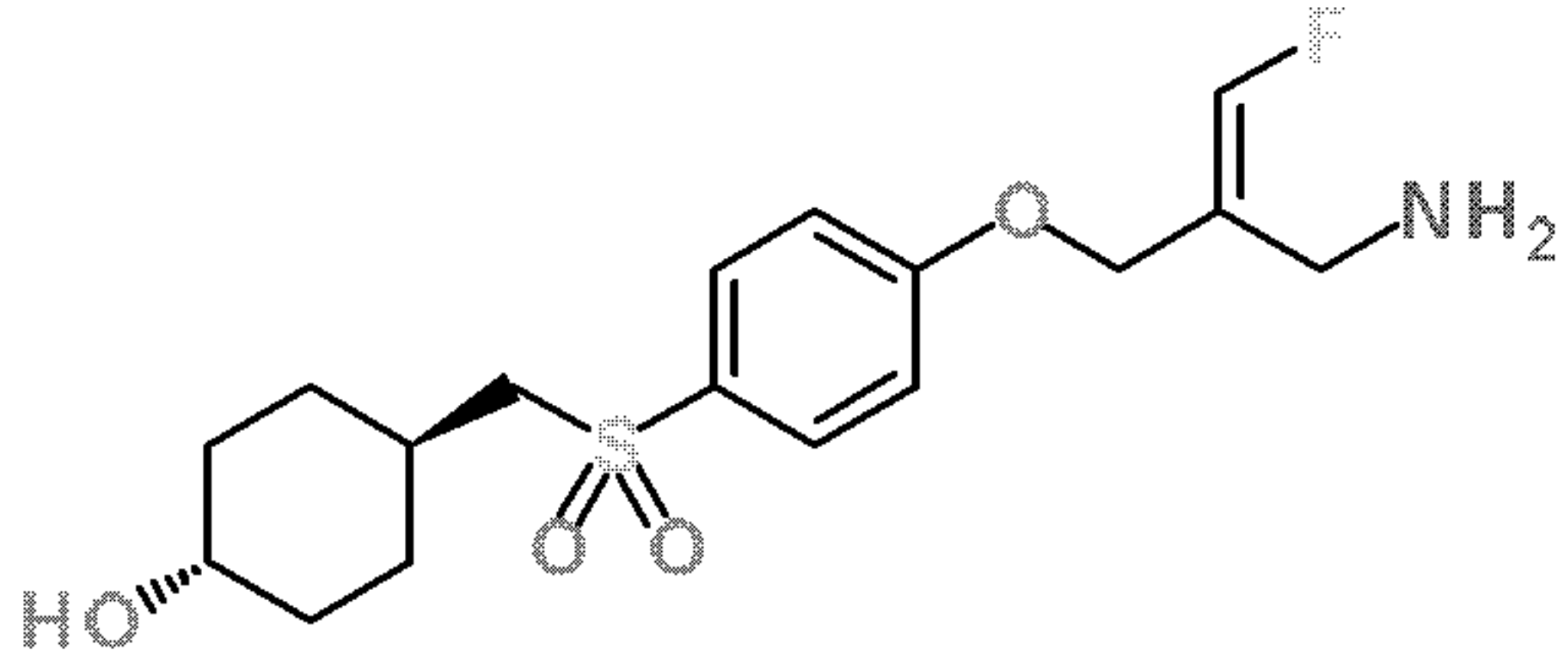
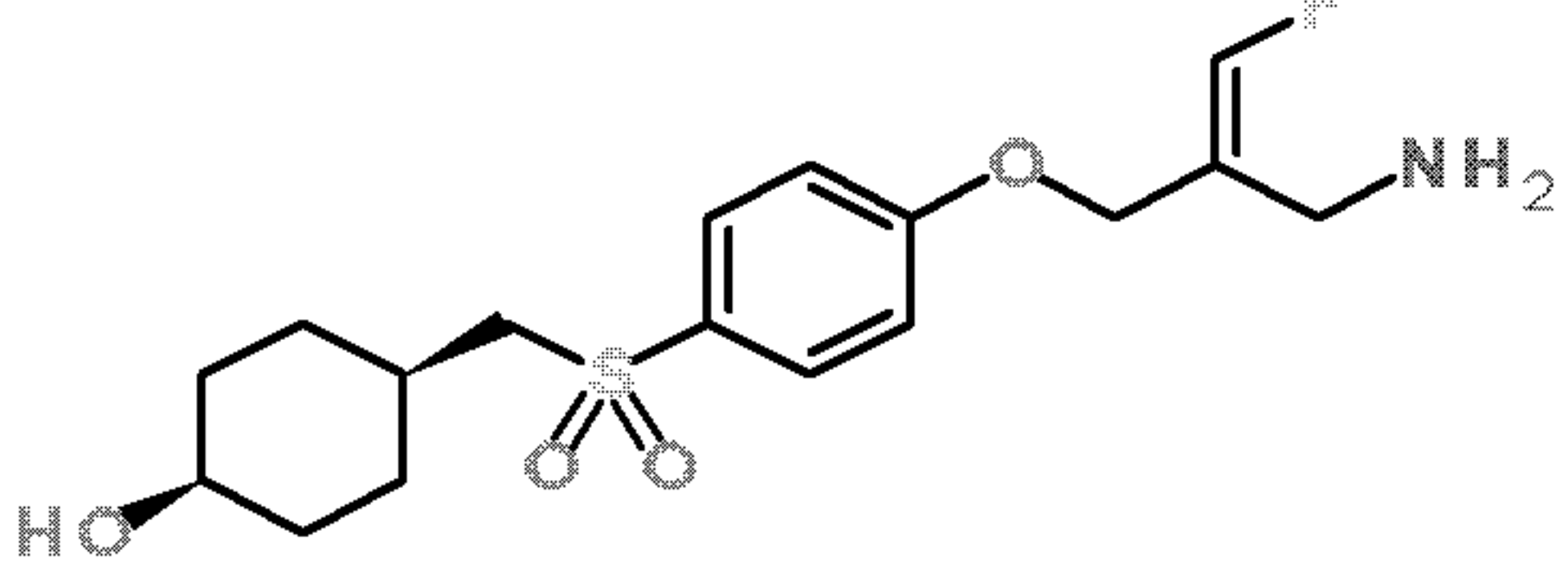
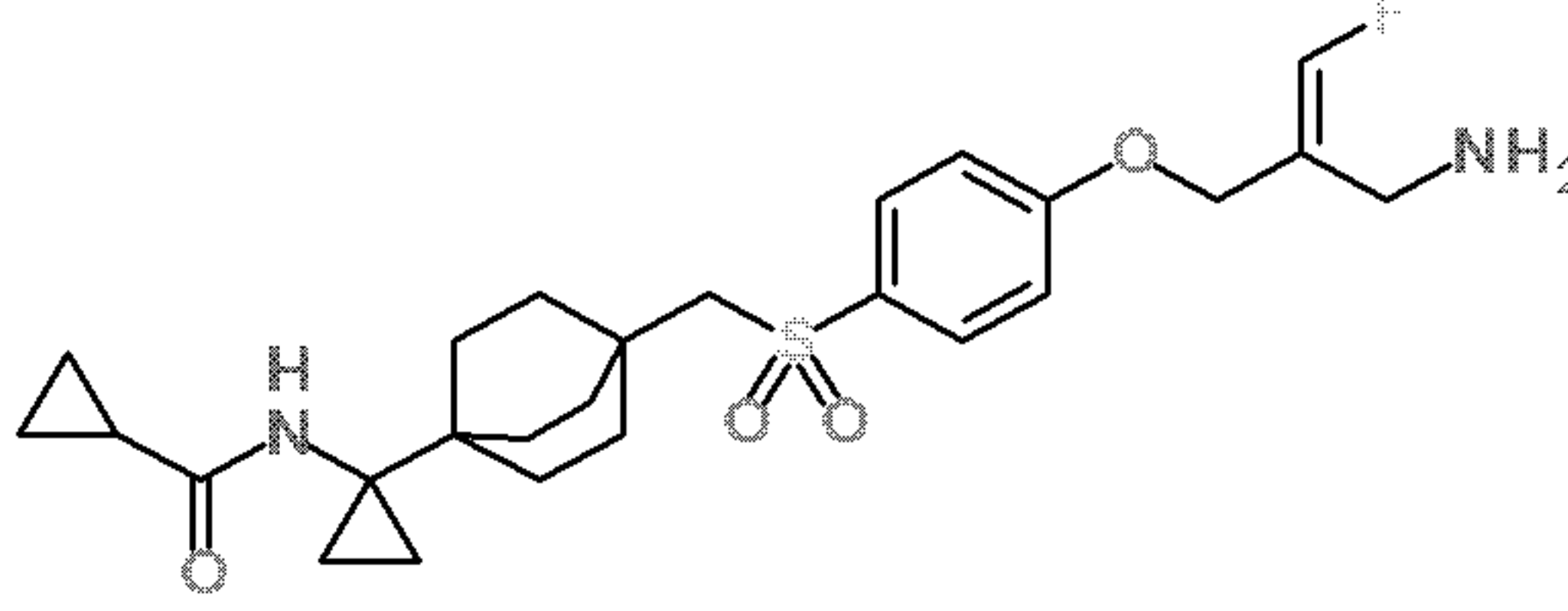
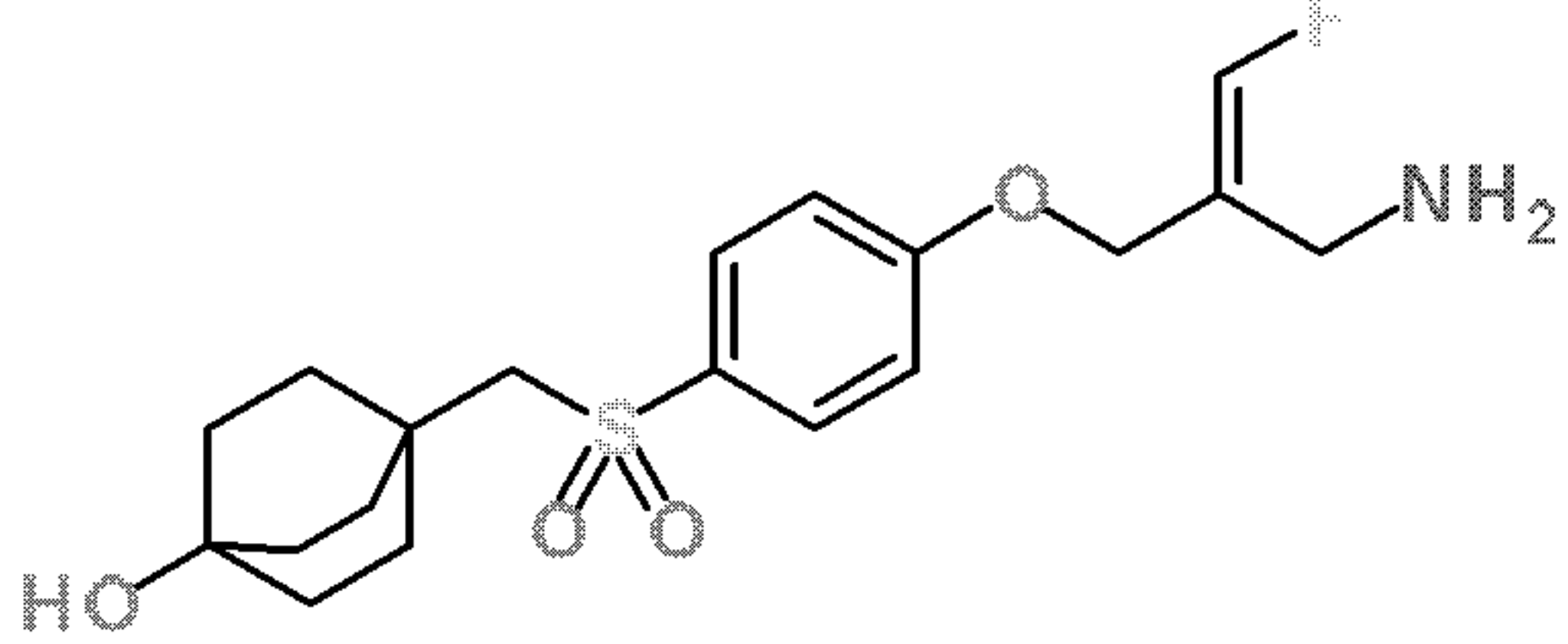
[00136] Non-limiting illustrative compounds of the application include those in Table 1.

Table 1

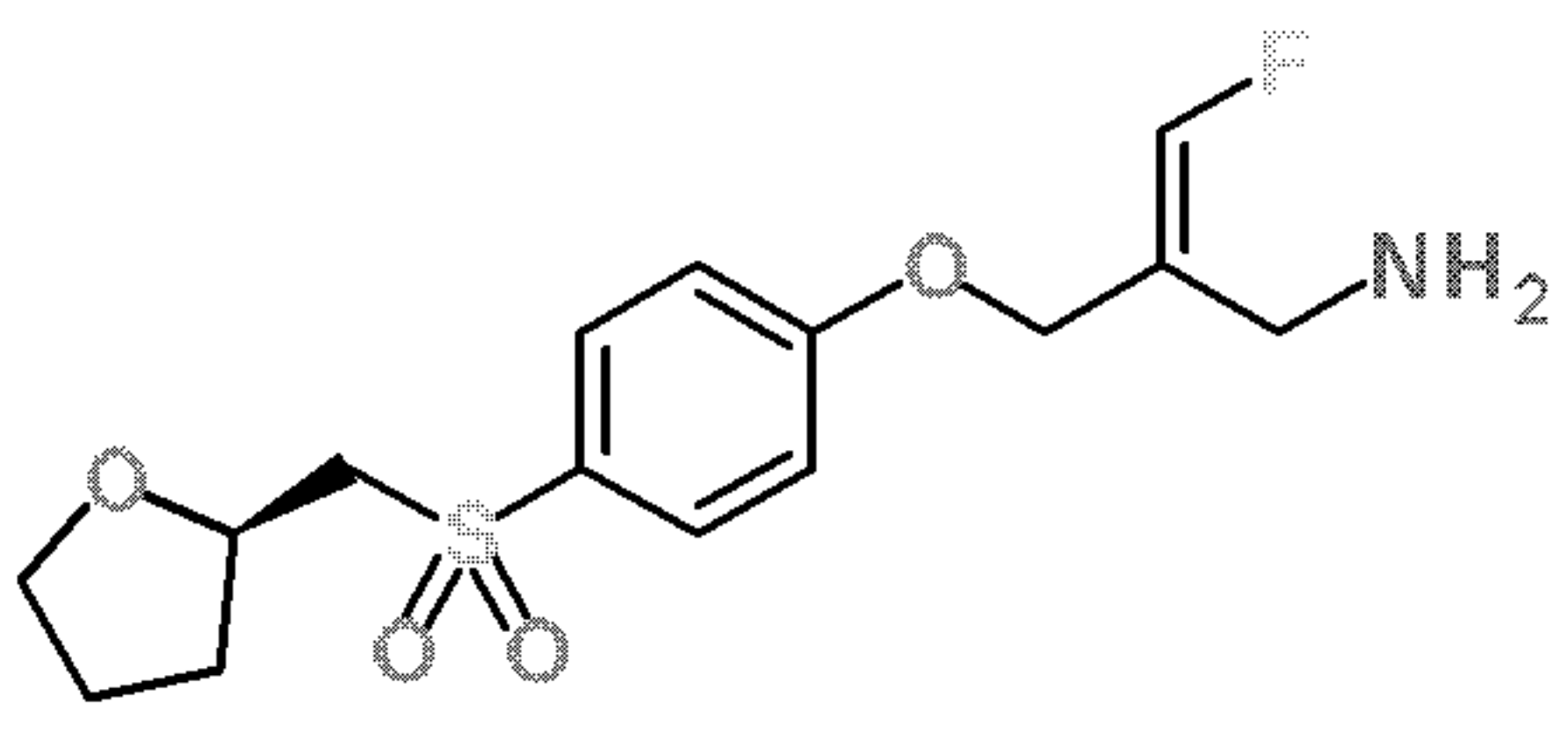
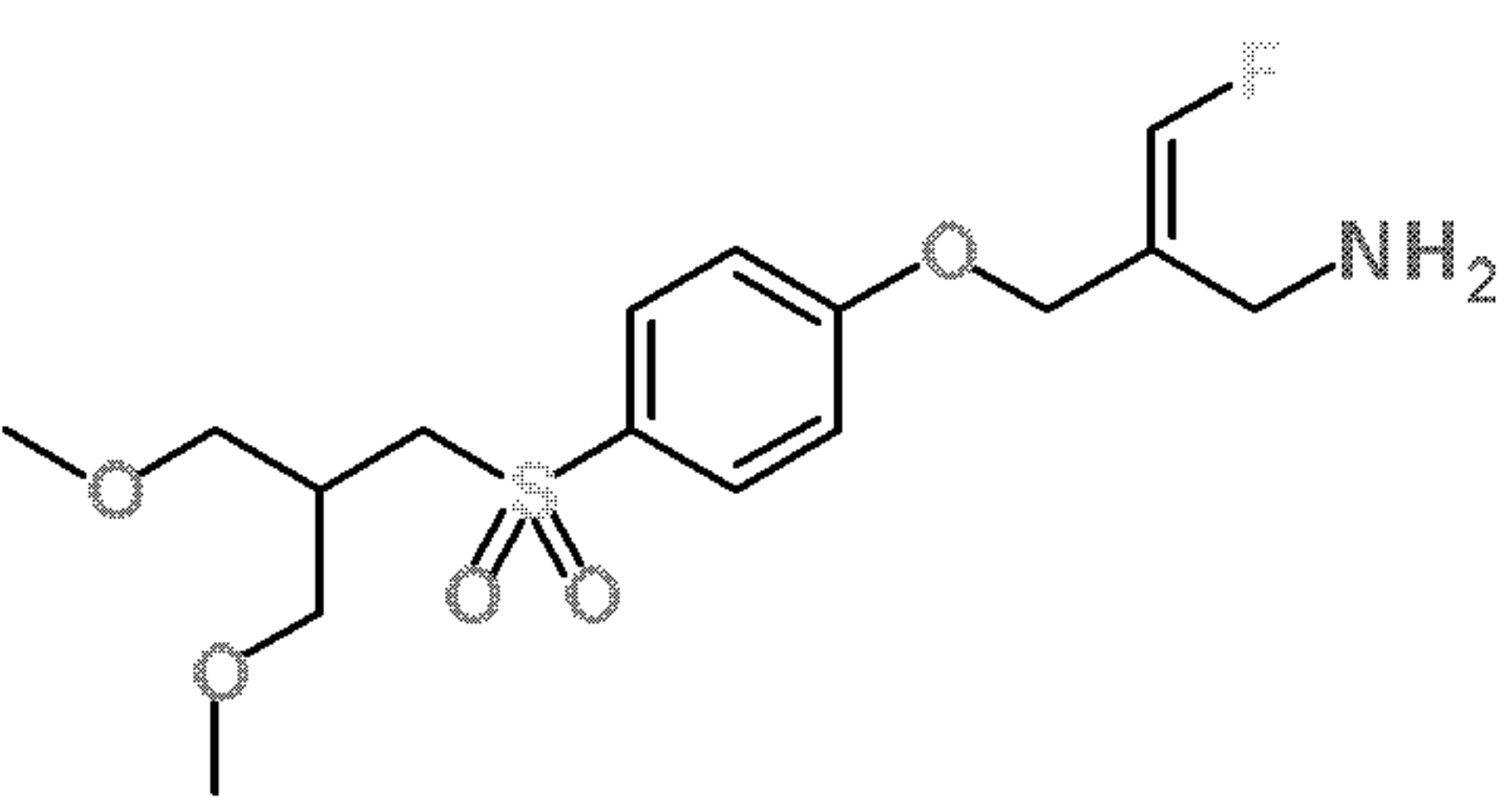
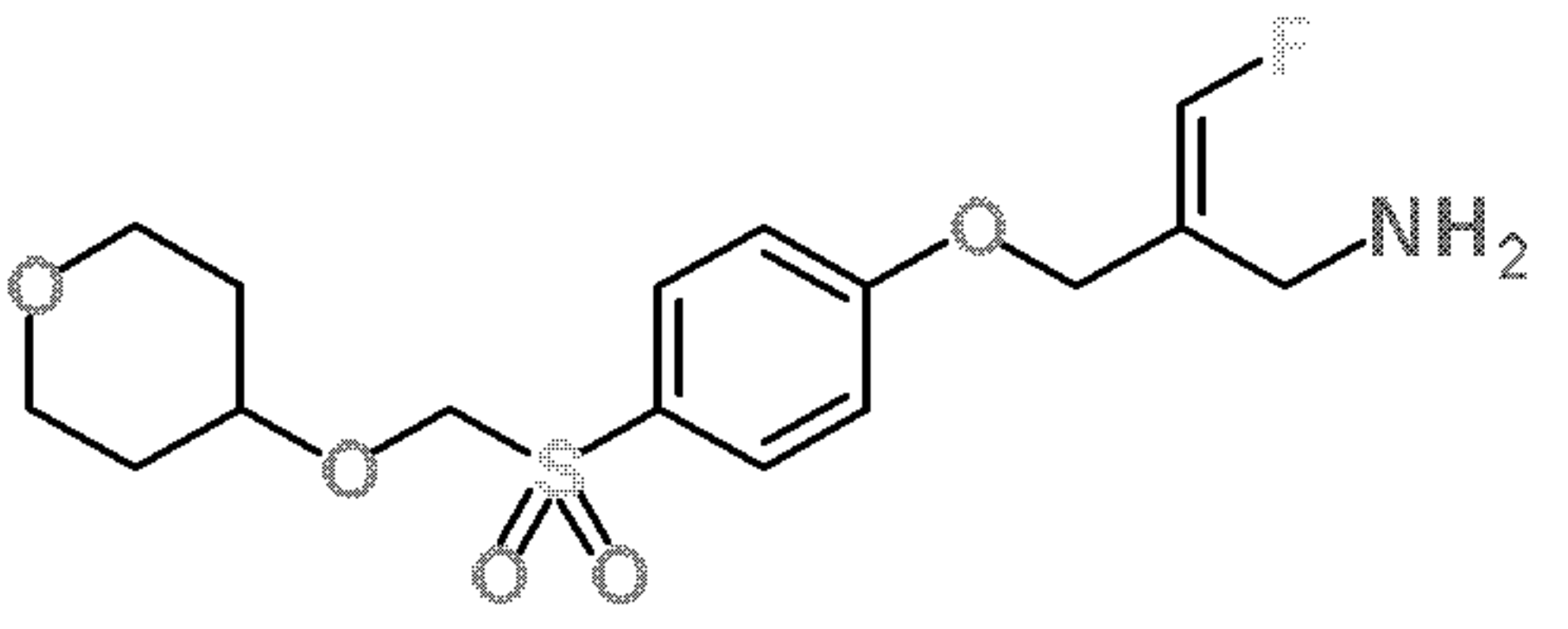
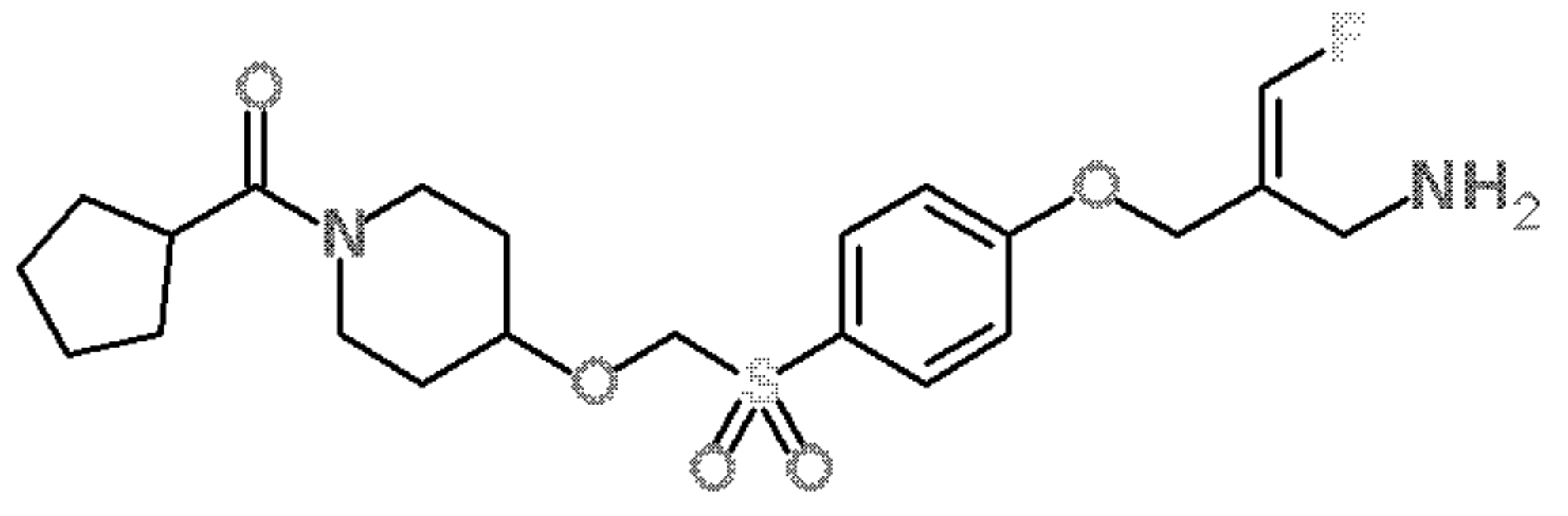
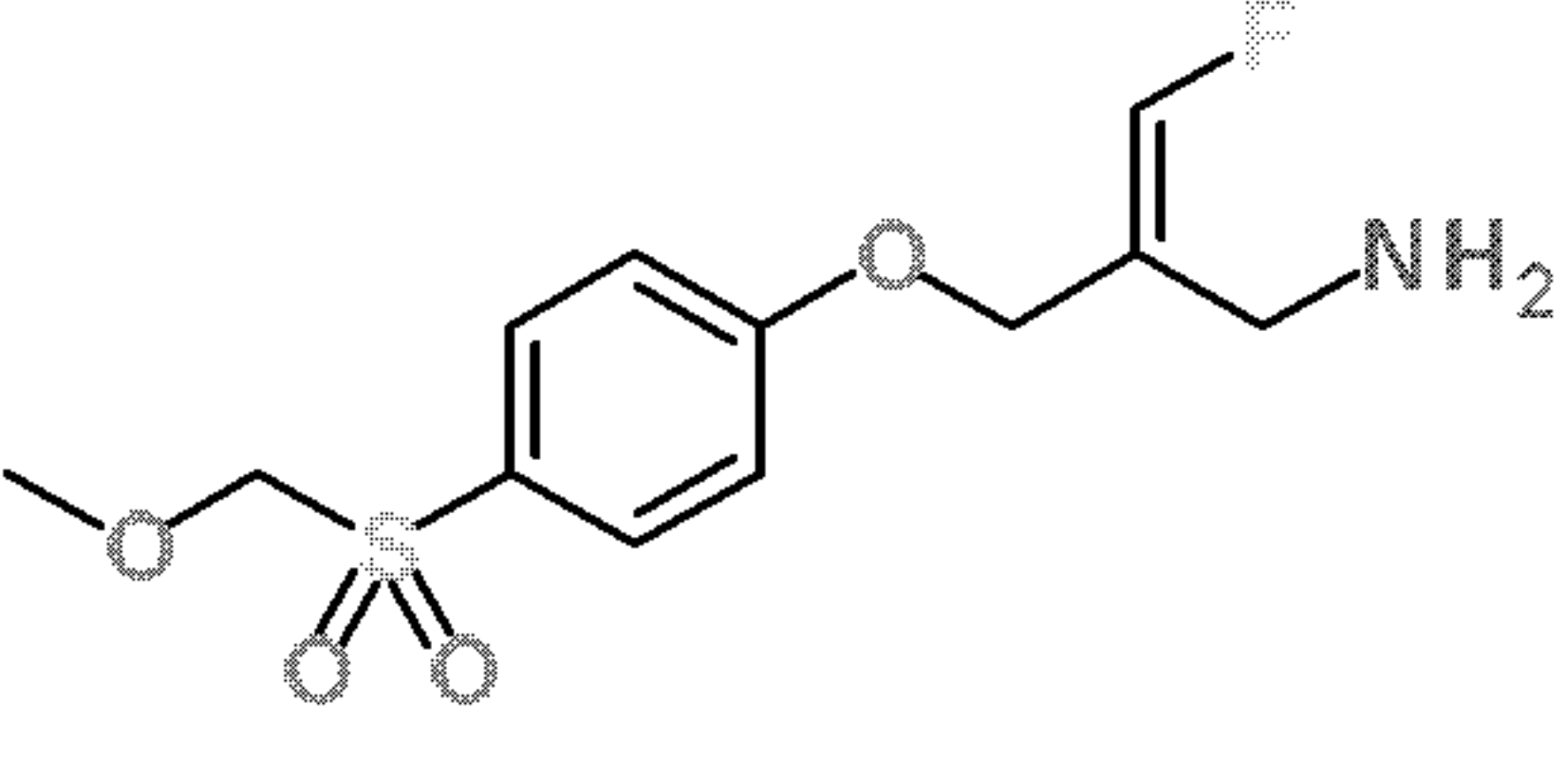
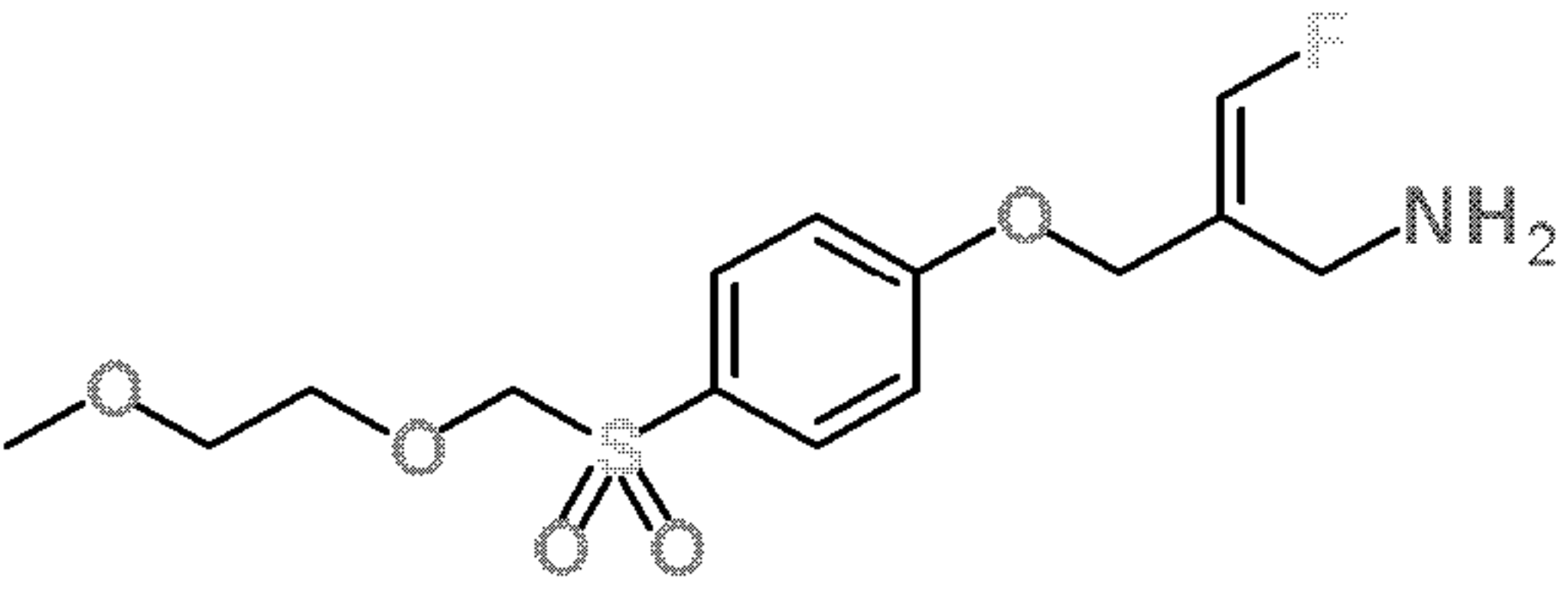
Cmpd No.	Structure	Chemical name
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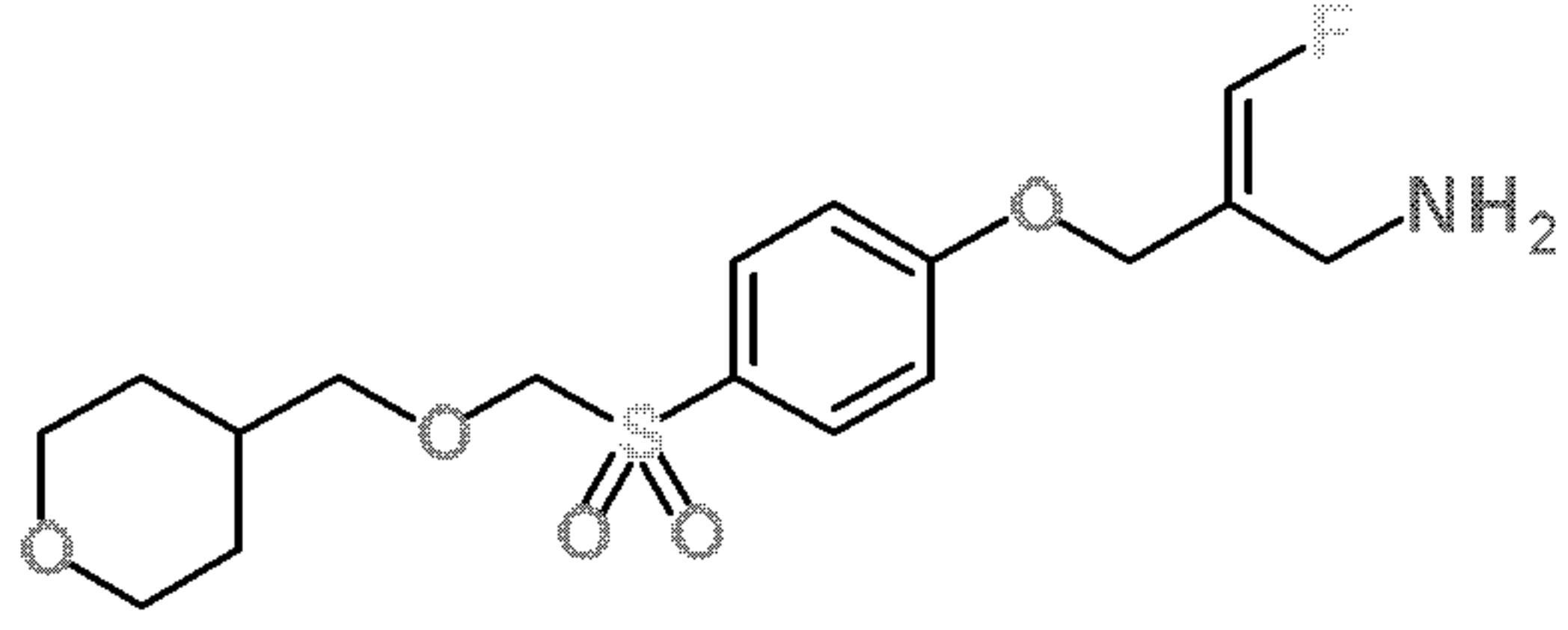
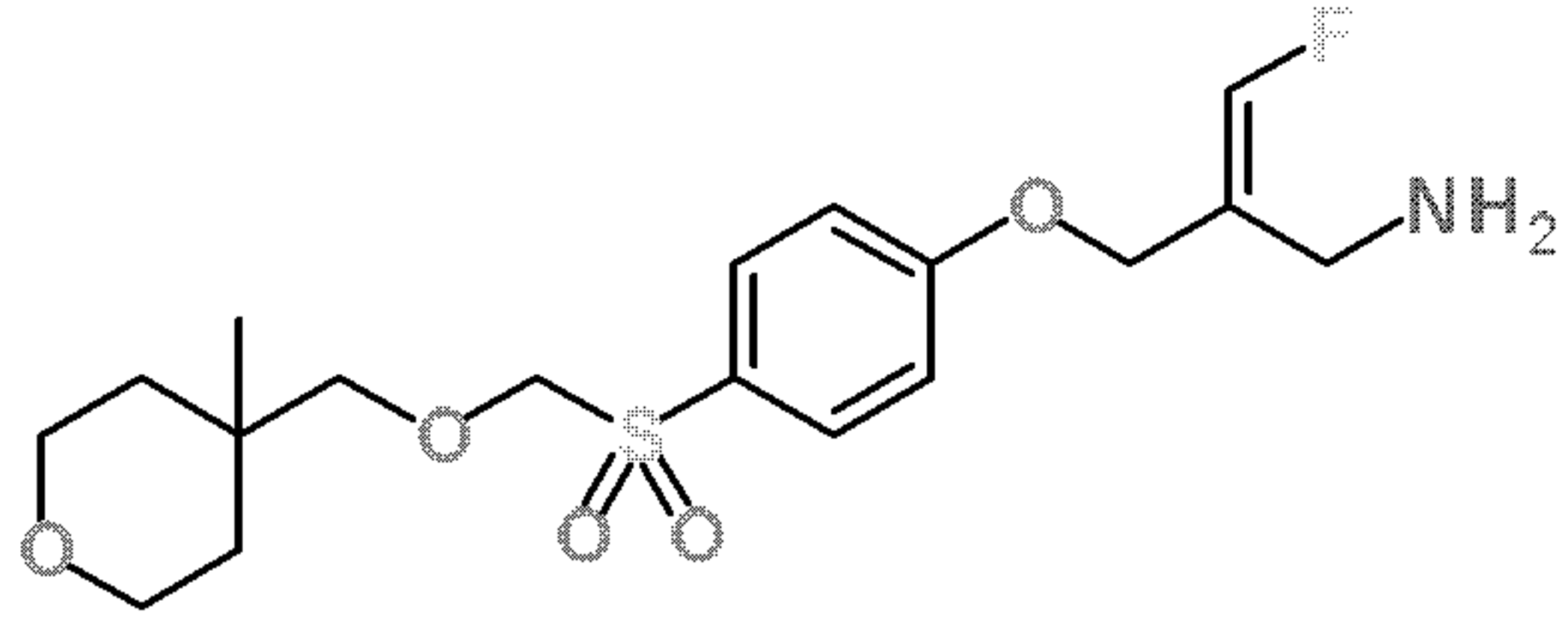
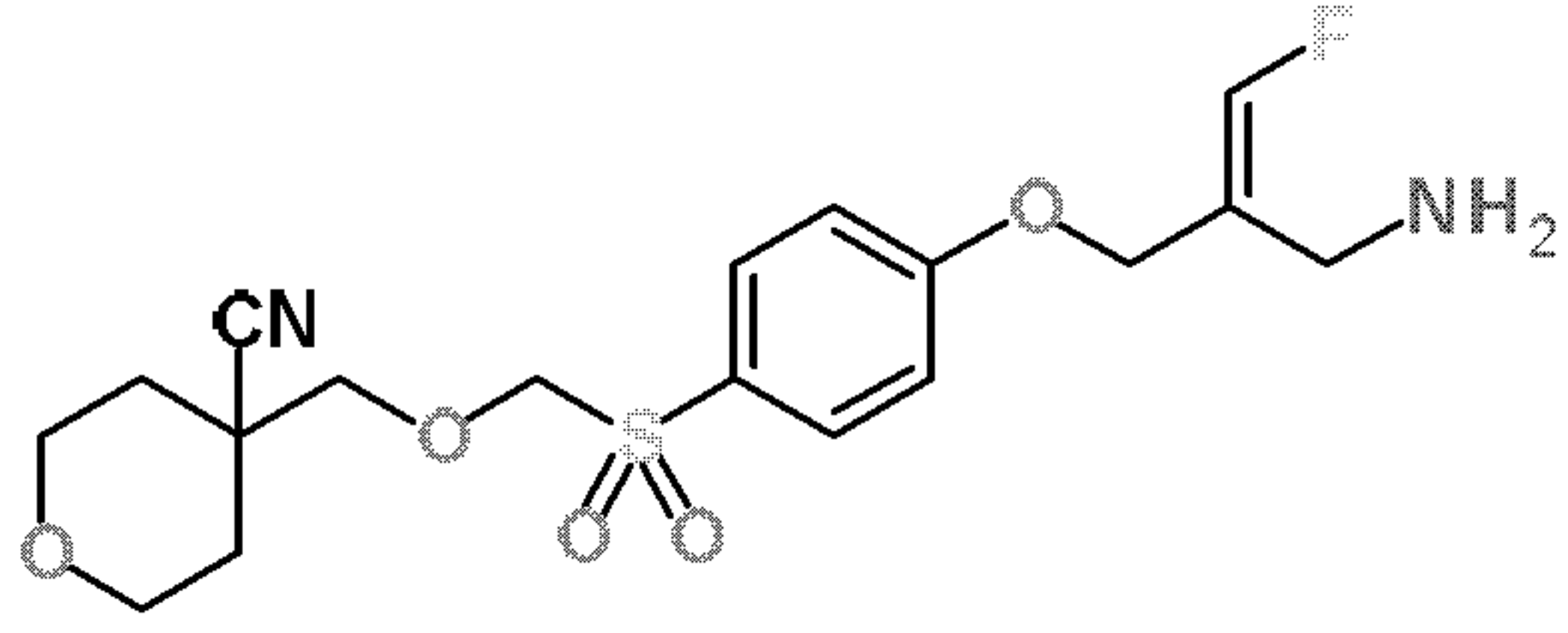
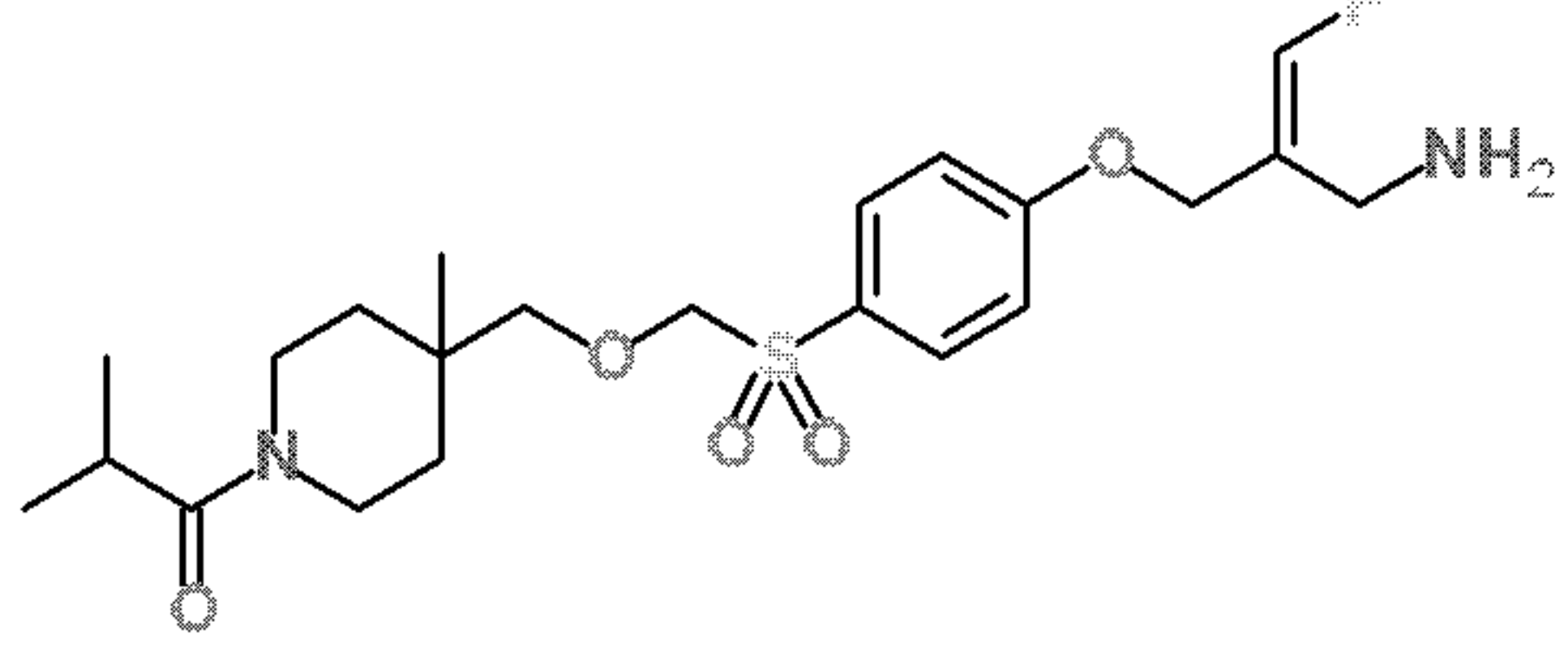
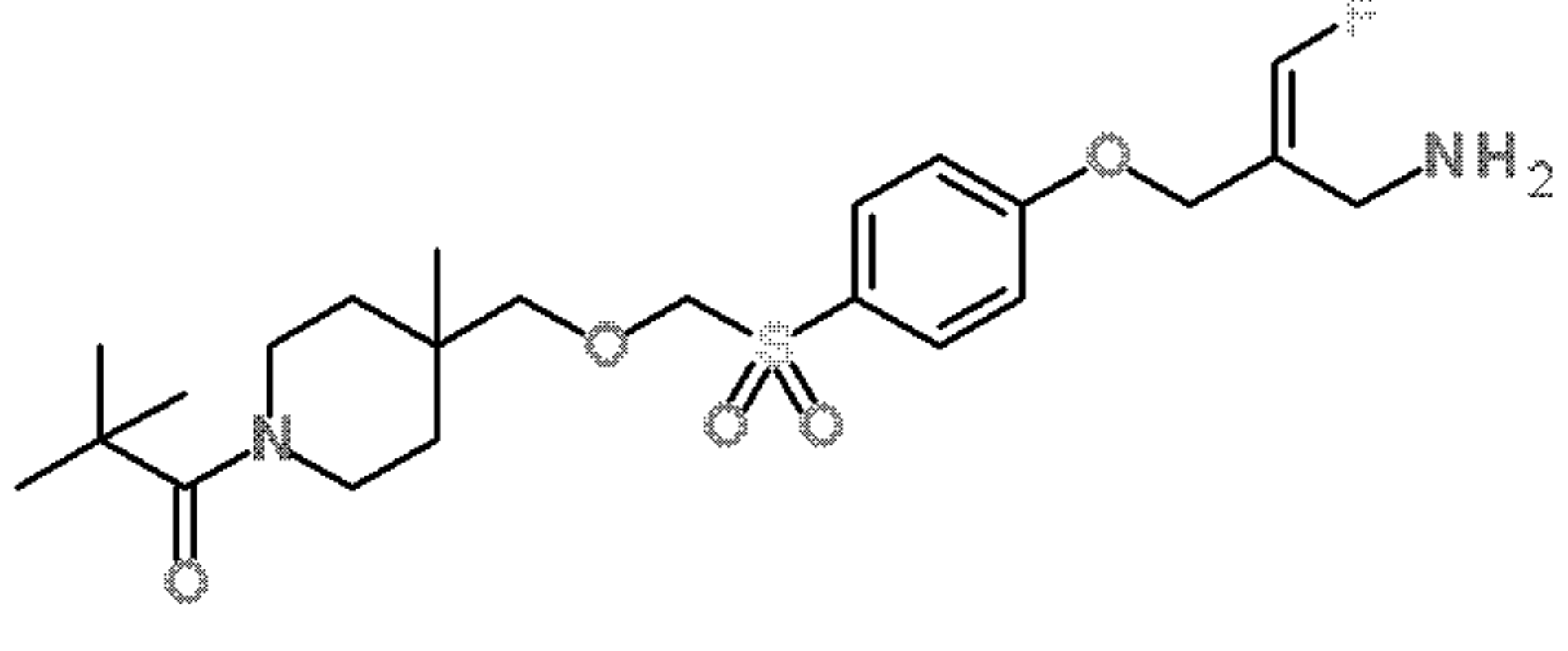
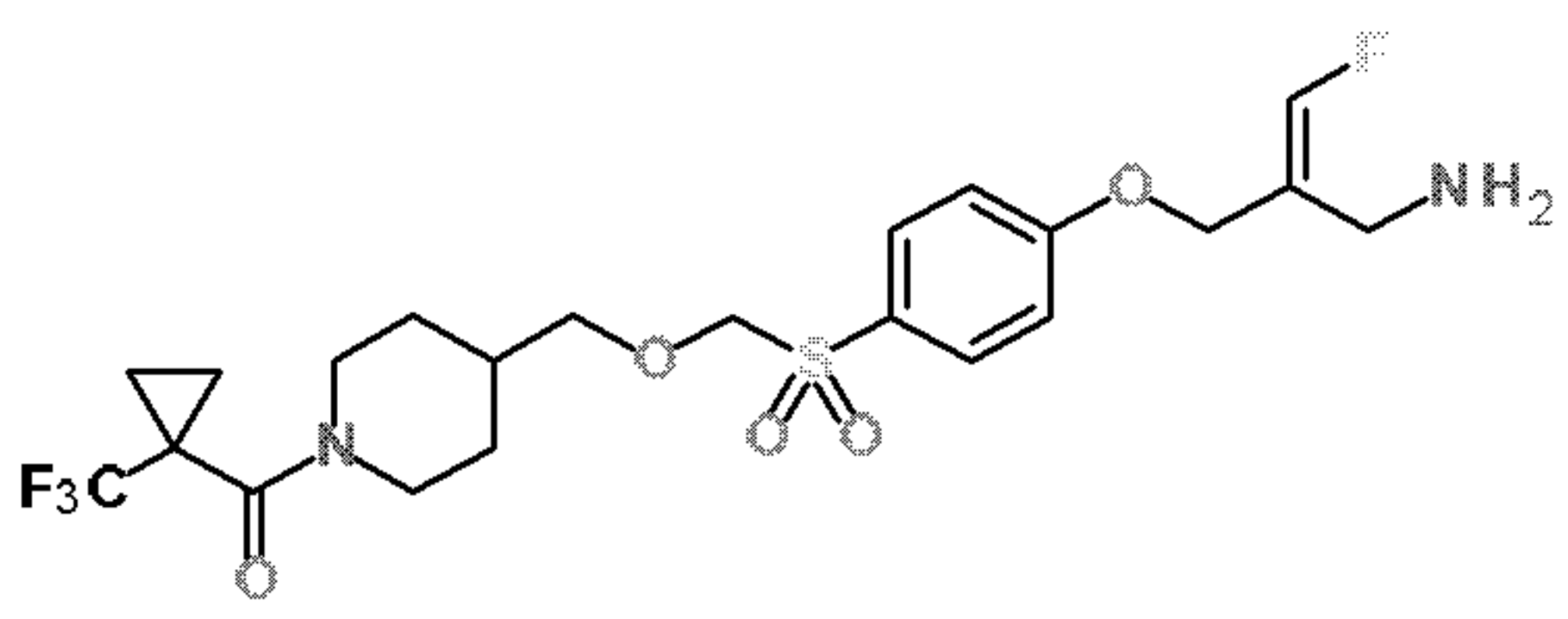
Cmpd No.	Structure	Chemical name
1		(E)-3-fluoro-2-((4-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
2		(E)-2-((4-(((5,5-dimethyl-1,4-dioxan-2-yl)methyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
3		(S,E)-2-((4-(((5,5-dimethyl-1,4-dioxan-2-yl)methyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
4		(R,E)-2-((4-(((5,5-dimethyl-1,4-dioxan-2-yl)methyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
5		(E)-3-fluoro-2-((4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
6		(E)-3-fluoro-2-((3-fluoro-4-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine

Cmpd No.	Structure	Chemical name
7		(E)-3-fluoro-2-((3-fluoro-4-(((4-methyltetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
8		(E)-2-((3-chloro-4-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
9		(E)-3-fluoro-2-((2-fluoro-4-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
10		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)tetrahydro-2H-pyran-4-ol
11		(E)-3-fluoro-2-((4-(((4-methoxytetrahydro-2H-pyran-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
12		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)tetrahydro-2H-pyran-4-carbonitrile

Cmpd No.	Structure	Chemical name
13		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-fluorophenyl)sulfonyl)methyl)tetrahydro-2H-pyran-4-carbonitrile
14		(1r,4r)-4-(((4-(((E)-2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)cyclohexan-1-ol
15		(1s,4s)-4-(((4-(((E)-2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)cyclohexan-1-ol
16		(E)-N-(1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclopropyl)cyclopropanecarboxamide
17		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-ol

Cmpd No.	Structure	Chemical name
18		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclopropan-1-ol
19		(E)-3-fluoro-2-((4-(((1r,4r)-4-methoxycyclohexyl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
20		(E)-3-fluoro-2-((4-(((1s,4s)-4-methoxycyclohexyl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
21		(R,E)-3-fluoro-2-((4-(((tetrahydrofuran-3-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
22		(S,E)-3-fluoro-2-((4-(((tetrahydrofuran-3-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
23		(S,E)-3-fluoro-2-((4-(((tetrahydrofuran-2-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine

Cmpd No.	Structure	Chemical name
24		(R,E)-3-fluoro-2-(((4-(((tetrahydrofuran-2-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
25		(E)-3-fluoro-2-(((4-((3-methoxy-2-(methoxymethyl)propyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
26		(E)-3-fluoro-2-(((4-((((tetrahydro-2H-pyran-4-yl)oxy)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
27		(E)-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methoxy)piperidin-1-yl)(cyclopentyl)methanone
28		(E)-3-fluoro-2-(((4-(((methoxymethyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
29		(E)-3-fluoro-2-(((4-(((2-methoxyethoxy)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine

Cmpd No.	Structure	Chemical name
30		(E)-3-fluoro-2-((4-(((4-(tetrahydro-2H-pyran-4-yl)methoxy)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
31		(E)-3-fluoro-2-((4-(((4-methyltetrahydro-2H-pyran-4-yl)methoxy)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
32		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methoxy)methyl)tetrahydro-2H-pyran-4-carbonitrile
33		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methoxy)methyl)-4-methylpiperidin-1-yl)-2-methylpropan-1-one
34		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methoxy)methyl)-4-methylpiperidin-1-yl)-2,2-dimethylpropan-1-one
35		(E)-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopropyl)methanone

Cmpd No.	Structure	Chemical name
36		(E)-2-((4-(((1,3-dimethoxypropan-2-yl)oxy)methyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
37		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)-2-methylpropan-1-one
38		(E)-3-fluoro-2-((4-(((1-(methanesulfonyl)piperidin-4-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
39		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(4-fluorophenyl)methanone
40		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(3-fluorobicyclo[1.1.1]pentan-1-yl)methanone
41		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)-2,2-dimethylpropan-1-one
42		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)-3,3-dimethylbutan-1-one

Cmpd No.	Structure	Chemical name
		1-one
43		(E)-adamantan-1-yl(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)methanone
44		(E)-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(cyclopropyl)methanone
45		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)phenyl)isobutyramide
46		(E)-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)phenyl)(pyrrolidin-1-yl)methanone
47		(E)-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)phenyl)(pyrrolidin-1-yl)methanone
48		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)-2-cyclopropylethan-1-one
49		(E)-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopropyl)methanone

Cmpd No.	Structure	Chemical name
50		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(cyclobutyl)methanone
51		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(3,3-difluorocyclobutyl)methanone
52		(E)-1-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)azetidin-1-yl)-2-methylpropan-1-one
53		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)-2-methylpropan-1-one
54		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)-2,2-dimethylpropan-1-one
55		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)(1-(trifluoromethyl)cyclopropyl)methanone
56		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)(1-methylcyclobutyl)methanone

Cmpd No.	Structure	Chemical name
57		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-methylpiperidin-1-yl)(1-methylcyclopropyl)methanone
58		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)(cyclopentyl)methanone
59		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-fluorophenyl)sulfonyl)methyl)piperidin-1-yl)-3,3,3-trifluoropropan-1-one
60		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-chlorophenyl)sulfonyl)methyl)piperidin-1-yl)(cyclopropyl)methanone
61		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)(pyrrolidin-1-yl)methanone
62		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N,N-dimethylbicyclo[2.2.2]octane-1-carboxamide
63		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)(4,4-difluoropiperidin-1-yl)methanone

Cmpd No.	Structure	Chemical name
64		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclobutylbicyclo[2.2.2]octane-1-carboxamide
65		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(2,2,2-trifluoroethyl)bicyclo[2.2.2]octane-1-carboxamide
66		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(cyclopropylmethyl)bicyclo[2.2.2]octane-1-carboxamide
67		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(1-methylcyclopropyl)bicyclo[2.2.2]octane-1-carboxamide
68		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(2-isopropoxyethyl)bicyclo[2.2.2]octane-1-carboxamide
69		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(3,3-difluorocyclobutyl)bicyclo[2.2.2]octane-1-carboxamide

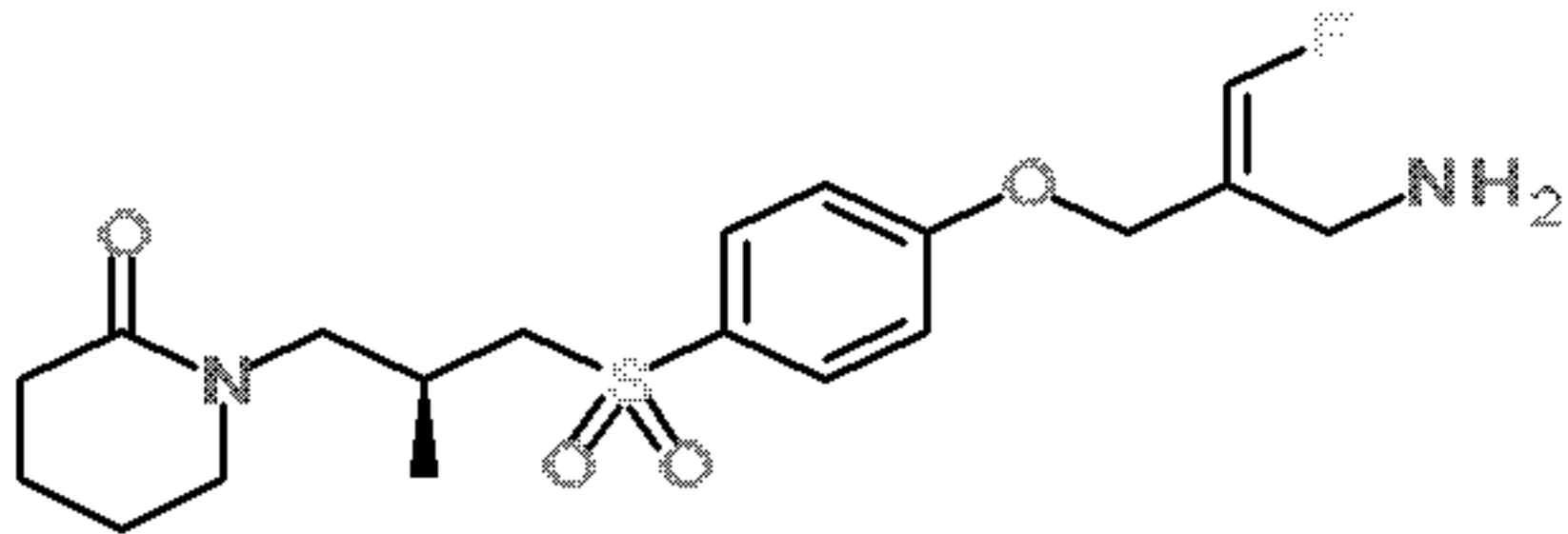
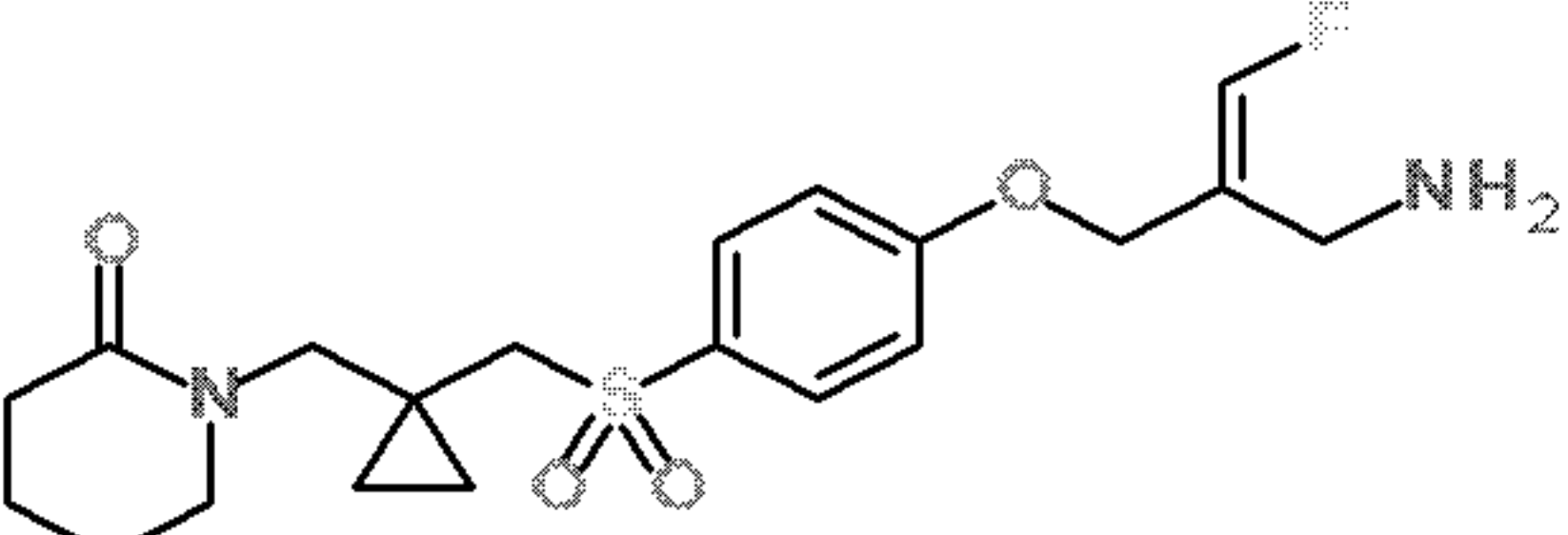
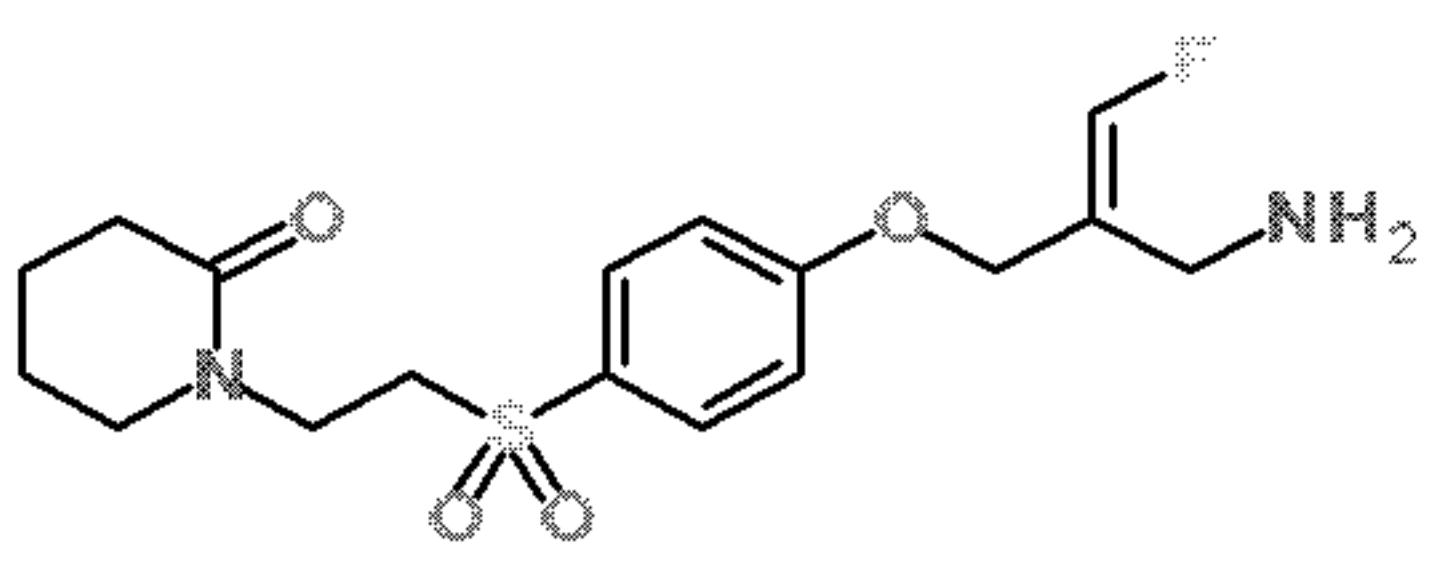
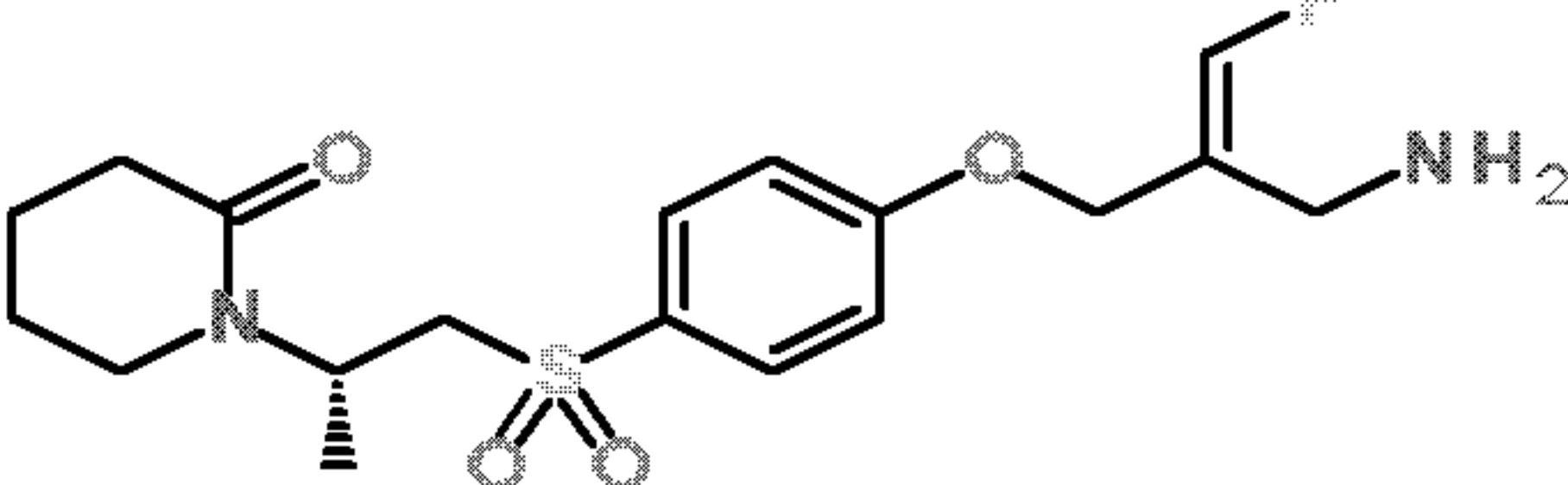
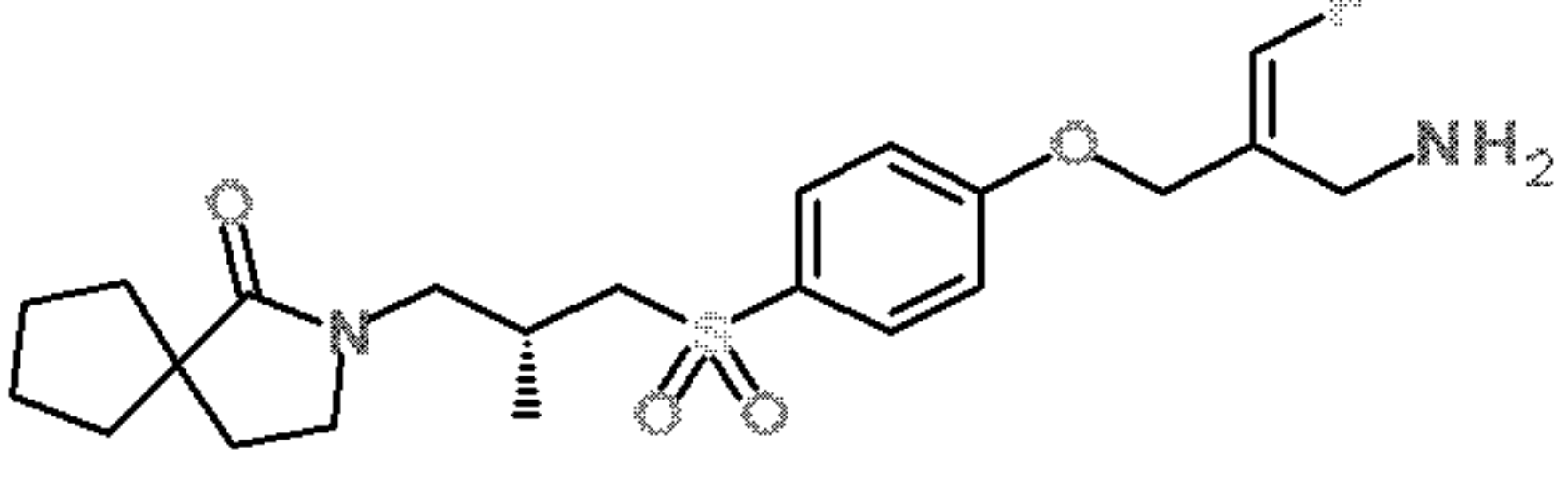
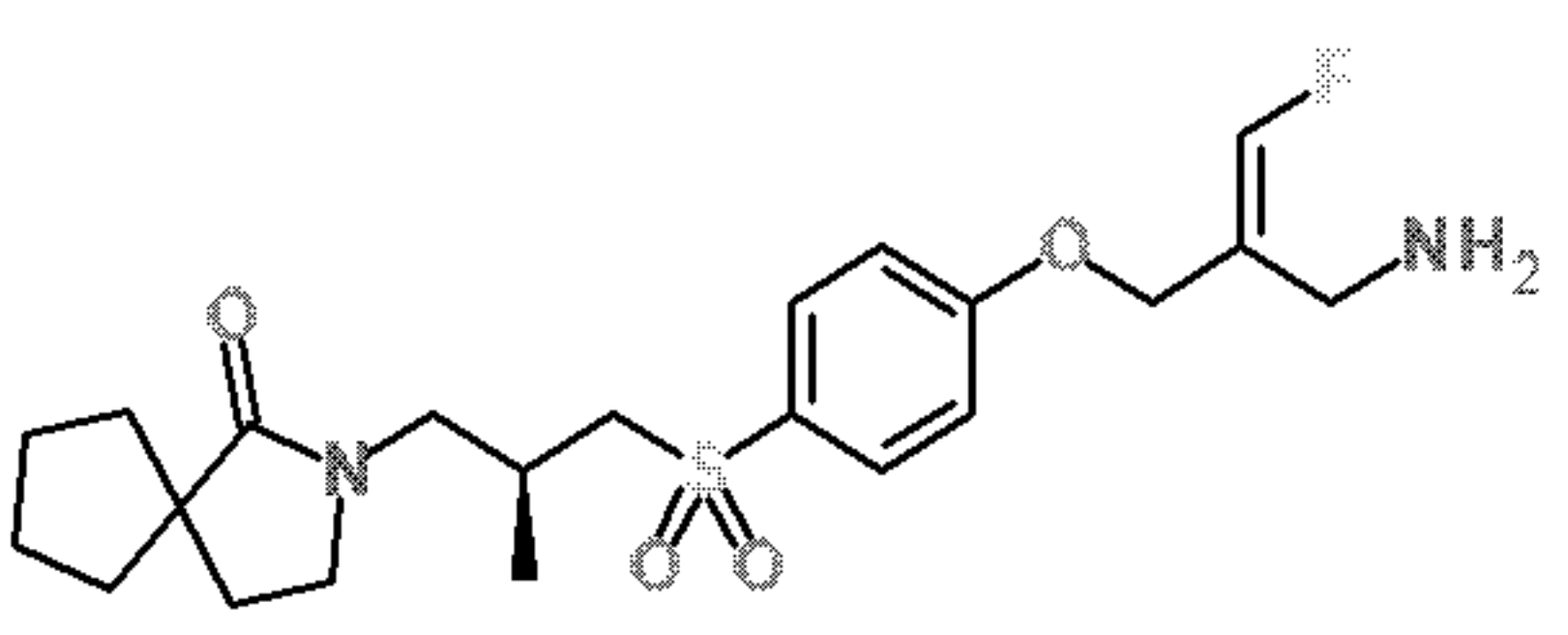
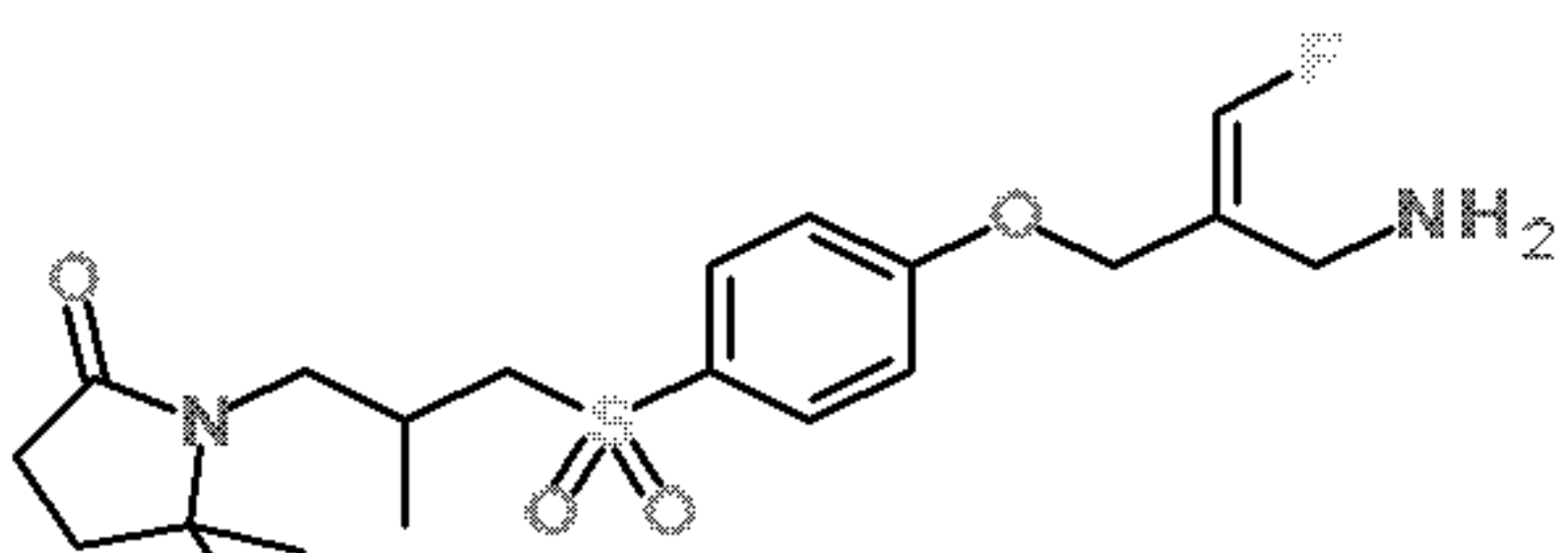
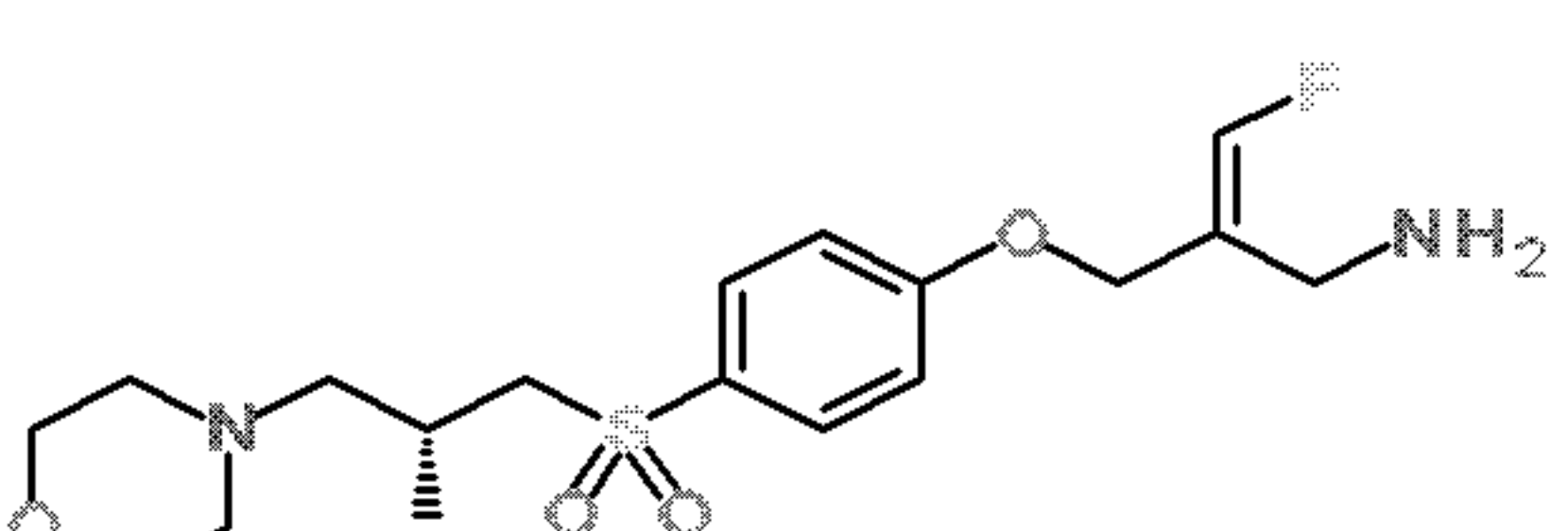
Cmpd No.	Structure	Chemical name
		ne-1-carboxamide
70		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(tert-butyl)bicyclo[2.2.2]octane-1-carboxamide
71		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)(azetidin-1-yl)methanone
72		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)(3,3-difluoroazetidin-1-yl)methanone
73		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclopropyl-N-methylbicyclo[2.2.2]octane-1-carboxamide
74		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N,N-diethylbicyclo[2.2.2]octane-1-carboxamide
75		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclopropylbicyclo[2.2.2]octane-1-carboxamide

Cmpd No.	Structure	Chemical name
76		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclopropanecarboxamide
77		(E)-N-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[1.1.1]pentan-1-yl)pivalamide
78		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-N-methylcyclopropanecarboxamide
79		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-3,3,3-trifluoropropanamide
80		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)isobutyramide
81		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide
82		(E)-2-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)isothiazolidine 1,1-dioxide

Cmpd No.	Structure	Chemical name
83		(E)-1-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-3-methylpyrrolidin-2-one
84		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-2,2-difluorocyclopropane-1-carboxamide
85		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-1-(trifluoromethyl)cyclopropane-1-carboxamide
86		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-1-fluorocyclopropane-1-carboxamide
87		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octane-1-carbonitrile
88		N-((1r,4r)-4-(((4-(((E)-2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)cyclohexyl)cyclopropanecarboxamide
89		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclobutyl-2-(trifluoromethyl)benzamide

Cmpd No.	Structure	Chemical name
90		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)pivalamide
91		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)-1-methylcyclopropane-1-carboxamide
92		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclobutanecarboxamide
93		(R,E)-1-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)pyrrolidin-2-one
94		(S,E)-1-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)pyrrolidin-2-one
95		(E)-3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-N-isopropyl-N,2,2-trimethylpropanamide
96		(E)-N-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2,2-dimethylpropyl)-N-methylisobutyramide

Cmpd No.	Structure	Chemical name
97		(E)-N-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)-N-ethylisobutyramide
98		(E)-N-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2,2-dimethylpropyl)-N-ethylisobutyramide
99		(E)-1-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)pyrrolidin-1-yl)-2-methylpropan-1-one
100		(E)-(3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-1-yl)(cyclopentyl)methanone
101		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-1-isopropylpyridin-2(1H)-one
102		(E)-6-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-2-isopropylpyridazin-3(2H)-one
103		(E)-3-fluoro-2-((4-(((2-(pyrrolidin-1-yl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
104		(R,E)-1-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)piperidin-2-one

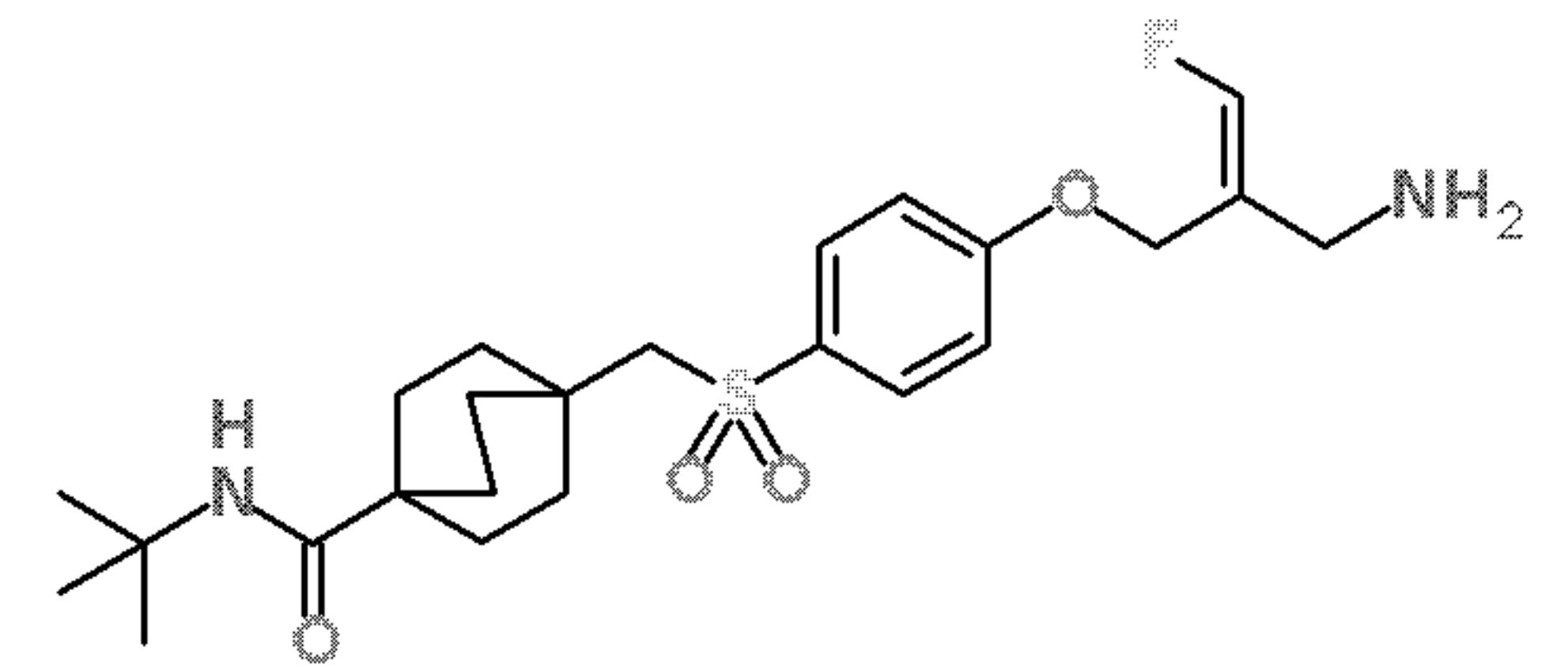
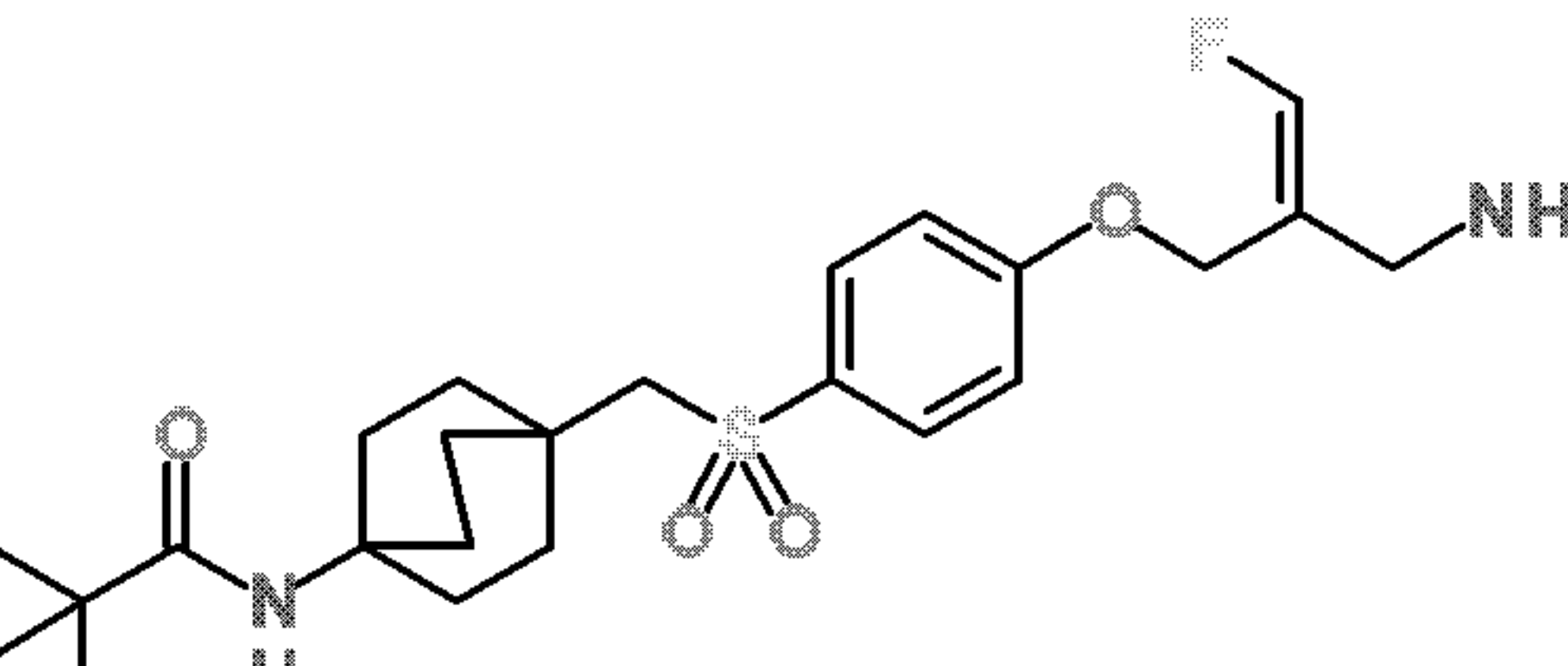
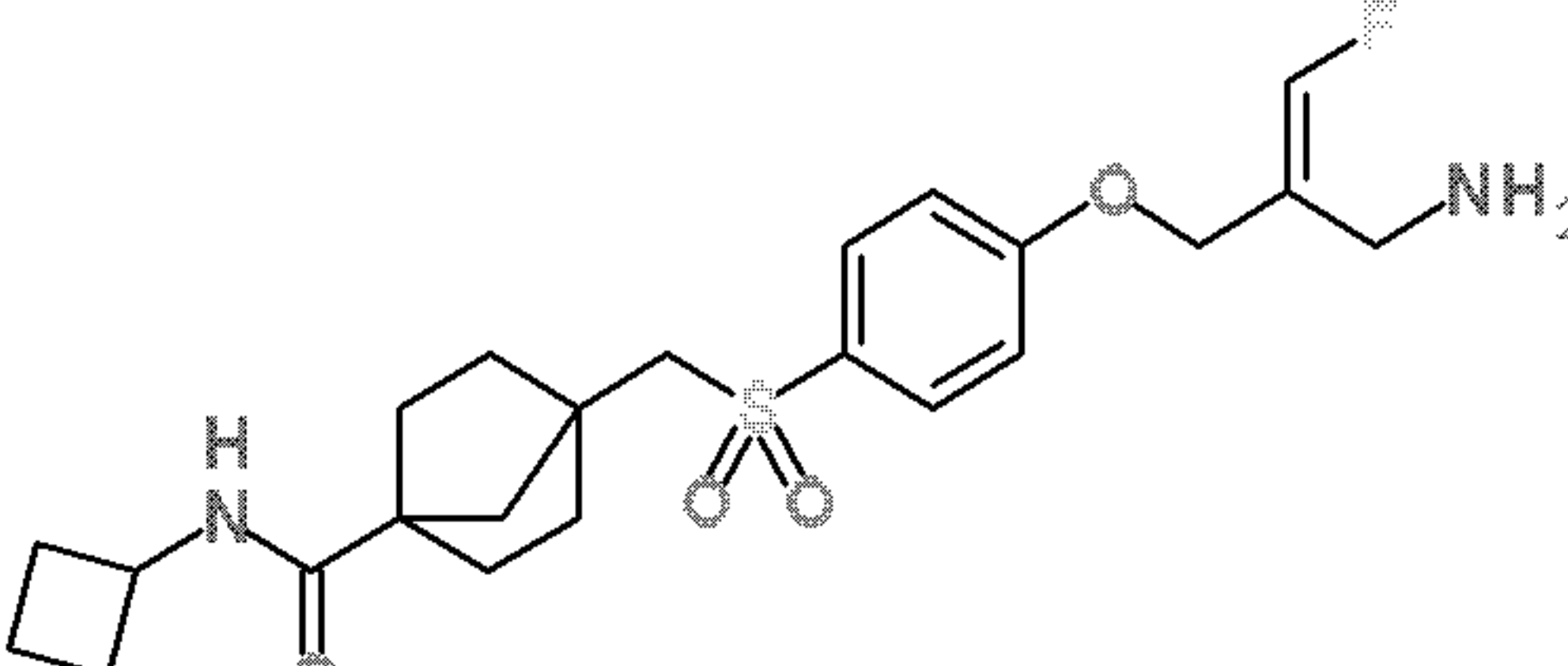
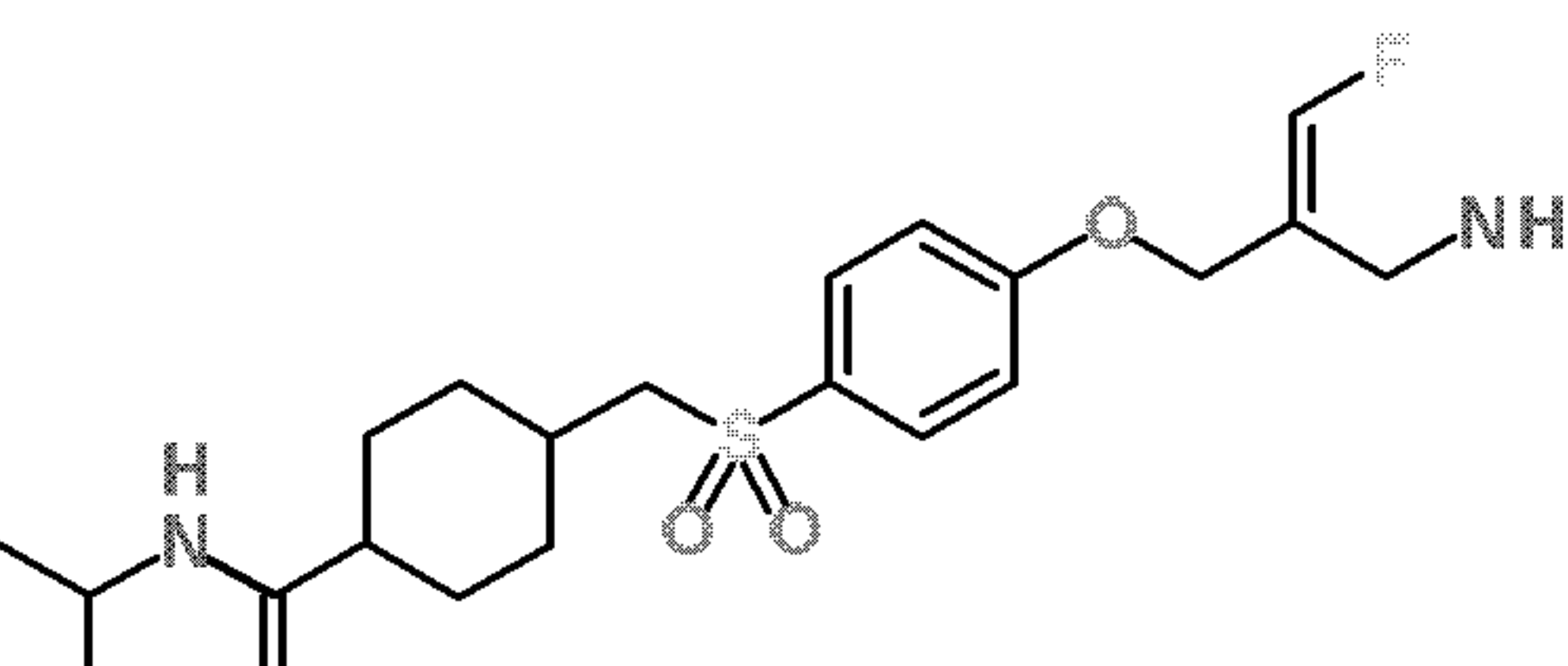
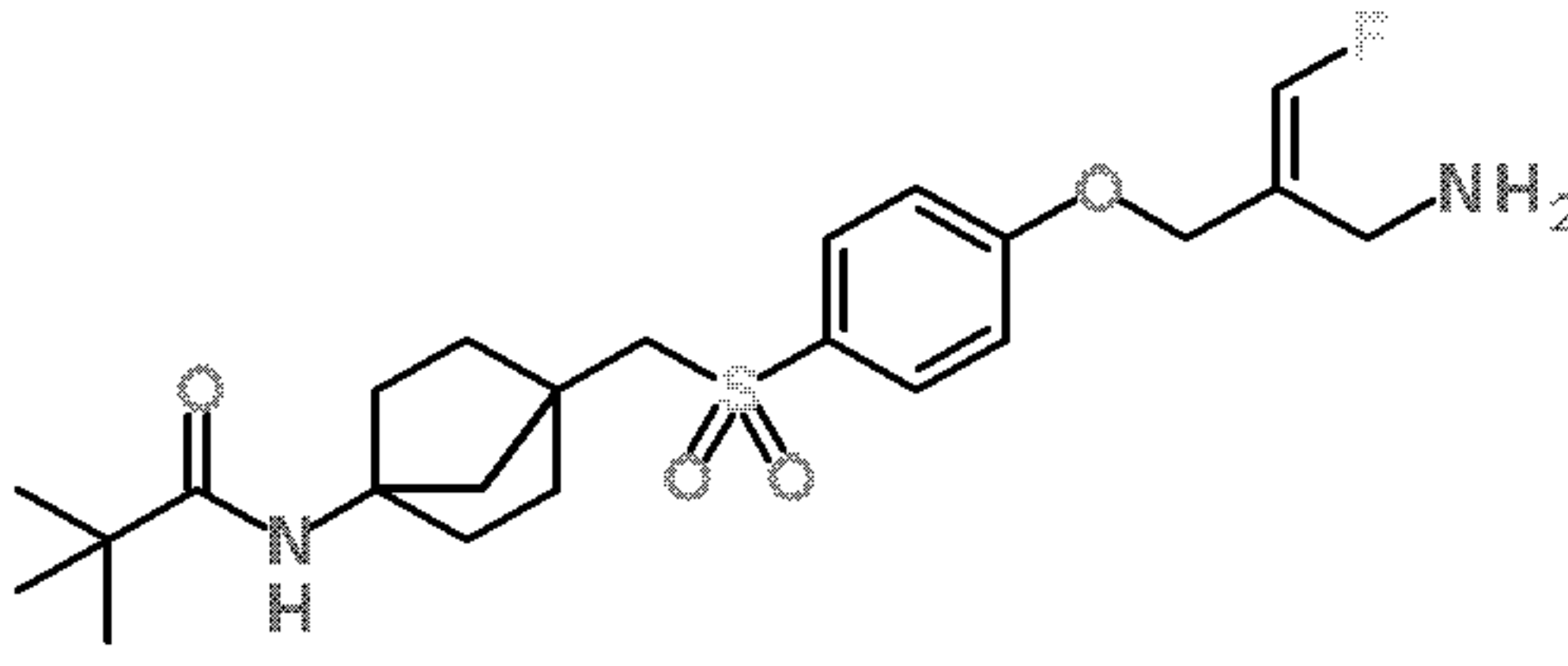
Cmpd No.	Structure	Chemical name
105		(S,E)-1-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)piperidin-2-one
106		(E)-1-((1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)cyclopropyl)methyl)piperidin-2-one
107		(E)-1-(2-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)ethyl)piperidin-2-one
108		(S,E)-1-(1-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)propan-2-yl)piperidin-2-one
109		(R,E)-2-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)-2-azaspiro[4.4]nonan-1-one
110		(S,E)-2-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)-2-azaspiro[4.4]nonan-1-one
111		(E)-1-(3-((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)-2-methylpropyl)-5,5-dimethylpyrrolidin-2-one
112		(R,E)-3-fluoro-2-((4-((2-methyl-3-morpholinopropyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine

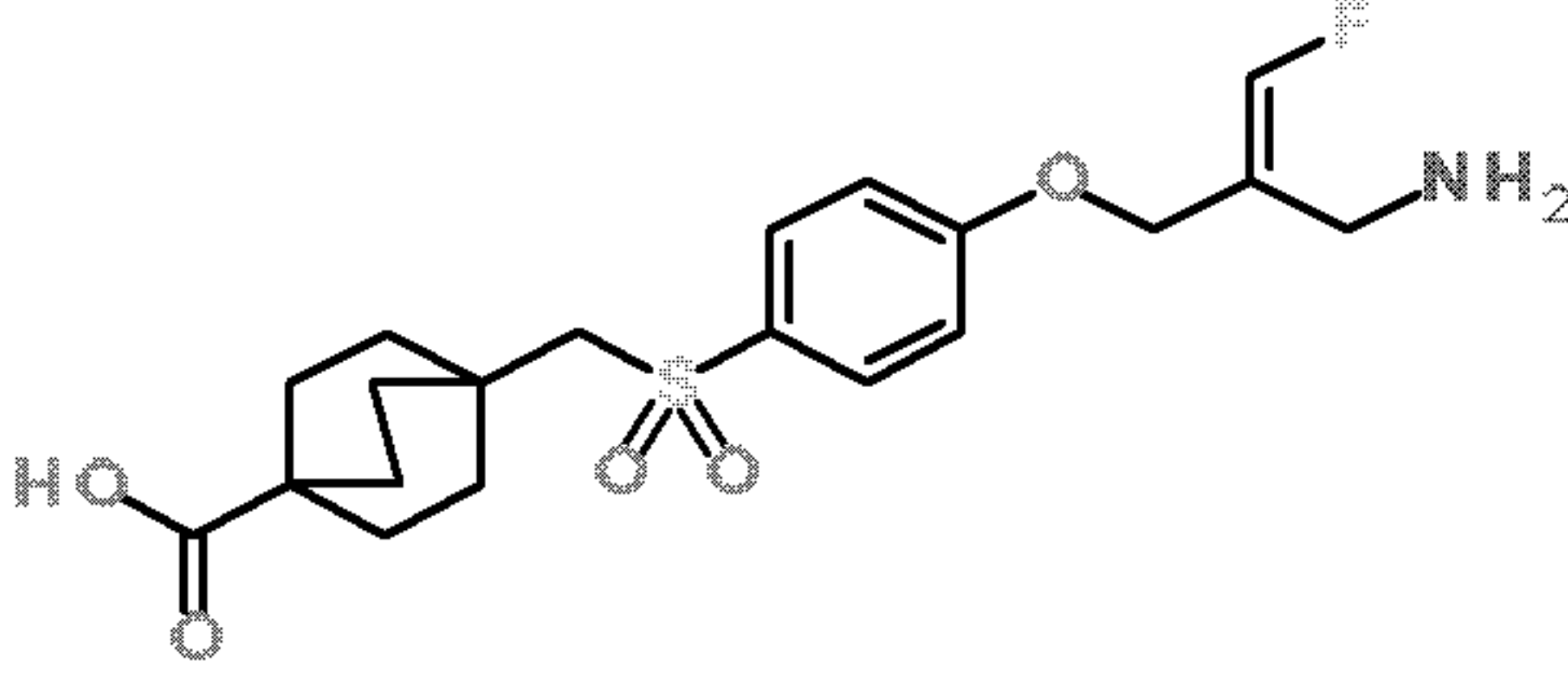
Cmpd No.	Structure	Chemical name
113		(S,E)-3-fluoro-2-((4-((2-methyl-3-morpholinopropyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
114		(E)-3-fluoro-2-((3-fluoro-4-((2-methyl-3-morpholinopropyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
115		(E)-2-((4-((2,2-dimethyl-3-morpholinopropyl)sulfonyl)phenoxy)methyl)-3-fluoroprop-2-en-1-amine
116		(E)-3-fluoro-2-((4-(((1-(morpholinomethyl)cyclopropyl)methyl)sulfonyl)phenoxy)methyl)prop-2-en-1-amine
117		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)pyrrolidin-2-one
118		(E)-2-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)isoindolin-1-one
119		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-3,4-dihydroquinolin-2(1H)-one
120		(E)-1'-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)spiro[cyclopropane-1,3'-indolin]-

Cmpd No.	Structure	Chemical name
		2'-one
121		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)pyridin-2(1H)-one
122		(E)-N-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-methylisobutyramide
123		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-5,5-dimethylpyrrolidin-2-one
124		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-chlorophenyl)sulfonyl)methyl)-5,5-dimethylpyrrolidin-2-one
125		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-3,3-dimethylpyrrolidin-2-one
126		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4,4-dimethylpyrrolidin-2-one
127		(E)-2-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-2-azaspiro[4.4]nonan-1-one

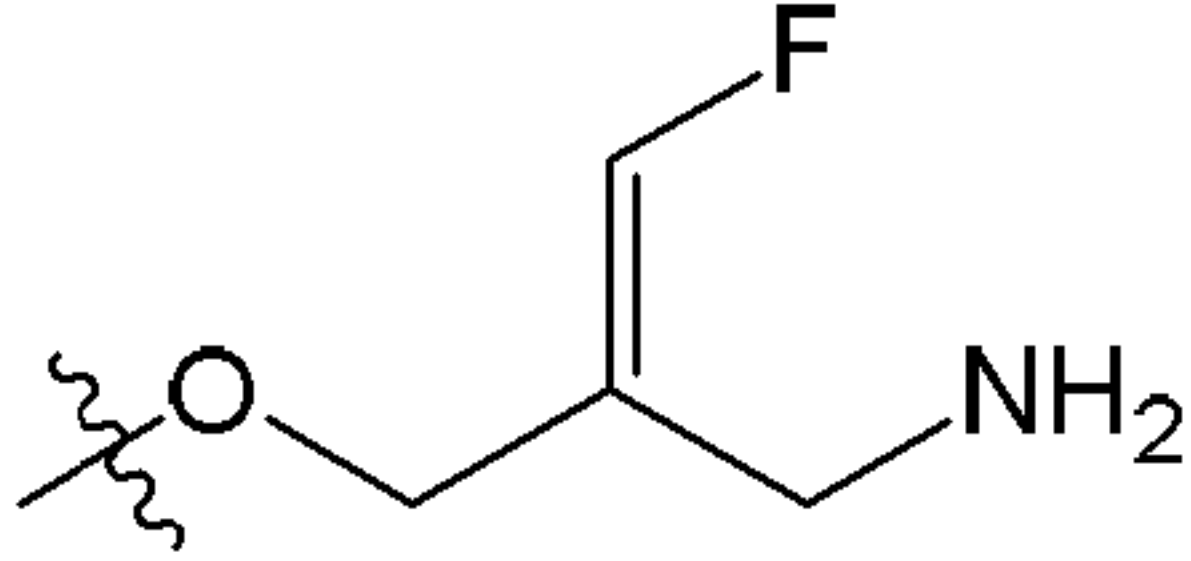
Cmpd No.	Structure	Chemical name
128		(E)-2-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-fluorophenyl)sulfonyl)methyl)-2-azaspiro[4.4]nonan-1-one
129		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)piperidin-2-one
130		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)morpholin-3-one
131		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)-2-fluorophenyl)sulfonyl)methyl)morpholin-3-one
132		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-5,5-dimethylmorpholin-3-one
133		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-pivaloylpiperazin-2-one
134		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-(1-methylcyclobutane-1-carbonyl)piperazin-2-one

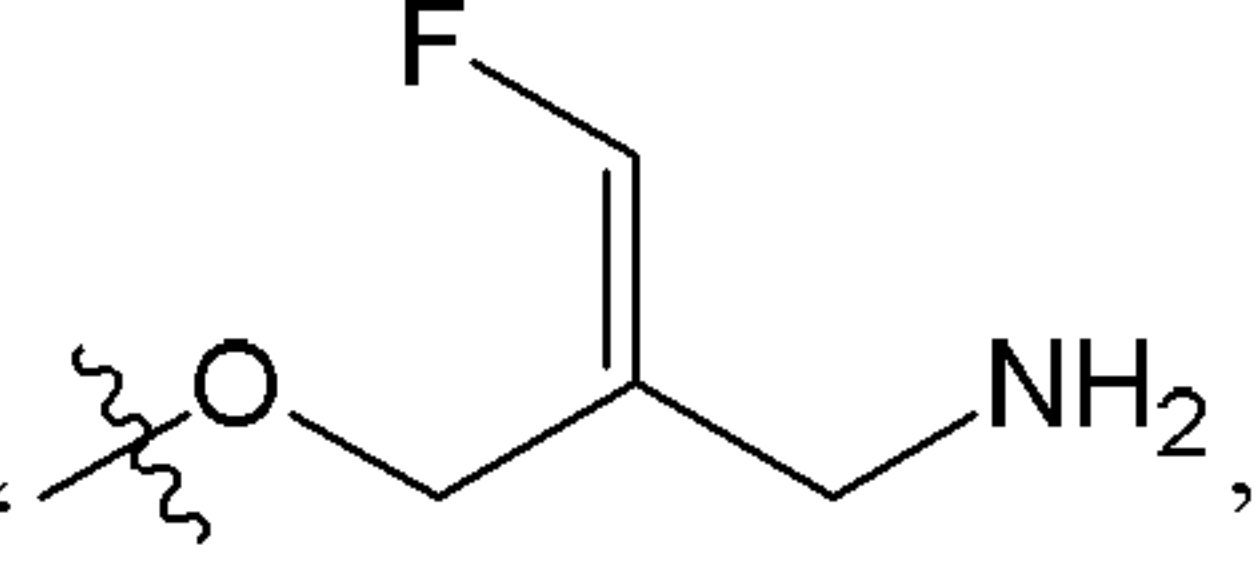
Cmpd No.	Structure	Chemical name
135		(E)-1-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-4-isopropylpiperazin-2-one
136		(5r,8r)-8-(((4-(((E)-2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-2-isopropyl-2-azaspiro[4.5]decan-1-one
137		(5s,8s)-8-(((4-(((E)-2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-2-isopropyl-2-azaspiro[4.5]decan-1-one
138		(E)-3-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclobutylbicyclo[1.1.1]pentane-1-carboxamide
139		(Z)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)cyclopropanecarboxamide
140		(Z)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclobutylbicyclo[2.2.2]octane-1-carboxamide

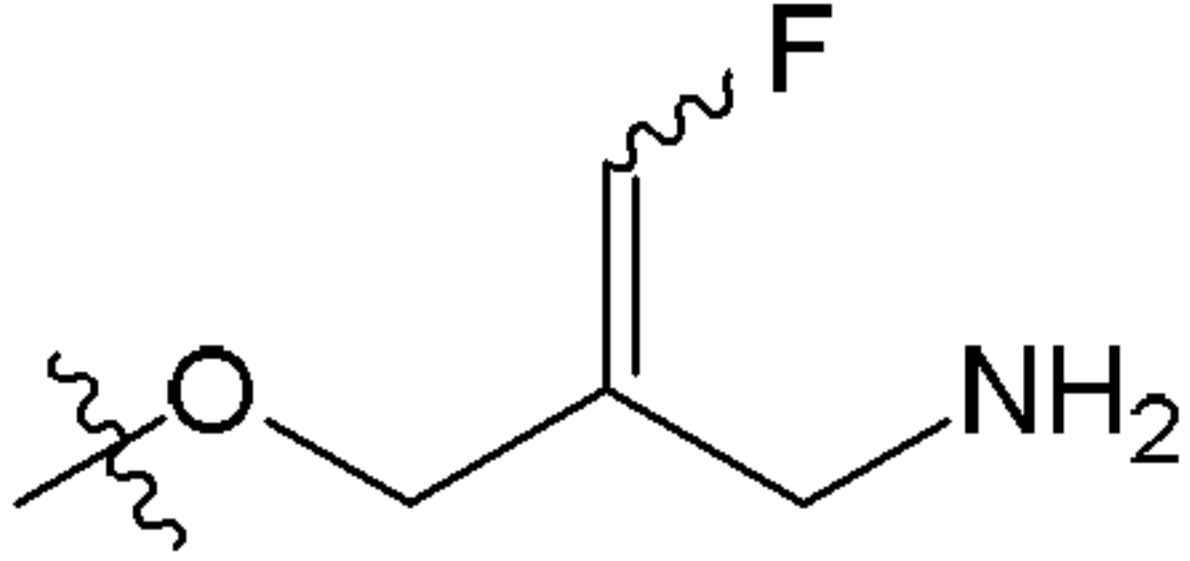
Cmpd No.	Structure	Chemical name
141		(Z)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-(tert-butyl)bicyclo[2.2.2]octane-1-carboxamide
142		(Z)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octan-1-yl)pivalamide
143		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-cyclobutylbicyclo[2.2.1]heptane-1-carboxamide
144		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)-N-isopropylcyclohexane-1-carboxamide
145		(E)-N-(4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.1]heptan-1-yl)pivalamide

Cmpd No.	Structure	Chemical name
146		(E)-4-(((4-((2-(aminomethyl)-3-fluoroallyl)oxy)phenyl)sulfonyl)methyl)bicyclo[2.2.2]octane-1-carboxylic acid

[00137] Due to the existence of double bonds, the compounds of the present application may be in *cis* or *trans*, or *Z* or *E*, configuration. It is understood that although one configuration may be depicted in the structure of the compounds or formulae of the present application, the present application also encompasses the other configuration. For example, the compounds or formulae

of the present application may be depicted with the group “”, the present application also encompasses the the compounds or formulae with the other configuration which

has the group “”. In some instances, the compounds or formulae of the

present application may be depicted with the group “”, which means that the compounds or formulae may be in *cis* or *trans*, or *Z* or *E*, configuration.

[00138] In one embodiment, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a pharmaceutically acceptable salt. In another embodiment, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a solvate. In another embodiment, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a hydrate.

[00139] The details of the application are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present application, illustrative methods and materials are now

described. Other features, objects, and advantages of the application will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this application belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

[00140] The articles "a" and "an" are used in this application to refer to one or more than one (*i.e.*, at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[00141] The term "and/or" is used in this application to mean either "and" or "or" unless indicated otherwise.

[00142] The application also includes pharmaceutical compositions comprising an effective amount of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) and a pharmaceutically acceptable carrier.

[00143] The term "alkyl," as used herein, refers to saturated, straight or branched-chain hydrocarbon radicals containing, in certain embodiments, between one and six carbon atoms. Examples of C₁-C₈ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, *n*-heptyl, and *n*-octyl radicals. Examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, and *n*-hexyl radicals.

[00144] The term "alkenyl," as used herein, denotes a monovalent group derived from a hydrocarbon moiety containing, in certain embodiments, from two to six carbon atoms having at least one carbon-carbon double bond. The double bond may or may not be the point of attachment to another group. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl and the like.

[00145] The term "alkoxy" refers to an -O-alkyl radical.

[00146] The terms "hal," "halo," and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

[00147] The term "aryl," as used herein, refers to a mono- or poly-cyclic carbocyclic ring system having one or more aromatic rings, fused or non-fused, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

[00148] The term "aralkyl," as used herein, refers to an alkyl residue attached to an aryl ring.

5 Examples include, but are not limited to, benzyl, phenethyl and the like.

[00149] The term "cycloalkyl," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated or partially unsaturated carbocyclic ring compound (fused, bridged, or spiro rings). Examples of C₃-C₈ cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₃-C₁₂-

10 cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Also contemplated is a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Examples of such groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 15 cyclooctenyl, and the like.

[00150] The term "heteroaryl," as used herein, refers to a mono- or poly-cyclic (*e.g.*, bi-, or tri-cyclic or more) fused or non-fused, radical or ring system having at least one aromatic ring, having from five to ten ring atoms of which one ring atoms is selected from S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from S, O, and N; and 20 the remaining ring atoms are carbon. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinoliny, isoquinoliny, benzimidazolyl, benzooxazolyl, quinoxaliny, and the like.

[00151] The term "heteroaralkyl" as used herein, refers to an alkyl residue attached to a

25 heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

[00152] The term "heterocycl" or "heterocycloalkyl," as used herein, refers to a saturated or unsaturated non-aromatic 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (fused, bridged, or spiro rings), or 11-, 12, 13, or 14- membered tricyclic ring 30 system (fused, bridged, or spiro rings), where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring

has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, and (iv) the nitrogen heteroatom may optionally be quaternized. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolanyl, pyrrolidinyl, pyrazolidinyl, pyrazolinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-pyridone, oxazolidinyl, isoxazolidinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuryl, dioxanyl, oxetanyl, azetidiny, thietanyl, oxiranyl, aziridinyl, thiiranyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl, 2-azaspiro[3.3]heptan-5-amine, 1-azaspiro[3.3]heptan-5-amine, 1-oxa-6-azaspiro[3.3]heptan-3-amine, 2-azaspiro[3.3]heptan-6-amine, 1-azaspiro[3.3]heptan-6-amine, 6-azaspiro[3.4]octan-2-amine, 5-azaspiro[3.4]octan-2-amine, 6-azaspiro[3.4]octan-1-amine, 5-azaspiro[3.4]octan-1-amine, 5-oxa-2-azaspiro[3.4]octan-7-amine, 7-amino-5-thia-2-azaspiro[3.4]octane 5,5-dioxide, 5-oxa-2-azaspiro[3.4]octan-8-amine, 8-amino-5-thia-2-azaspiro[3.4]octane 5,5-dioxide, and the like.

[00153] The term "alkylamino" refers to a group having the structure, *e.g.*, NH(C₁-C₆ alkyl), where C₁-C₆ alkyl is as previously defined.

[00154] The term "dialkylamino" refers to a group having the structure, *e.g.*, N(C₁-C₆ alkyl)₂, where C₁-C₆ alkyl is as previously defined.

[00155] In accordance with the application, any of the aryls, substituted aryls, heteroaryl and substituted heteroaryl described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

[00156] As described herein, compounds of the application may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the application. It will be appreciated that the phrase

"optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted."

In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent.

Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The terms "optionally substituted",

"optionally substituted alkyl," "optionally substituted alkenyl," "optionally substituted cycloalkyl," "optionally substituted cycloalkenyl," "optionally substituted aryl," "optionally substituted heteroaryl," "optionally substituted aralkyl," "optionally substituted heteroaralkyl," "optionally substituted heterocyclyl," and any other optionally substituted group as used herein,

5 refer to groups that are substituted or unsubstituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to:

-F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, protected amino, -NH-C₁-C₁₂-alkyl, -NH-C₂-C₁₂-alkenyl, -NH-C₂-C₁₂-alkenyl, -NH-C₃-C₁₂-cycloalkyl,

10 -NH-aryl, -NH-heteroaryl, -NH-heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkenyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C₁-C₁₂-alkyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkenyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH-C₁-C₁₂-alkyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkenyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl,

15 -CONH-heterocycloalkyl, -OCO₂-C₁-C₁₂-alkyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₂-C₁₂-alkenyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH-C₁-C₁₂-alkyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₂-C₁₂-alkenyl, -OCONH-C₃-C₁₂-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkenyl,

20 -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂-C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂-C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂-heteroaryl, -NHCO₂-heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH-C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl,

25 -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, -NHC(S)NH₂, -NHC(S)NH-C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH-C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkenyl,

30 -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl,

- NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl,
 -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl,
 -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkenyl, C(NH)NH-C₃-C₁₂-cycloalkyl,
 -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NHheterocycloalkyl,
 5 -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkenyl,
 -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂,
 -SO₂NH-C₁-C₁₂-alkyl, -SO₂NH-C₂-C₁₂-alkenyl, -SO₂NH-C₂-C₁₂-alkenyl,
 -SO₂NH-C₃-C₁₂-cycloalkyl, -SO₂NH-aryl, -SO₂NH-heteroaryl, -SO₂NH-heterocycloalkyl,
 -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkenyl,
 10 -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl,
 -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl,
 -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH,
 -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkenyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl,
 -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.
- 15 **[00157]** The term "carrier", as used in this application, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.
- 20 **[00158]** The compounds of the present application may form salts which are also within the scope of this application. Reference to a compound of the Formulae herein is understood to include reference to salts thereof, unless otherwise indicated.
- [00159]** Representative "pharmaceutically acceptable salts" include, *e.g.*, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate),
 25 benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumerate, fiunarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium,
 30 malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate,

palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

5 [00160] The compounds of the present application, for example, including the pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers of the compounds, can exist in a solvated form with other solvent molecules or in an unsolvated form.

[00161] "Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds or salts have a tendency to trap a fixed
10 molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[00162] All stereoisomers (for example, geometric isomers, optical isomers and the like) of
15 the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this application, as are positional
20 isomers (such as, for example, 4-pyridyl and 3-pyridyl). For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the *cis*- and *trans*-forms, as well as mixtures, are embraced within the scope of the application. Individual stereoisomers of the compound of the application may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of
25 the present application can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", "ester," "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

[00163] The term "isomer" refers to compounds that have the same composition and
30 molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light

(stereoisomers). With regard to stereoisomers, the compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures or as individual enantiomers or diastereomers.

5 [00164] In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present application includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like.

[00165] “Isomerism” means compounds that have identical molecular formulae but differ in
10 the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”. Stereoisomers that are not mirror images of one another are termed “diastereoisomers”, and stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of
15 opposite chirality is termed a “racemic mixture”.

[00166] The compounds of the application may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the application as well as mixtures thereof, including racemic mixtures, form part of the present application. In addition, the present application embraces all geometric and
20 positional isomers. For example, if a compound of the application incorporates a double bond or a fused ring, both the *cis*- and *trans*-forms, as well as mixtures, are embraced within the scope of the application. Each compound herein disclosed includes all the enantiomers that conform to the general structure of the compound. The compound may be in a racemic or enantiomerically pure form, or any other form in terms of stereochemistry. The assay results may reflect the data
25 collected for the racemic form, the enantiomerically pure form, or any other form in terms of stereochemistry.

[00167] A carbon atom bonded to four non-identical substituents is termed a “chiral center”.

[00168] “Chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of
30 diastereomers, termed “diastereomeric mixture”. When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center.

Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[00169] “Geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes *cis* and *trans*, or *Z* and *E*, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[00170] In another embodiment of the application, the compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is an enantiomer. In some embodiments the compound is the (*S*)-enantiomer. In other embodiments the compound is the (*R*)-enantiomer. In yet other embodiments, the compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) may be (+) or (-) enantiomers. The compound may contain more than one stereocenter.

[00171] In another embodiment of the application, the compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) are diastereomers. In some embodiments, the compounds are the syn diastereomer. In other embodiments, the compounds are the anti diastereomer.

[00172] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (*e.g.*, chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (*e.g.*, hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[00173] It is also possible that the compounds of the application may exist in different tautomeric forms, and all such forms are embraced within the scope of the application. Also, for

example, all keto-enol and imine-enamine forms of the compounds are included in the application.

[00174] “Tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solid form, usually one tautomer predominates. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerizations is called tautomerism.

[00175] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[00176] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), amine-enamine and enamine-imine.

[00177] The present application relates to a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, capable of inhibiting SSAO, which are useful for the treatment of diseases and disorders associated with modulation of SSAO. The application further relates to compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, which are useful for inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is a mutant SSAO.

[00178] In some embodiments, the application provides a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), wherein the compound possesses advantageous characteristics, such as decreased brain

penetration, *i.e.*, decreased penetration through the blood-brain-barrier, compared to one or more known SSAO inhibitors, including, but not limited to BI 1467335 (PXS-4728A).

[00179] In some embodiments, the application provides a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein),

5 wherein the compound is at least as potent as one or more known SSAO inhibitors, including, but not limited to BI 1467335 (PXS-4728A), at inhibiting the activity of the SSAO, and possesses additional advantageous characteristics, such as decreased brain penetration, *i.e.*, decreased penetration through the blood-brain-barrier, compared to one or more known SSAO inhibitors, including, but not limited to BI 1467335 (PXS-4728A).

10 [00180] In some embodiments, the application provides a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), wherein the compound is more potent than one or more known SSAO inhibitors, including, but not limited to BI 1467335 (PXS-4728A), at inhibiting the activity of the SSAO.

[00181] In some embodiments, the application provides a compound of the present application
15 (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), wherein the compound is more potent than one or more known SSAO inhibitors, including, but not limited to BI 1467335 (PXS-4728A), at inhibiting the activity of the SSAO, and possesses additional advantageous characteristics, such as decreased brain penetration, *i.e.*, decreased penetration through the blood-brain-barrier, compared to one or more known SSAO inhibitors,
20 including, but not limited to BI 1467335 (PXS-4728A).

[00182] Potency of the inhibitor can be determined by IC₅₀ value. A compound with a lower IC₅₀ value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC₅₀ value. Brain penetration property can be determined by Brain K_p value. A compound with a lower brain K_p value, as determined under
25 substantially similar conditions, is less brain penetrable

[00183] The compounds of the present application can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, 3-chloroperoxybenzoic acid (*m*-CPBA) and/or hydrogen peroxides) to afford other compounds of the present application. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both
30 the compound as shown and its N-oxide derivative (which can be designated as N→O or N⁺-O⁻). Furthermore, in other instances, the nitrogens in the compounds of the present application can be

converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compounds as shown and its N-hydroxy (*i.e.*, N-OH) and N-alkoxy (*i.e.*, N-OR, wherein R is substituted or unsubstituted C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[00184] The term "prodrug," as used in this application, means a compound which is convertible *in vivo* by metabolic means (*e.g.*, by hydrolysis) to a disclosed compound.

[00185] Since prodrugs are known to enhance numerous desirable qualities of

pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*) the compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof can be delivered in prodrug form. Thus, the present application is intended to cover prodrugs of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present application *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the application wherein a hydroxyl or amino, group is bonded to any group that, when the prodrug of the present application is administered to a mammalian subject, it cleaves to form a free hydroxyl or free amino group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of each of the formulae described herein or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof.

[00186] The term "crystal polymorphs", "polymorphs" or "crystal forms" means crystal structures in which a compound (or a salt or solvate thereof) can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Different crystal forms usually have different X-ray diffraction patterns, infrared spectral, melting points, density

hardness, crystal shape, optical and electrical properties, stability and solubility.

Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate.

[00187] As used herein, the term “analog” refers to a compound that is structurally similar to another compound but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[00188] The application also comprehends isotopically-labeled compounds, which are identical to those recited in the each of the formulae described herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature. Examples of isotopes that can be incorporated into compounds of the application include isotopes of hydrogen, carbon, nitrogen, fluorine, such as ^3H , ^{11}C , ^{14}C , ^2H and ^{18}F .

[00189] Compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present application. Isotopically-labeled compounds of the present application, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^3H , and carbon-14, *i.e.*, ^{14}C , isotopes are useful for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are useful in PET (positron emission tomography). PET is useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances, isotopically labeled compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples described herein, by substituting a readily available isotopically labeled reagent for a non-

isotopically labeled reagent. In one embodiment, the compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, is not isotopically labelled.

5 [00190] The term "administer", "administering", or "administration" as used in this application refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug, derivative or analog of the compound or pharmaceutically acceptable salt of the compound or a composition to the subject, which can form an equivalent amount of active compound within the
10 subject's body.

[00191] A "patient" or "subject" is a mammal, *e.g.*, a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

[00192] An "effective amount" or "therapeutically effective amount" when used in connection with a compound or pharmaceutical composition is an amount effective for treating or
15 preventing a disease in a subject as described herein.

[00193] The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

[00194] The compounds of the present application, or a pharmaceutically acceptable salt,
20 solvate, prodrug, stereoisomer, or tautomer thereof, can also be used to prevent a disease, condition or disorder. As used herein, "preventing" or "prevent" describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[00195] The term "disorder" is used in this application to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

25 [00196] As used herein, the term "SSAO-mediated" diseases or disorders means any disease or other deleterious condition in which SSAO, or a mutant thereof, is known to play a role. Accordingly, another embodiment of the present application relates to treating or lessening the severity of one or more diseases in which SSAO, or a mutant thereof, is known to play a role. Specifically, the present application relates to a method of treating or lessening the severity of a
30 disease or condition selected from a liver disease, liver inflammation, liver fibrosis, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), atherosclerosis, stroke and

complications thereof, chronic kidney disease, Alzheimer's disease, cardiovascular disease, metabolic disease, inflammation, pain, and pain associated with osteoarthritis, neuroinflammation, wherein said method comprises administering to a subject in need thereof a compounds of the present application (*e.g.*, a compound of any of the formulae or any individual
5 compounds disclosed herein), or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, or a composition according to the present application.

Methods for Preparing the Compounds

[00197] The compounds of the present application may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

10 [00198] The compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the scheme described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting
15 groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of the
20 compounds of the present application.

[00199] Those skilled in the art will recognize if a stereocenter exists in the compounds of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). Accordingly, the present application includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compound but the individual
25 enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. *See*, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander
30 (Wiley-Interscience, 1994).

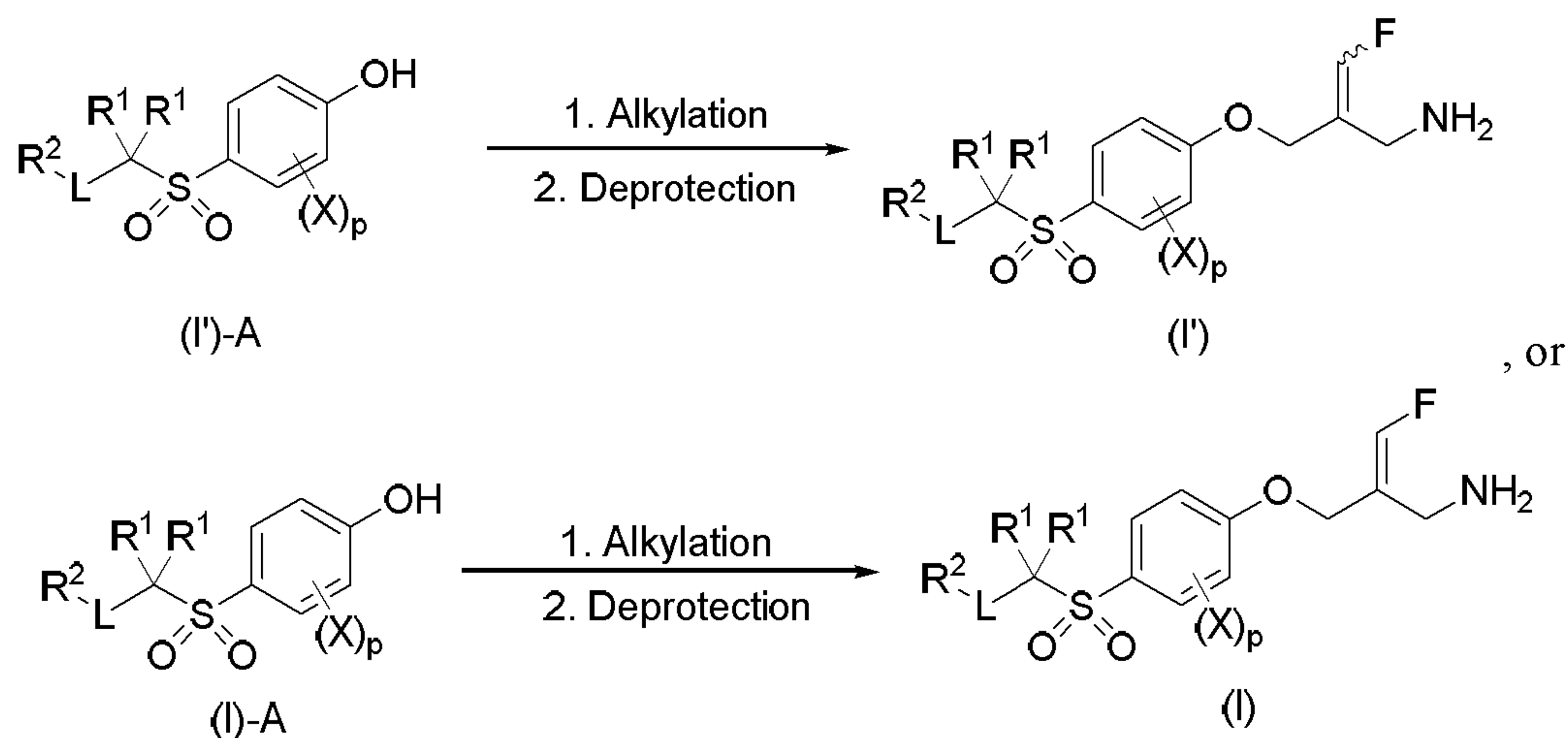
[00200] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

[00201] The compounds of the present application can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, the compounds of the

present application can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. The compounds of the present application (*i.e.*, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein)) can be synthesized by following the steps outlined in **General Scheme 1**.

Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

General Scheme 1



[00202] Scheme 1 depicts a generic synthesis of compounds of Formula (I') or (I).

Specifically, the hydroxyl group of Compound (I)-A or Compound (I')-A can be alkylated with a suitably protected amine, typically under basic conditions, which can be deprotected to give compounds of Formula (I') or (I).

[00203] A mixture of enantiomers, diastereomers, *cis/trans* isomers resulting from the processes described above can be separated into their single components by chiral salt technique, chromatography using normal phase, reverse phase or chiral column, depending on the nature of the separation.

Analytical Methods, Materials, and Instrumentation

[00204] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 400 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Liquid chromatography-mass spectrometry (LC/MS) were collected using a SHIMADZU LCMS-2020EV or Agilent 1260-6125B LCMS. Purity and low resolution mass spectral data were measured using Agilent 1260-6125B LCMS system (with Diode Array Detector, and Agilent G6125BA Mass spectrometer) or using Waters Acquity UPLC system (with Diode Array Detector, and Waters 3100 Mass Detector). The purity was characterized by UV wavelength 214 nm, 220 nm, 254 nm and ESI. Column: poroshell 120 EC-C18 2.7 μ m 4.6 X 100 mm; Flow rate 0.8 mL/min; Solvent A (100/0.1 water/formic acid), Solvent B (100 acetonitrile); gradient: hold 5% B to 0.3 min, 5-95% B from 0.3 to 2 min, hold 95% B to 4.8 min, 95-5% B from 4.8 to 5.4 min, then hold 5% B to 6.5 min. Or, column: Acquity UPLC BEH C18 1.7 μ m 2.1 X 50 mm; Flow rate 0.5 mL/min; Solvent A (0.1%formic acid water), Solvent B (acetonitrile); gradient: hold 5%B for 0.2 min, 5-95% B from 0.2 to 2.0 min, hold 95% B to 3.1 min, then 5% B at 3.5 min.

[00205] Abbreviations used in the following examples and elsewhere herein are:

DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
IPA	<i>iso</i> -propyl alcohol
IPE	di-isopropyl ether
MeCN	acetonitrile
AMMN	Ammonia, 7.0 M solution in MeOH
THF	tetrahydrofuran
m-CPBA	3-chlorobenzenecarboperoxoic acid
FCC	Flash column chromatography
DCM	dichloromethane
LC/MS	liquid chromatography-mass spectrometry
MeOH	methanol

MS	mass spectrometry
n-BuOH	<i>n</i> -butyl alcohol
NMP	N-methyl pyrrolidinone
NMR	nuclear magnetic resonance
ppm	parts per million
TEA	triethylamine

Biological Assays

[00206] The biological activities of the compounds of the present application can be assessed with methods and assays known in the art. For example, the potency of the compounds of the present application can be evaluated with an SSAO Activity Assay. Briefly, compounds of the present application can be applied to recombinant hSSAO, hMAO-A, and hMAO-B isoforms and the amine oxidase activity of the enzymes are measured after the addition and subsequent oxidation of the luminogenic substrate (*e.g.*, with the MAO-Glo assay kit from Promega). The IC₅₀ can be calculated, for example, by fitting the dose response curve using a 4-parameter non-linear regression routine.

[00207] In addition, the compounds of the preset application possess additional advantageous biological activities, such as decreased brain penetration, which can be evaluated with methods and assays known in the art. For example, Brain K_{puu} assay composed of Blood-Brain-Barrier (BBB) assay and protein binding assay, can be utilized. The protein binding assay comprises equilibrium dialysis against brain lysate and plasma to calculate $f_{u(brain)}$ and $f_{u(plasma)}$, respectively. The BBB assay can be conducted in experimental animals at 1mg/kg IV dosage. After dosing with the compounds of the present application, plasma and brain samples can be collected to analyze compound concentration (C_{plasma} and C_{brain}). The K_{puu} value of the tested compounds can be calculated by the equation:

$$K_{puu} = \frac{C_{brain}}{C_{plasma}} \times \frac{f_{u(brain)}}{f_{u(plasma)}} \quad (1)$$

Methods of Using the Compounds

[00208] The compounds of the present invention are useful for modulating (*e.g.*, inhibiting) an amine oxidase enzyme, such as membrane-bound SSAO/VAP-1 or soluble SSAO/VAP-1. The relative inhibitory potencies of the compounds can be determined by the amount needed to inhibit the amine oxidase activity of SSAO/VAP-1 in a variety of ways, *e.g.*, in *in vitro* assays

with recombinant human protein or with recombinant non-human enzyme, in cellular assays expressing normal enzyme, or in *in vivo* tests. Accordingly, the present application relates to methods of modulating (*e.g.*, inhibiting) an amine oxidase enzyme, such as membrane-bound SSAO/VAP-1 or soluble SSAO/VAP-1, for the treatment of a disease or disorder.

5 [00209] The compounds of the present application are useful for the treatment of a disease or disorder associated with the SSAO (*e.g.*, overexpression, dysregulation, or aberrant activity of SSAO). A disease or disorder associated with the SSAO includes, but is not limited to, inflammation or an inflammatory disease, fibrosis or a fibrotic disease, a liver disease, a cardiovascular disease, autoimmune disease, and a metabolic disease.

10 [00210] Inflammation or an inflammatory disease (*e.g.*, inflammation or an inflammatory disease associated with the SSAO) includes, but is not limited to, arthritis, synovitis, Crohn's disease, ulcerative colitis, irritable bowel disease, asthma (*e.g.*, eosinophilic asthma, severe asthma, virally exacerbated asthma), chronic pain, chronic pain from osteoarthritis, chronic pulmonary obstructive disease, cystic fibrosis, bronchiectasis, liver autoimmune disease,
15 autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, autoimmune cholangitis, alcoholic liver disease, NAFLD, NASH, neuroinflammation, cirrhosis, atherosclerosis, chronic heart failure, congestive heart failure, ischemic disease, stroke and complications thereof, myocardial infarction and complications thereof, inflammatory cell-mediated tissue destruction following stroke, psoriasis, contact dermatitis, inflammation due to diabetes, skin inflammation,
20 pulmonary inflammation, liver inflammation, and the like.

[00211] Fibrosis or a fibrotic disease (*e.g.*, a fibrotic disease associated with the SSAO) includes, but is not limited to, cystic fibrosis, pulmonary fibrosis (*e.g.*, idiopathic pulmonary fibrosis), liver fibrosis, kidney fibrosis, lung fibrosis, fibrosis of other organs and tissues, radiation induced fibrosis, and other diseases where excessive fibrosis contributes to disease
25 pathology, and the like.

[00212] A liver disease (*e.g.*, a liver disease associated with the SSAO) includes, but is not limited to, liver inflammation, liver fibrosis, NASH, NAFLD, cirrhosis, liver autoimmune diseases, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, autoimmune cholangitis, and alcoholic liver disease.

30 [00213] A respiratory disease (*e.g.*, a respiratory disease, associated with the SSAO) includes, but is not limited to, lung fibrosis, lung inflammation, asthma (*e.g.*, eosinophilic asthma, severe

asthma, virally exacerbated asthma), chronic pulmonary obstructive disease, cystic fibrosis, and bronchiectasis.

[00214] Another aspect of the application relates to a method of treating, preventing, inhibiting, or eliminating a disease or disorder associated with modulation of SSAO (*e.g.*, inhibition of SSAO). The method comprises administering to a subject in need of a treatment for diseases or disorders associated with modulation of SSAO an effective amount a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof or a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). In one embodiment, the SSAO-mediated disorder is a disease or disorder described herein. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00215] Another aspect of the application relates to a method of modulating SSAO, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, or a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). In one embodiment, modulating SSAO is inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00216] Another aspect of the application relates to a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in a method of treating a SSAO-mediated disorder. In one embodiment, the SSAO-mediated disorder is a disease or disorder described herein. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00217] In another aspect, the present application relates to a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in a method of treating a SSAO-mediated disorder. In

one embodiment, the SSAO-mediated disorder is a disease or disorder described herein. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00218] Another aspect of the application relates to a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in modulating SSAO. In one embodiment, modulating SSAO is inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00219] In another aspect, the present application relates to a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in modulating SSAO. In one embodiment, modulating SSAO is inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00220] Another aspect of the application relates to the use of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a SSAO-mediated disease or disorder. In one embodiment, the SSAO-mediated disorder is a disease or disorder described herein. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00221] In another aspect, the present application relates to the use of a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a SSAO-mediated disease or disorder. In one embodiment, the SSAO-mediated disorder is a disease or disorder described herein. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00222] Another aspect of the application relates to the use of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for modulating SSAO. In one embodiment, modulating

SSAO is inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00223] In another aspect, the present application relates to the use of a pharmaceutical composition of a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, 5 prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for modulating SSAO. In one embodiment, modulating SSAO is inhibiting SSAO. In some embodiments, the SSAO is wild-type SSAO. In other embodiments, the SSAO is mutant SSAO.

[00224] The disclosed compound of the application can be administered in effective amounts 10 to treat or prevent a disorder and/or prevent the development thereof in subjects.

[00225] The compound of the application can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, *e.g.*, non-drug therapies. For example, synergistic effects can occur with other anti-proliferative, anti-cancer, immunomodulatory or anti-inflammatory substances.

15 In some embodiments, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is administered in combination with an additional therapeutic agent selected from an anti-inflammatory agent, an immunomodulatory agent, a chemotherapeutic agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an agent for treating lung disease, an agent for 20 treating kidney disease, an agent for treating ocular disease, an agent for treating skin disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders. Where the compound of the application is administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on 25 the condition being treated and so forth.

[00226] Combination therapy includes the administration of the subject compound in further combination with other biologically active ingredients (such as, but not limited to, an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, 30 an agent for treating blood disorders, an agent for treating diabetes, an agent for treating immunodeficiency disorders, and an agent for treating pain) and non-drug therapies (such as, but

not limited to, surgery or radiation treatment). For instance, the compound of the application can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compound of the application. The compound of the application can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

Pharmaceutical Compositions

[00227] The present application also provides pharmaceutical compositions comprising a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein), or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in combination with at least one pharmaceutically acceptable excipient or carrier.

[00228] A “pharmaceutical composition” is a formulation containing the compound of the present application in a form suitable for administration to a subject. In one embodiment, the pharmaceutical composition is in bulk or in unit dosage form. The unit dosage form is any of a variety of forms, including, for example, a capsule, an IV bag, a tablet, a single pump on an aerosol inhaler or a vial. The quantity of active ingredient (*e.g.*, a formulation of the disclosed compound or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof thereof) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this application include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In one embodiment, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers or propellants that are required.

[00229] As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound

medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00230] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[00231] A pharmaceutical compositions of the application are formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00232] A compound or pharmaceutical composition of the application can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. The dose chosen should be sufficient to constitute effective treatment but not as high as to cause unacceptable side effects. The state of the disease condition and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[00233] The term “therapeutically effective amount”, as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective

amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In one embodiment, the disease or disorder is a disease or disorder described herein.

[00234] For any compound, the therapeutically effective amount can be estimated initially
5 either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or
10 experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient,
15 and the route of administration.

[00235] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and
20 tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[00236] The pharmaceutical compositions containing active compound (*i.e.*, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds
25 disclosed herein)) of the present application may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active
30 compound into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[00237] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00238] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00239] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier

is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an
5 excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00240] For administration by inhalation, the compound is delivered in the form of an aerosol
10 spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[00241] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for
15 example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compound is formulated into ointments, salves, gels, or creams as generally known in the art.

[00242] The active compound can be prepared with pharmaceutically acceptable carriers that
20 will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained
25 commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00243] It is especially advantageous to formulate oral or parenteral compositions in dosage
30 unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit

containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the application are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

5 [00244] In therapeutic applications, the dosages of the pharmaceutical compositions used in accordance with the application vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. An effective amount of a
10 pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. As used herein, the term “dosage effective manner” refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[00245] The pharmaceutical compositions can be included in a container, pack, or dispenser
15 together with instructions for administration.

[00246] As used herein, “pharmaceutically acceptable salts” refer to derivatives of the compound of the present application wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic
20 residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic,
25 bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic,
30 succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, *etc.*.

[00247] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present application also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[00248] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[00249] The compound of the present application can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, an acetate, propionate or other ester.

[00250] The compound of the present application can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms “pro-drug” and “prodrug” are used interchangeably herein and refer to any compound which releases an active parent drug *in vivo*. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*), the compound of the present application can be delivered in prodrug form. Thus, the present application is intended to cover prodrugs of the presently claimed compound, methods of delivering the same and compositions containing the same. “Prodrugs” are intended to include any covalently bonded carriers that release an active parent drug of the present application *in vivo* when such prodrug is administered to a subject. Prodrugs in the present application are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include the compound of the present application wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be

cleaved *in vivo* to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[00251] Examples of prodrugs include, but are not limited to, esters (*e.g.*, acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (*e.g.*, N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (*e.g.*, ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (*e.g.*, N-acetyl) N-Mannich bases, Schiff bases and enaminones of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in the compound of the application, and the like, See Bundegaard, H., *Design of Prodrugs*, p1-92, Elsevier, New York-Oxford (1985).

[00252] The compound, or pharmaceutically acceptable salts, tautomers, prodrugs, solvates, metabolites, polymorphs, analogs or derivatives thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[00253] The dosage regimen utilizing the compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[00254] Techniques for formulation and administration of the disclosed compound of the application can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compound described herein, and the pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compound or pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, or tautomers thereof will be present in such

pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[00255] All percentages and ratios used herein, unless otherwise indicated, are by weight.

Other features and advantages of the present application are apparent from the different

5 examples. The provided examples illustrate different components and methodology useful in practicing the present application. The examples do not limit the claimed application. Based on the present application the skilled artisan can identify and employ other components and methodology useful for practicing the present application.

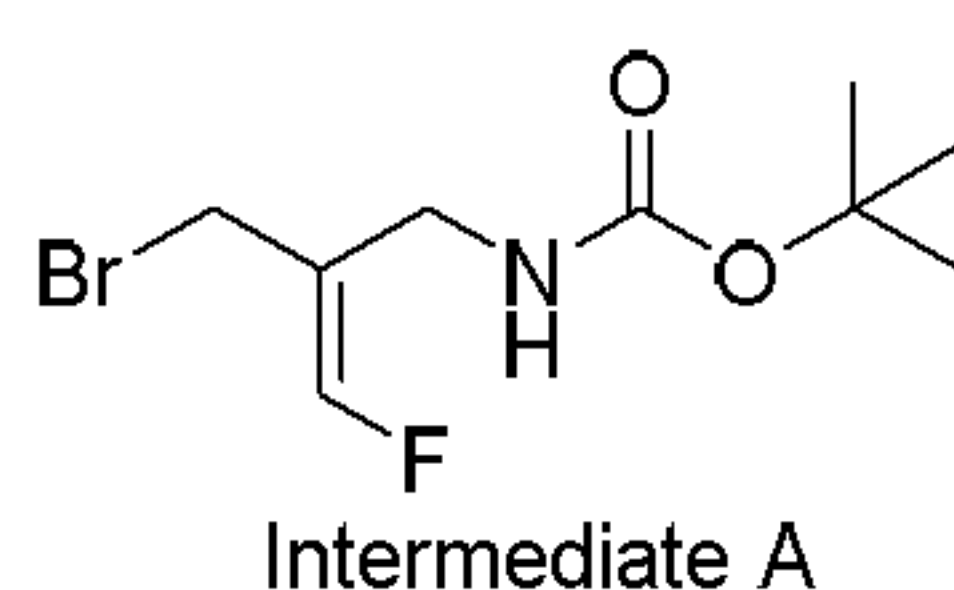
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Examples

[00256] The application is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this application in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the application is intended

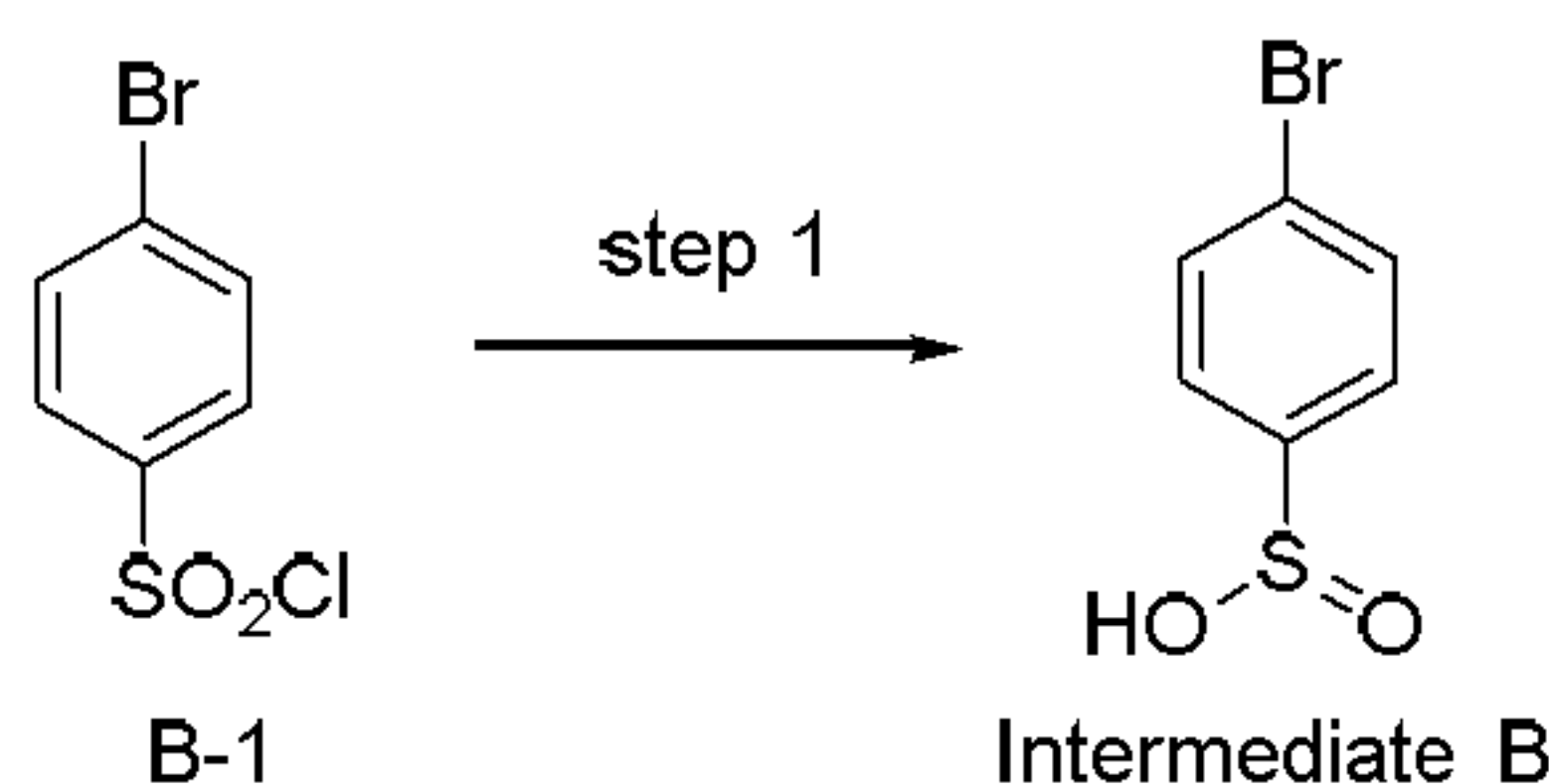
15 thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present application and/or scope of the appended claims.

Example 1: Synthesis of Intermediate A



20 [00257] **Intermediate A** can be synthesized according to methods known in the art, such as the methods described in WO 2013/163675 A1.

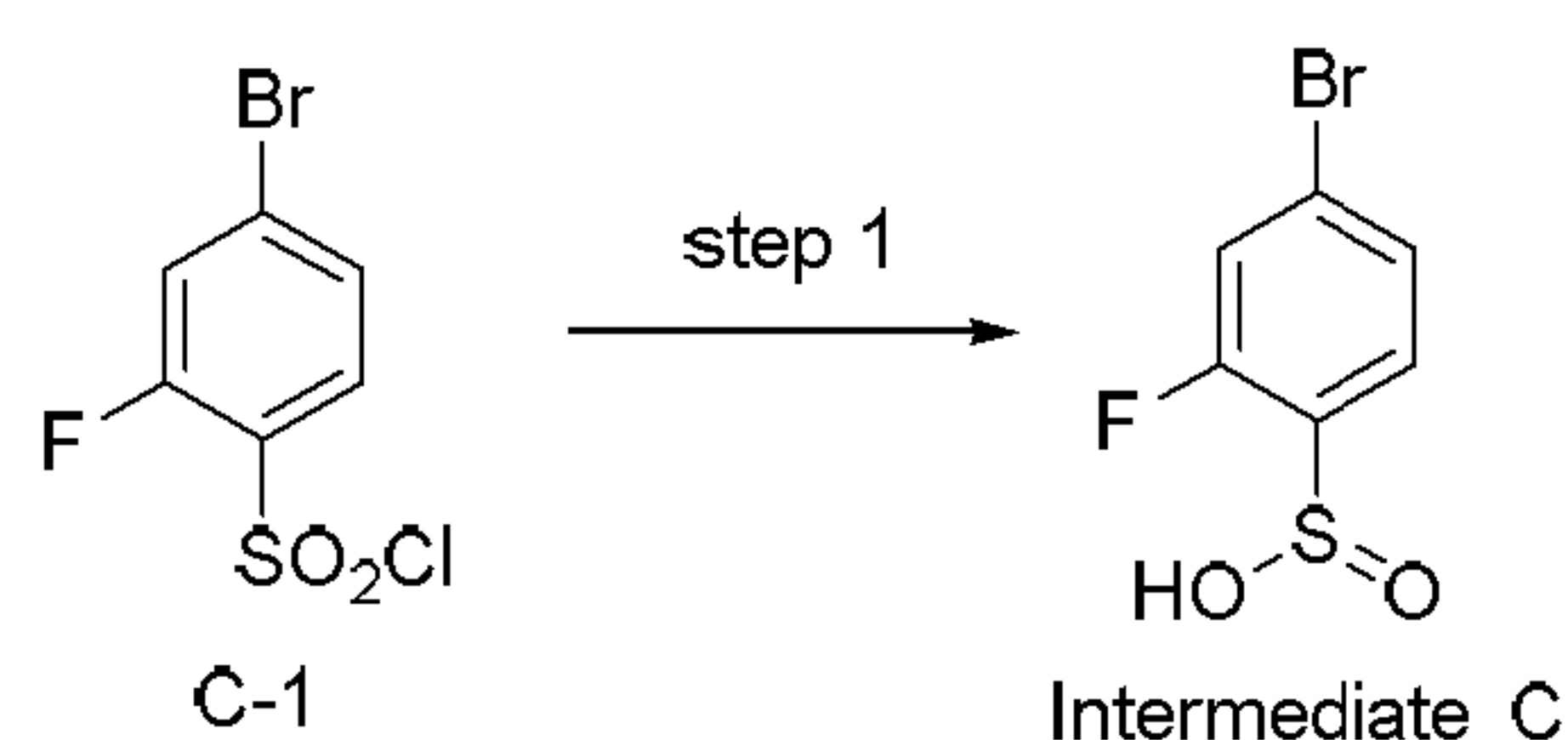
Example 2: Synthesis of Intermediate B



Step 1: Intermediate B

[00258] A mixture of **B-1** (1.5 g, 5.87 mmol), NaHCO₃ (902.48 mg, 10.74 mmol) and Na₂SO₃ (1.38 g, 10.92 mmol) in H₂O (10 mL) was heated to 100 °C for 1 hr. After cooling to room temperature, the reaction mixture was diluted with H₂O (30ml) and acidized to pH=1 with *con.*HCl. The white solid was collected by filtration and washed with H₂O to give **Intermediate B** (1.2 g, crude). The crude product was used for the next step without further purification. MS: m/z = 219 (M-1).

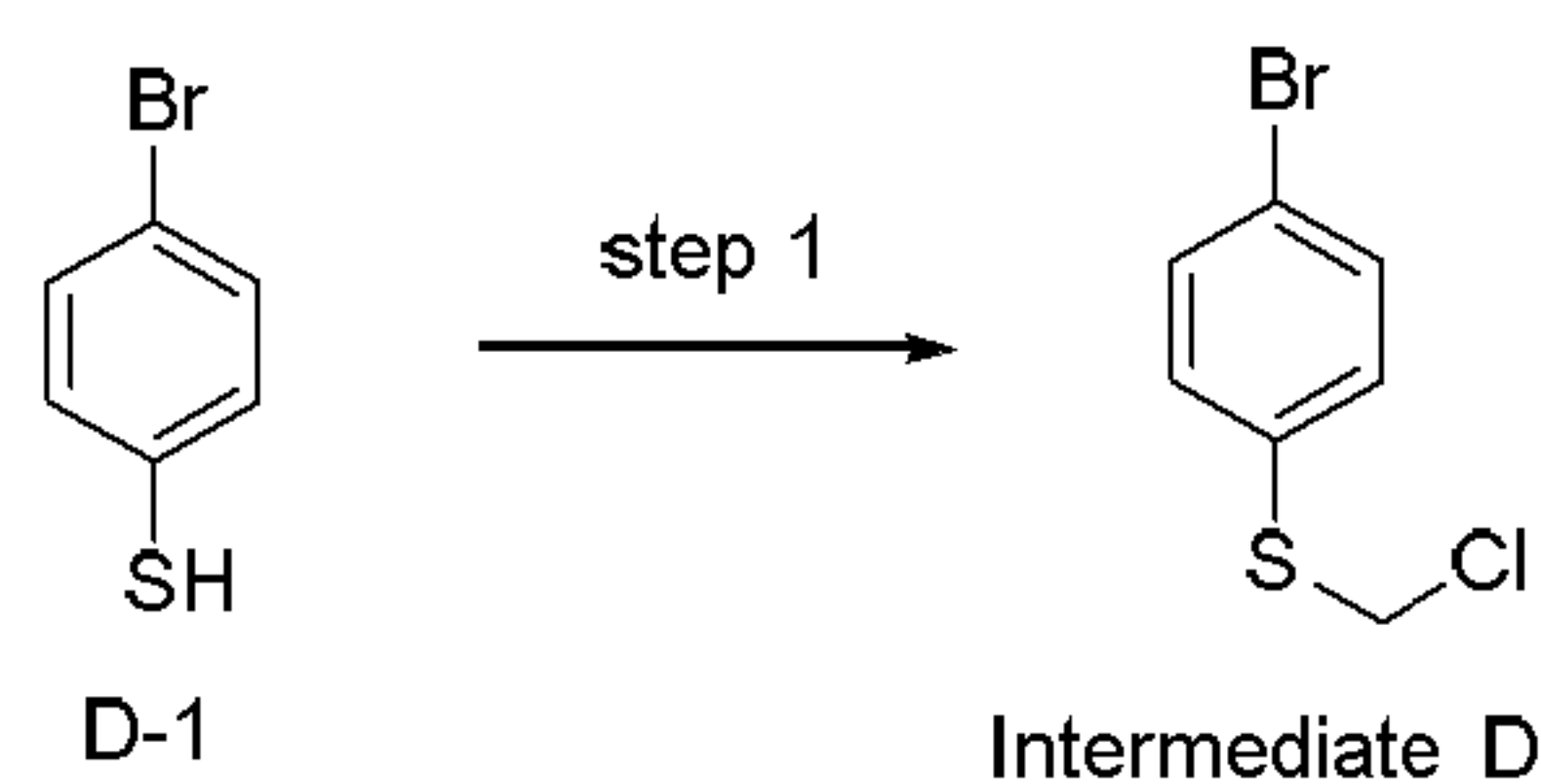
Example 3: Synthesis of Intermediate C



Step 1: Intermediate C

[00259] A mixture of **C-1** (1.5 g, 5.48 mmol), NaHCO₃ (843.12 mg, 10.04 mmol) and Na₂SO₃ (1.29 g, 10.26 mmol) in H₂O (20 mL) was heated to 100 °C for 1 hr. After cooling to room temperature, the reaction mixture was diluted with H₂O (30ml) and acidized to pH=1 with *con.*HCl. The white solid was collected by filtration and washed with H₂O to give **Intermediate C** (1.2 g, crude). The crude product was used for the next step without further purification. MS: m/z = 237 (M-1).

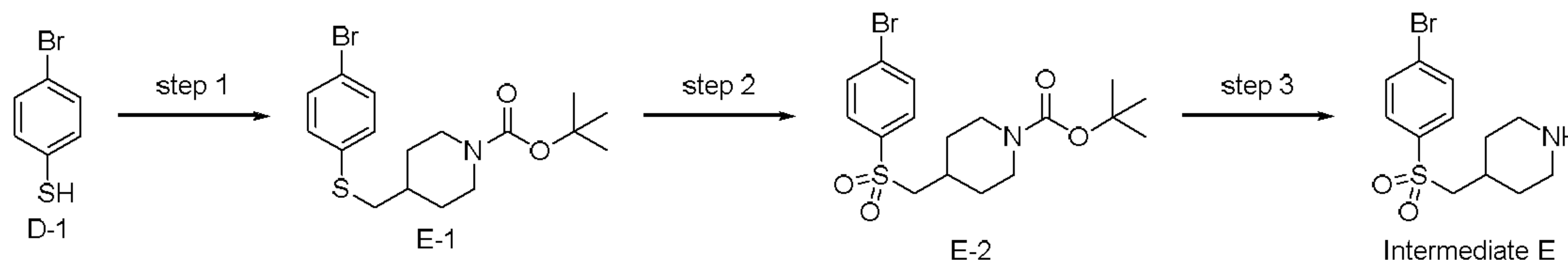
Example 4: Synthesis of Intermediate D



Step 1: Intermediate D

[00260] To a mixture of D-1 (1.5 g, 7.93 mmol), 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (1.21 g, 7.93 mmol, 1.18 mL) in toluene (30 mL) was added bromo(chloro)methane (20.53 g, 158.67 mmol) at 20 °C. The reaction solution was stirred for 2 hr at 20 °C. Then, the reaction mixture was filtered, and the filtrate was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate /petroleum ether 0 to 5%) to obtain **Intermediate D** (1.1 g, crude).

Example 5: Synthesis of Intermediate E



Step 1: E-1

[00261] To a solution of **D-1** (500 mg, 2.64 mmol) in DMF (10 mL) was added NaH (126.92 mg, 3.17 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (882.79 mg, 3.17 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate /petroleum ether 0 to 20%) to obtain **E-1** (920 mg, 2.38 mmol, 90.05% yield). MS: $m/z = 386$ (M+1).

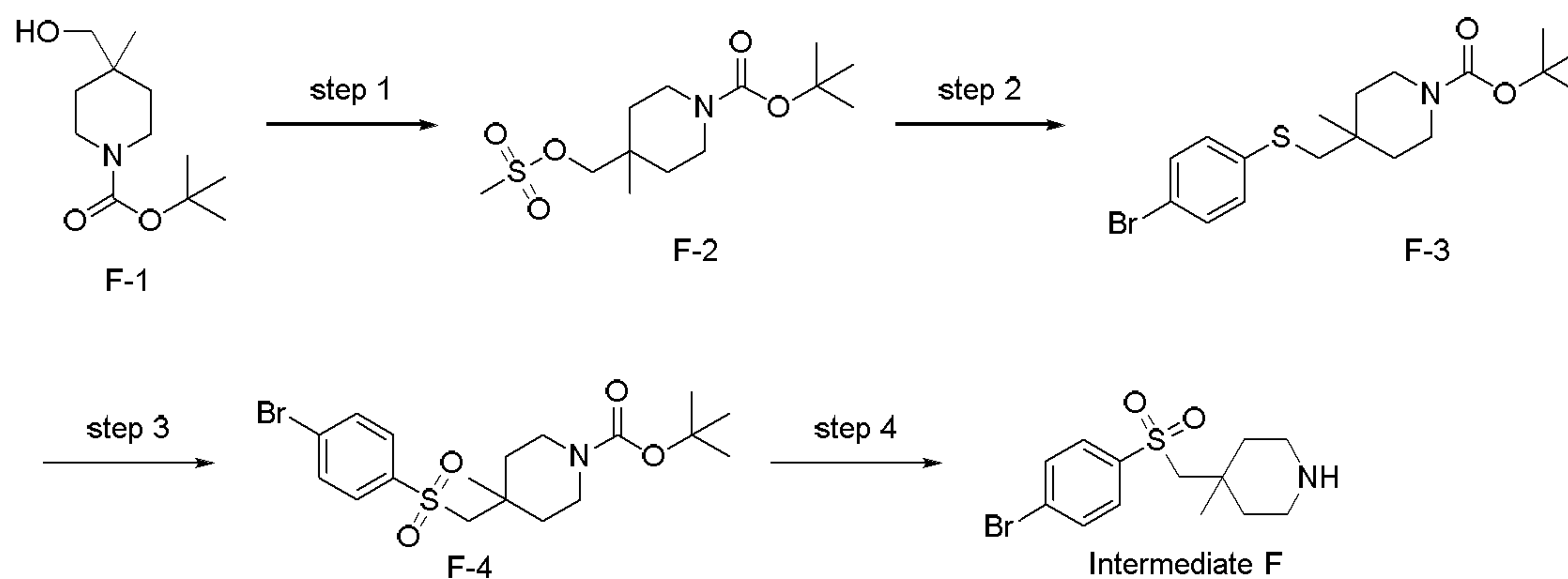
Step 2: E-2

[00262] To a mixture of **E-1** (450 mg, 1.16 mmol) in DCM (30 mL) was added 3-chlorobenzenecarboperoxoic acid (709.42 mg, 3.49 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na_2SO_3 (10 mL), saturated aqueous NaHCO_3 (20 mL $\times$ 2) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator to obtain **E-2** (450 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 418$ (M+1).

Step3: Intermediate E

[00263] To a solution of **E-2** (450 mg, 1.08 mmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **Intermediate E** (380 mg, crude, HCl salt). The crude product was used for the next step without further purification. MS: $m/z = 318$ (M+1).

Example 6: Synthesis of Intermediate F



Step 1: F-2

[00264] To a mixture of **F-1** (2.0 g, 8.72 mmol), Et₃N (2.65 g, 26.16 mmol) in DCM (30 mL) was added methanesulfonyl chloride (1.10 g, 9.59 mmol, 742.55 μ L) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the mixture was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate /petroleum ether 0 to 50%) to obtain **F-2** (2.5 g, 8.13 mmol, 93.25% yield). MS: m/z = 308 (M+1).

Step 2: F-3

[00265] To a solution of 4-bromobenzenethiol (500 mg, 2.64 mmol) in DMF (15 mL) was added NaH (116.35 mg, 2.91 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **F-2** (975.51 mg, 3.17 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate /petroleum ether 0 to 10%) to obtain **F-3** (150 mg, 374.65 μ mol, 14.17% yield). MS: m/z = 400 (M+1).

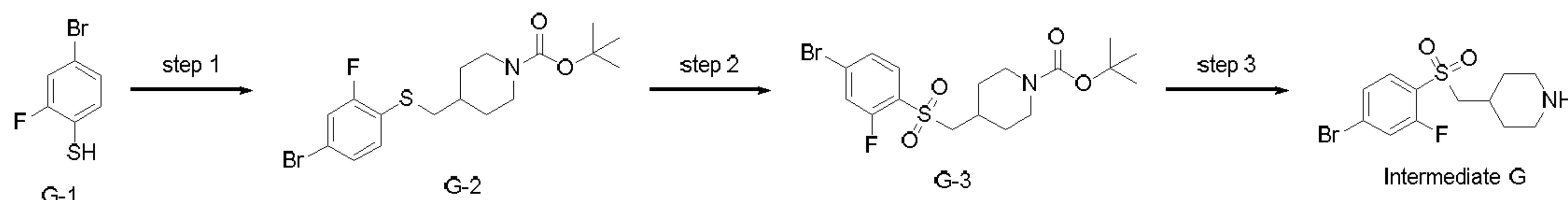
Step 3: F-4

[00266] To a mixture of **F-3** (150 mg, 374.65 μ mol) in DCM (20 mL) was added 3-chlorobenzenecarboxoperoxoic acid (228.19 mg, 1.12 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL $\times$ 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **F-4** (170 mg, crude). The crude product was used for the next step without further purification. MS: m/z = 432 (M+1).

Step 4: Intermediate F

[00267] To a solution of **F-4** (170 mg, 393.18 μ mol) in DCM (15 mL) was added HCl/Dioxane (4 M, 2 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **Intermediate F** (160 mg, crude, HCl salt). The crude product was used for the next step without further purification. MS: m/z = 332 (M+1).

Example 7: Synthesis of Intermediate G



Step 1: **G-2**

[00268] To a mixture of **G-1** (1 g, 4.83 mmol), NaH (386.32 mg, 9.66 mmol, 60% purity) in DMF (20 mL) was added tert-butyl 4-methyl-4-(methylsulfonyloxymethyl)piperidine-1-carboxylate (1.61 g, 5.80 mmol) at 0 °C. The reaction solution was stirred for 12 hr at 50 °C. To the mixture, saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (100 mL) was added. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (50 mL $\times$ 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate /petroleum ether 10% to 80%) to give **G-2** (1.3 g, 3.22 mmol, 66.57% yield). MS: m/z = 404.3 (M+1).

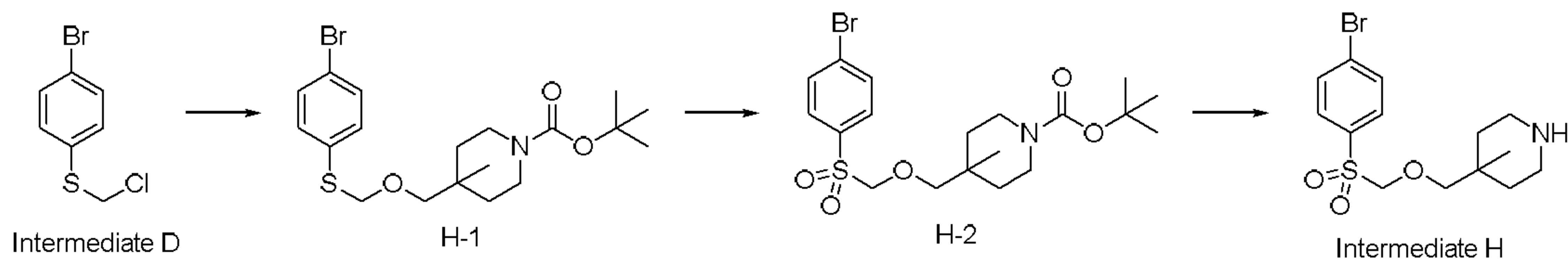
Step 2: **G-3**

[00269] A mixture of **G-2** (600 mg, 1.48 mmol) and m-CPBA (903.78 mg, 4.45 mmol, 85% purity) in DCM (20 mL) was stirred at 25 °C for 1 hr. Na_2SO_3 (14 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethylacetate = 30/1-3/1, v/v) to obtain **G-3** (500 mg, 1.15 mmol, 77.22% yield). MS: m/z = 436.3 (M+1).

Step 3: **Intermediate G**

[00270] A mixture of **G-3** (500 mg, 1.15 mmol) in HCl/Dioxane (4 M, 4.0 mL) at 20 °C and the reaction mixture was stirred at 30 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **Intermediate G** (600 mg, crude, HCl salt), which was used for the next step without further purification. MS: m/z = 372.6 (M+1).

Example 8: Synthesis of Intermediate H



Step 1: H-1

[00271] To a mixture of **F-1** (1.74 g, 7.58 mmol) in DMF (15 mL) was added NaH (328.33 mg, 8.21 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (1.5 g, 6.31 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **H-1** (420 mg, 975.84 μmol, 15.45% yield). MS: $m/z = 430$ (M+1).

Step 2: H-2

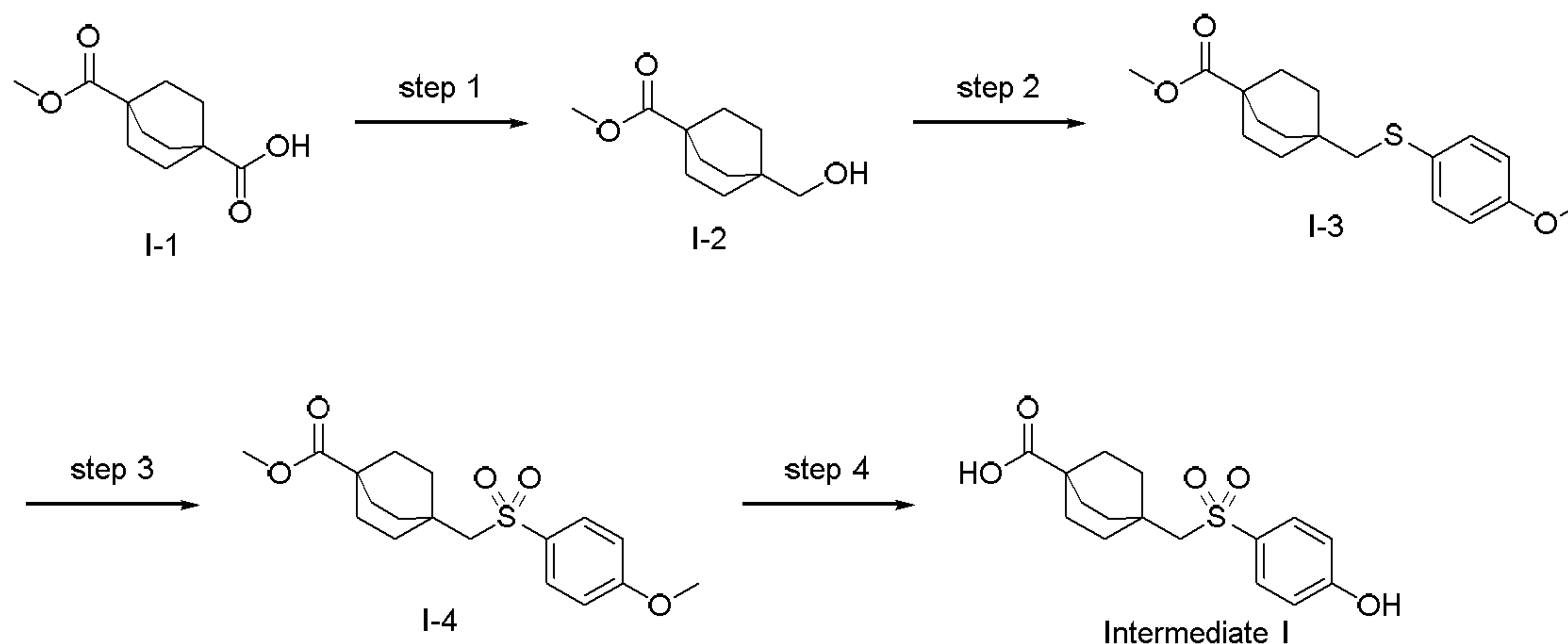
[00272] To a mixture of **H-2** (420 mg, 975.84 μmol) in DCM (30 mL) was added m-CPBA (594.34 mg, 2.93 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **H-3** (510 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 462$ (M+1).

Step 3: Intermediate H

[00273] To a mixture of **H-3** (510 mg, 1.10 mmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 4 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **Intermediate H** (450 mg, crude, HCl salt).

The crude product was used for the next step without further purification. MS: $m/z = 362$ (M+1).

Example 9: Synthesis of Intermediate I



Step 1: I-2

[00274] To a mixture of **I-1** (5 g, 23.56 mmol) in anhydrous tetrahydrofuran (100 mL) at 0 °C was added a tetrahydrofuran solution of Borane-tetrahydrofuran complex (1 M, 47.12 mL) under nitrogen. The reaction mixture was stirred at 25 °C for 3 hr, then concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, aqueous HCl solution, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give **I-2** (4.5 g, crude). The crude product was used directly for the next step. LC/MS: $m/z = 199.2$ (M+1).

Step 2: I-3

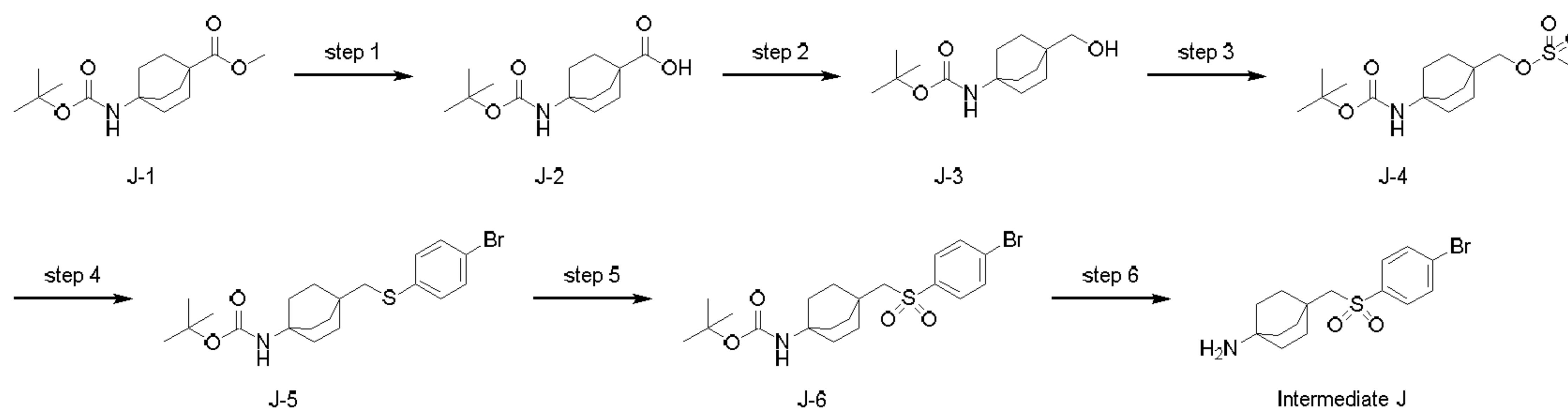
[00275] To a mixture of **I-2** (1.78 g, 8.98 mmol) and 1-methoxy-4-[(4-methoxyphenyl)disulfanyl]benzene (3.00 g, 10.77 mmol) in acetonitrile (20 mL) was added tributylphosphine (2.54 g, 12.57 mmol, 3.1 mL) at 25 °C under the nitrogen atmosphere. The reaction mixture was stirred for 16 hr at 80 °C. The mixture was concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether = 0~10%, v/v) to afford **I-3** (2.1 g, 6.55 mmol, 72.99% yield). LC/MS: $m/z = 321.1$ (M+1).

Step 3: I-4

[00276] To a mixture of **I-3** (2.1 g, 6.55 mmol) in DCM (10 mL) was added m-CPBA (3.39 g, 19.66 mmol) at 20 °C. The mixture was stirred for 2 hr at 25 °C. Then, the solution was washed with saturated aqueous sodium sulfite (10 mL), saturated aqueous sodium bicarbonate (20 mL × 2) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to give the crude product. The crude product was recrystallized by dichloromethane/petroleum ether to obtain **I-4** (1.94 g, 5.50 mmol, 83.86% yield). LC/MS: $m/z = 353.1$ (M+1).

Step 4: Intermediate I

[00277] A mixture of **I-4** (1.9 g, 5.39 mmol) and boron tribromide (1 M in DCM, 20 mL) was stirred at 20 °C. The mixture was poured into ice and warmed to 25 °C. The mixture was filtered. The cake was washed by petroleum ether, dried under the vacuum to afford **Intermediate I** (1.74 g, 5.36 mmol, 99.50% yield). LC/MS: $m/z = 325.0$ (M+1).

Example 10: Synthesis of Intermediate J**Step 1: J-2**

[00278] To a mixture of **J-1** (5.9 g, 20.82 mmol) in tetrahydrofuran (30 mL) and water (30 mL) was added Lithium hydroxide monohydrate, 98% (4.37 g, 104.11 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the reaction mixture was adjusted to pH ~ 6 by citric acid, extracted with ethyl acetate (50 mL × 3). The combined organic layers washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to obtain **J-2** (5.6 g, crude).

Step 2: J-3

[00279] To a mixture of **J-2** (5.6 g, 20.79 mmol) in anhydrous tetrahydrofuran (50 mL) was dropwise added Borane-tetrahydrofuran complex (1 M in tetrahydrofuran, 62.38 mL) at 0 °C under the nitrogen atmosphere. The reaction mixture was stirred for 2 hr at 25 °C. To the reaction mixture was dropwise added MeOH (20 mL) at 0~25 °C. The reaction mixture was stirred at room temperature (~25 °C) for 0.5 hr. The reaction mixture was concentrated with a rotary evaporator to obtain crude **J-3** (5.5 g, crude). The product was used in the next step directly without further purification.

Step 3: J-4

[00280] To a mixture of **J-3** (5.5 g, 21.54 mmol), triethylamine (6.54 g, 64.62 mmol, 9.01 mL) in DCM (100 mL) was added Methanesulfonic anhydride (5.63 g, 32.31 mmol, 3.56 mL) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a

rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether = 0~40%, v/v) to obtain **J-4** (6.2 g, 18.59 mmol, 86.33% yield).

Step 4: J-5

[00281] To a mixture of 4-bromobenzenethiol (8.79 g, 46.48 mmol), cesium carbonate (18.17 g, 55.78 mmol) and potassium iodide (1.54 g, 9.30 mmol) in DMF (50 mL) was added **J-4** (6.2 g, 18.59 mmol) under the nitrogen atmosphere. The reaction mixture was heated at 55 °C for 2 hr. Ethyl acetate (100 mL) and water (50 mL) were added, the organic layer was washed with brine (50 mL × 4), dried over anhydrous sodium sulfate, filtered and concentrated, which was purified by column chromatography on silica gel (120 g, ethyl acetate in petroleum ether = 0~15%, v/v) to give **J-5** (6.9 g, 16.18 mmol, 87.03% yield).

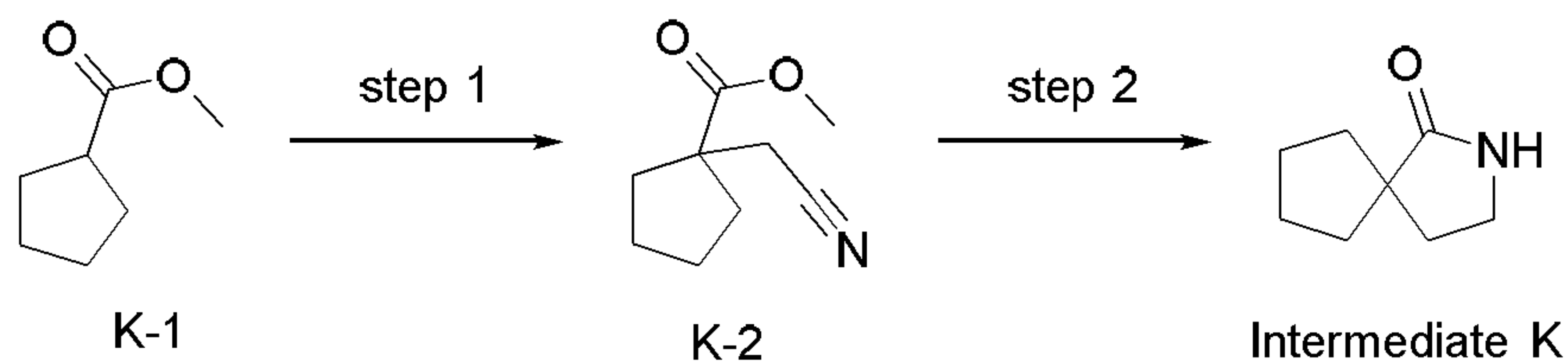
Step 5: J-6

[00282] A mixture of **J-5** (6.9 g, 16.18 mmol) and m-CPBA (9.85 g, 48.54 mmol, 85% purity) in DCM (100 mL) was stirred at 20 °C for 2 hr. Then, sodium sulfite (5 g) was added to the mixture and stirred for 20 min. Then, to the solution was added DCM (100 mL) and water (100 mL). The organic layer was washed with aqueous NaHCO₃ (50 mL × 3), brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered, concentrated to give a crude, which was purified by column chromatography on silica gel (80 g, ethyl acetate in petroleum ether = 0~20%, v/v) to give **J-6** (7 g, 15.27 mmol, 94.38% yield).

Step 6: Intermediate J

[00283] To a mixture of **J-6** (4 g, 8.73 mmol) in DCM (20 mL) was added HCl/Dioxane (15 mL, 4 M) at 20 °C and stirred at 20 °C for 1 hr. The reaction mixture was then concentrated to give **Intermediate J** (3.5 g, crude, HCl salt).

Example 11: Synthesis of Intermediate K



Step 1: K-2

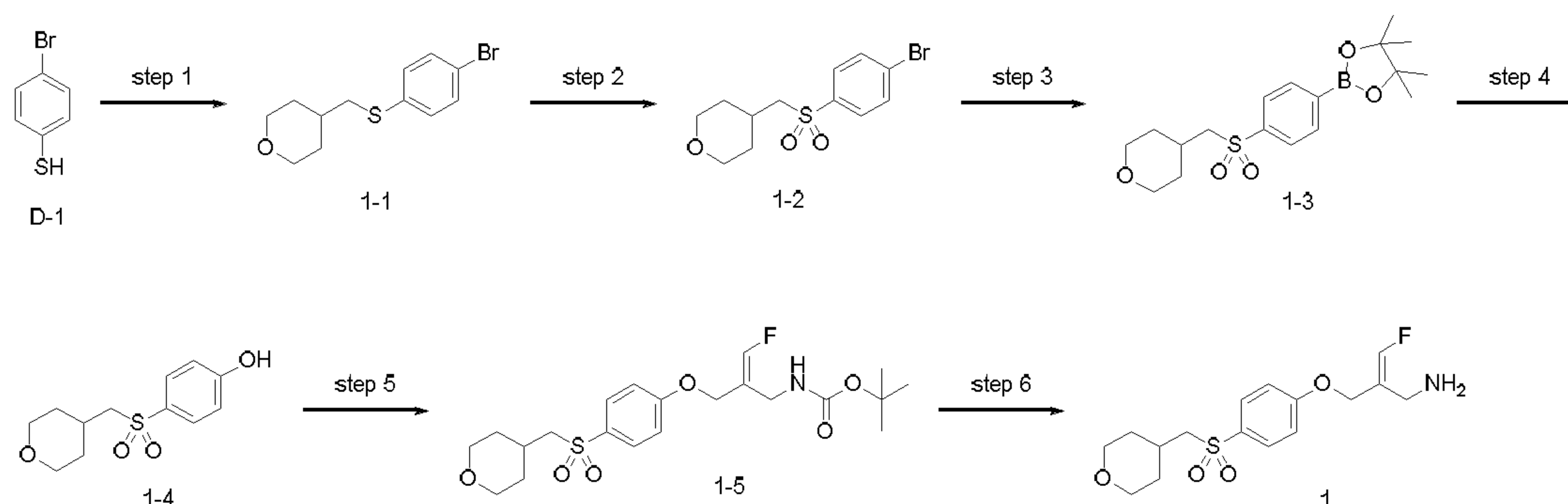
[00284] To a mixture of **K-1** (10 g, 78.02 mmol) in tetrahydrofuran (100 mL) was added lithium diisopropylamide (2 M in THF, 78.02 mL) dropwise at -30 °C under argon. After stirred at -30 °C for 1 hr, 2-chloroacetonitrile (7.07 g, 93.63 mmol) was added into the mixture above at

-30 °C. The resulting mixture was stirred at -30 °C for 30 min, then warmed up to 25 °C and stirred for another 3 hr. After quenched with aqueous ammonia chloride (150 mL), the resulting mixture was poured into water (250 mL) and extracted with ethyl acetate (200 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column (petroleum ether: ethyl acetate = 4: 1) to give **K-2** (4.5 g, 34.49% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 3.82 – 3.74 (m, 3H), 2.67 – 2.62 (m, 2H), 1.90 – 1.59 (m, 8H).

Step 2: Intermediate K

[00285] To a mixture of **K-2** (4.5 g, 26.91 mmol) in EtOH (50 mL) was added $\text{NH}_3 \cdot \text{H}_2\text{O}$ (5 mL) and Raney Nickel (1.5 g). The reaction mixture was stirred at 25 °C for 48 hr under the hydrogen atmosphere. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column (petroleum ether: ethyl acetate = 2: 1) to give **Intermediate K** (1.20 g, 32.03% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 5.96 (s, 1H), 3.23 (t, J = 6.7 Hz, 2H), 1.99 – 1.81 (m, 4H), 1.79 – 1.68 (m, 2H), 1.64 – 1.55 (m, 2H), 1.48 (dd, J = 11.1, 5.6 Hz, 2H).

Example 12: Synthesis of Compound 1



Step 1: 1-1

[00286] To a mixture of **D-1** (959.96 mg, 5.08 mmol) in DMF (10 mL) was added NaH (243.68 mg, 6.09 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, 4-(bromomethyl)tetrahydropyran (1.0 g, 5.58 mmol) was added. The reaction solution was stirred for further 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **1-1** (1.3 g, 4.53 mmol, 89.15% yield).

Step 2: 1-2

[00287] To a mixture of **1-1** (400 mg, 1.39 mmol) in DCM (30 mL) was added m-CPBA (848.24 mg, 4.18 mmol, 85% purity) at 20 °C. The mixture was stirred for 2 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 ml × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **1-2** (400 mg, crude). The crude product was used for the next step without further purification.

Step 3: 1-3

[00288] To a mixture of **1-2** (300 mg, 939.81 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (286.38 mg, 1.13 mmol) and KOAc (276.70 mg, 2.82 mmol) in Dioxane (6 mL) was added Pd(dppf)Cl₂ (68.77 mg, 93.98 μmol) at 20 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered, and the filtrate was concentrated. The residual material was dissolved in DCM (15 mL), washed with H₂O (15 mL) and brine (15 mL) and concentrated with a rotary evaporator to obtain **1-3** (410 mg, crude). The crude product was used for the next step without further purification.

Step 4: 1-4

[00289] To a mixture of **1-3** (410 mg, 1.12 mmol), acetic acid (525.00 mg, 8.74 mmol, 0.5 mL) in THF (15 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **1-4** (300 mg, crude). The crude product was used for the next step without further purification. MS: m/z = 255 (M-1).

Step 5: 1-5

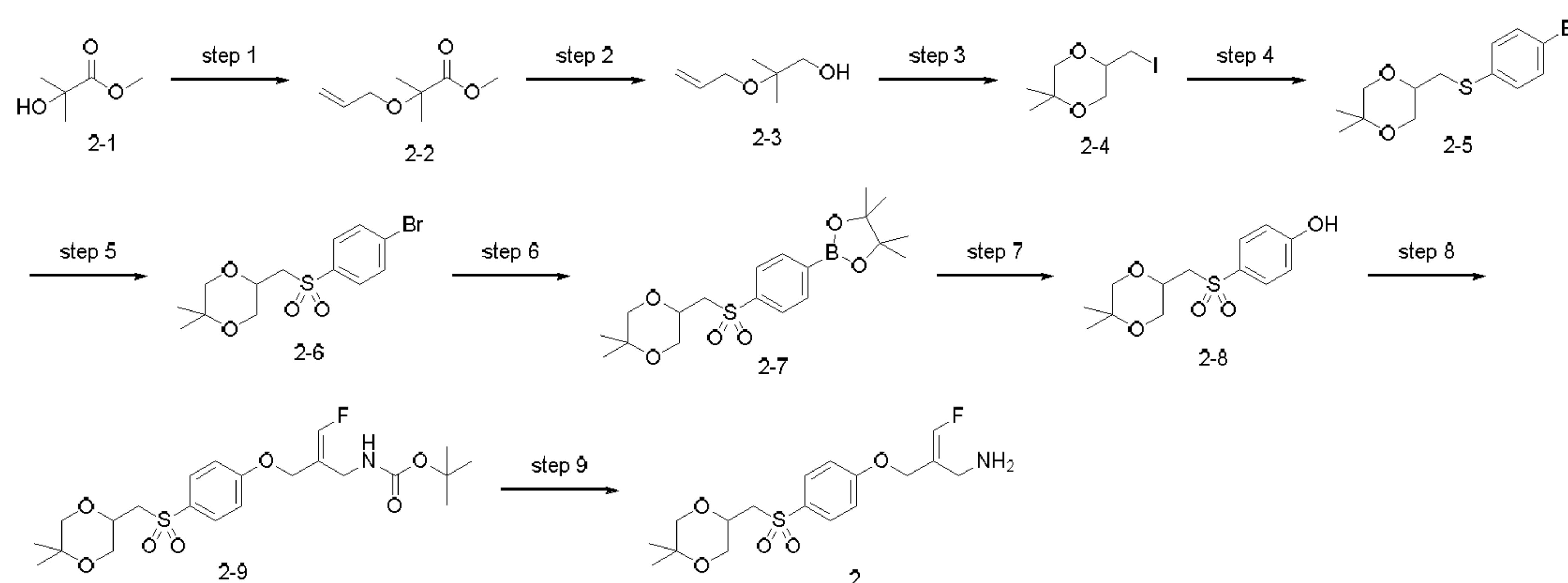
[00290] To a mixture of **1-4** (300 mg, 1.17 mmol), **Intermediate A** (100 mg, 372.96 μmol) in MeCN (20 mL) was added Cs₂CO₃ (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **1-5** (210 mg, crude). The crude product was used for the next step without further purification. MS: m/z = 444 (M+1).

Step 6: Compound 1

[00291] To a mixture of **1-5** (210 mg, 473.48 μmol) in DCM (10 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-

HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to give **Compound 1** (110 mg, 282.46 μ mol, 59.66% yield, HCO₂H salt). MS: m/z = 344 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.50 (s, 1H), 7.91 – 7.86 (m, 2H), 7.24 – 7.19 (m, 2H), 7.23 (d, J = 81.1 Hz, 1H), 4.71 (dd, J = 3.6, 1.1 Hz, 2H), 3.87-3.82 (m, 2H), 3.79 (d, J = 2.3 Hz, 2H), 3.37 (td, J = 11.8, 2.1 Hz, 2H), 3.15 (d, J = 6.3 Hz, 2H), 2.11-2.05 (m, 1H), 1.75-1.71 (m, 2H), 1.40-1.37 (m, 2H). MS: m/z = 344.00 (M+1, ESI+).

Example 13: Synthesis of Compound 2



Step 1: 2-2

[00292] To a mixture of **2-1** (2.0 g, 16.93 mmol) in DMF (30 mL) was added NaH (713.59 mg, 17.84 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, 3-bromoprop-1-ene (3.07 g, 25.40 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was quenched with H₂O (20 mL), and extracted by ethyl acetate (15 mL $\times$ 2). The combined organic layers were washed with H₂O (15 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 40%) to give **2-2** (2.3 g, 14.54 mmol, 85.88% yield). MS: m/z = 159 (M+1).

Step 2: 2-3

[00293] To a mixture of **2-2** (2.3 g, 14.54 mmol) in THF (60 mL) was added LiAlH₄ (201.65 mg, 5.31 mmol) at 0 °C slowly over 0.5 hr. The reaction solution was stirred for 18 hr at 20 °C. Then, the solution was cooled to 0 °C and quenched successively with H₂O (1.1 mL), NaOH (1.1 mL, 15% aqueous solution) and H₂O (3.3 mL). The mixture was stirred for 0.5 hr and then was

filtered and concentrated with a rotary evaporator to obtain **2-3** (1.9 g, crude). The crude product was used for the next step without further purification. MS: $m/z = 131$ (M+1).

Step 3: 2-4

[00294] To a mixture of **2-3** (1.9 g, 14.59 mmol) in MeCN (50 mL) was added NaHCO₃ (3.68 g, 43.78 mmol) and the mixture was cooled to 0 °C. Molecular iodine (11.11 g, 43.78 mmol) was added and the reaction mixture was allowed to warm up to 25 °C and stirred for 6 hr. The reaction mixture was diluted with saturated aqueous sodium thiosulfate solution and concentrated under reduced pressure removing most of the organic solvent. The residue was extracted with ethyl acetate (30 mL x 2) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate in petroleum ether, 0 to 20%) to give **2-4** (2.3 g, 8.98 mmol, 61.54% yield). MS: $m/z = 257$ (M+1).

Step 4: 2-5

[00295] To a mixture of 4-bromobenzenethiol (1.0 g, 5.29 mmol) in DMF (30 mL) was added NaH (250.0 mg, 6.25 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **2-4** (1.23 g, 4.81 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 30%) to obtain **2-5** (1.1 g, 3.47 mmol, 72.11% yield). MS: $m/z = 317$ (M+1).

Step 5: 2-6

[00296] To a mixture of **2-5** (1.1 g, 3.47 mmol) in DCM (50 mL) was added m-CPBA (2.11 g, 10.40 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL x 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to give **2-6** (440 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 349$ (M+1).

Step 6: 2-7

[00297] To a mixture of **2-6** (440 mg, 1.26 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (383.92 mg, 1.51 mmol) and KOAc (363.32 mg, 3.78 mmol) in Dioxane (15 mL) was added Pd(dppf)Cl₂ (46.09 mg, 62.99 μmol) at 20 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered

and evaporated to give **2-7** (550 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 397$ (M+1).

Step 7: 2-8

[00298] To a mixture of **2-7** (550 mg, 1.39 mmol), acetic acid (1.05 g, 17.49 mmol, 1 mL) in THF (20 mL) was added hydrogen peroxide (1 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was quenched by Na₂SO₃, filtered and concentrated with a rotary evaporator to obtain **2-8** (450 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 287$ (M+1).

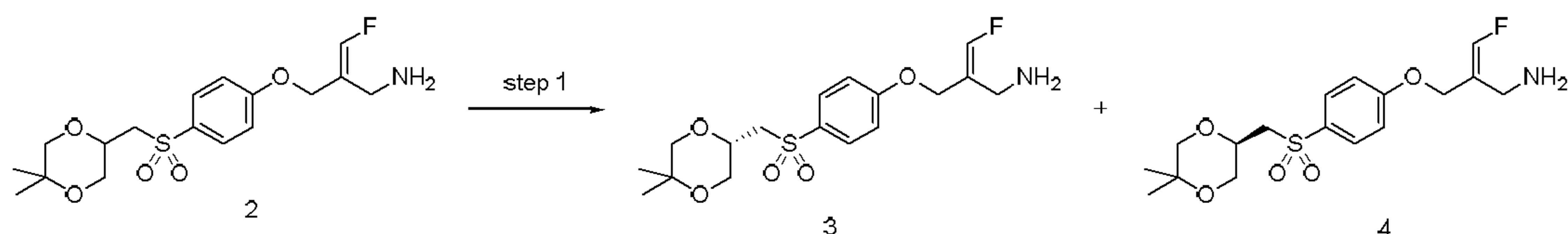
Step 8: 2-9

10 [00299] To a mixture of **2-8** (450 mg, 1.57 mmol), **Intermediate A** (421.37 mg, 1.57 mmol) in MeCN (50 mL) was added Cs₂CO₃ (1.54 g, 4.71 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate /petroleum ether 0 to 100%) to obtain **2-9** (330 mg, 696.86 μmol, 44.34% yield). MS: $m/z = 474$ (M+1).

Step 9: Compound 2

[00300] To a mixture of **2-9** (330 mg, 696.86 μmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 3 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 2** (210 mg, 500.64 μmol, 71.84% yield, HCO₂H salt). MS: $m/z = 374$ (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.94-7.84 (m, 2H), 7.27-7.17 (m, 2H), 7.26 (d, *J* = 81.0 Hz, 1H), 4.73 (dd, *J* = 3.6, 1.0 Hz, 2H), 3.89-3.84 (m, 1H), 3.84 (d, *J* = 2.2 Hz, 2H), 3.65-3.48 (m, 2H), 3.44-3.36 (m, 2H), 3.30-3.21 (m, 2H), 1.24 (s, 3H), 1.07 (s, 3H).

Example 14: Synthesis of Compound 3 & 4



Step 1: Compound 3 & 4

[00301] **Compound 2** (210 mg, 500.64 μ mol) was separated by SFC to obtain **Compound 3**

& 4 (enantiomer 1, R_t = 6.220 min, 67.4 mg, 180.48 μ mol, 52.05% yield, Column: Chiralpak

IG 250 mm*4.6 mm 5 μ m, Mobile phase: MeCN: IPA: AMMN = 80:20:0.2, F: 1 mL/min, T =

30 °C) and (enantiomer 2, R_t = 8.083 min, 53.2 mg, 142.46 μ mol, 41.08% yield, Column:

5 Chiralpak IG 250 mm*4.6 mm 5 μ m, Mobile phase: MeCN: IPA: AMMN = 80:20:0.2, F: 1

mL/min, T = 30 °C). Enantiomer 1: ^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.81 (m, 2H),

7.23-7.15 (m, 2H), 6.96 (dt, J = 83.2, 1.0 Hz, 1H), 4.68 (dd, J = 3.6, 1.1 Hz, 2H), 3.86-3.83 (m,

1H), 3.63-3.51 (m, 2H), 3.49 (dd, J = 2.4, 0.8 Hz, 2H), 3.44-3.36 (m, 2H), 3.31-3.23 (m, 2H),

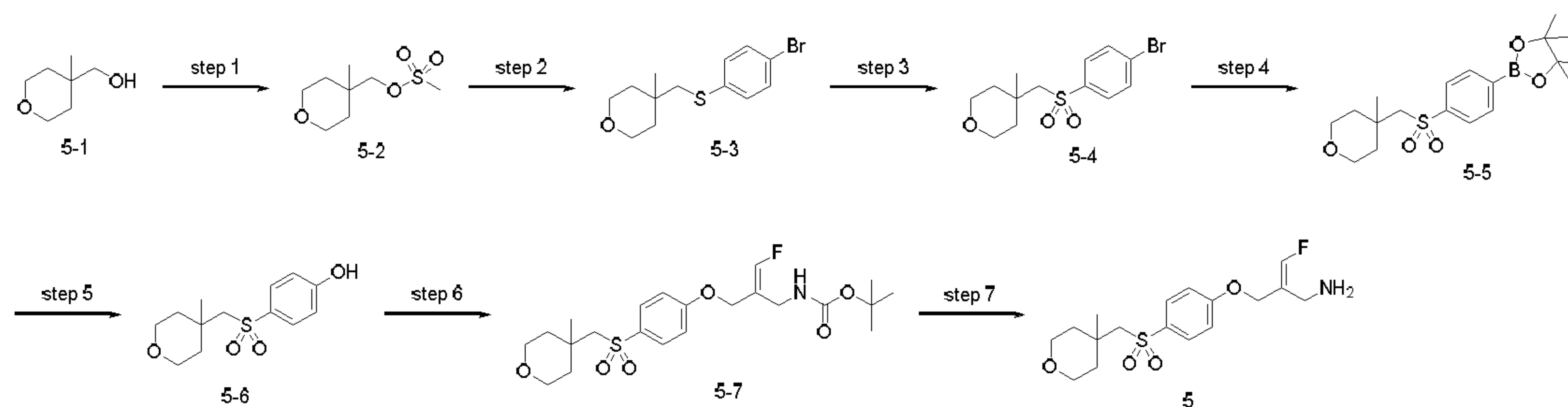
1.24 (s, 3H), 1.07 (s, 3H). Enantiomer 2: ^1H NMR (400 MHz, Methanol- d_4) δ 7.89-7.85 (m, 2H),

10 7.19 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 83.2 Hz, 1H), 4.68 (dd, J = 3.6, 1.1 Hz, 2H), 3.86-3.83 (m,

1H), 3.63-3.51 (m, 2H), 3.52-3.48 (m, 2H), 3.46-3.35 (m, 2H), 3.29-3.24 (m, 2H), 1.24 (s, 3H),

1.07 (s, 3H).

Example 15: Synthesis of Compound 5



15 Step 1: 5-2

[00302] To a mixture of methanesulfonic anhydride (200 mg, 1.15 mmol) and TEA (582.96 mg, 5.76 mmol, 802.98 μ L) in DCM (10 mL) was added **5-1** (250 mg, 1.92 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 0 °C. H₂O (5 mL) was added, the organic phase was separated, dried over Na₂SO₄ and concentrated to give **5-2** (300 mg, 1.44 mmol, 75.01% yield).

20 MS: m/z = 208.2 (M+1).

Step 2: 5-3

[00303] A mixture of **5-2** (300 mg, 1.44 mmol) and 4-bromobenzenethiol (326.81 mg, 1.73 mmol) in DMF (10 mL) was added Cs₂CO₃ (1.41 g, 4.32 mmol) at 20 °C. The reaction solution was stirred for 8 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator. The

25 crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4/1, v/v)

to obtain **5-3** (200 mg, 663.92 μ mol, 46.09% yield). MS: m/z = 301.2 (M+1).

Step 3: 5-4

[00304] A mixture of **5-3** (180 mg, 597.53 μmol) and m-CPBA (330.19 mg, 1.79 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. Na_2SO_3 (4 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1-1/1, v/v) to obtain **5-4** (180 mg, 540.15 μmol , 90.40% yield). MS: $m/z = 333.2$ (M+1).

Step 4: 5-5

[00305] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (194.32 mg, 765.21 μmol), **5-4** (170 mg, 510.14 μmol) and cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (37.33 mg, 51.01 μmol) in Dioxane (8 mL) was added KOAc (154.83 mg, 1.53 mmol) at 30 °C under the nitrogen atmosphere. The reaction solution was stirred for 2 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1-1/1, v/v) to obtain **5-5** (150 mg, 394.42 μmol , 77.32% yield). MS: $m/z = 380.3$ (M+1).

Step 5: 5-6

[00306] A mixture of **5-5** (120 mg, 315.54 μmol) in THF (4 mL) and acetic acid (1 mL) was added H_2O_2 (315.54 μmol , 1 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Na_2SO_3 (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **5-6** (0.7 g, crude), which was used in the next step without purification. MS: $m/z = 270.3$ (M+1).

Step 6: 5-7

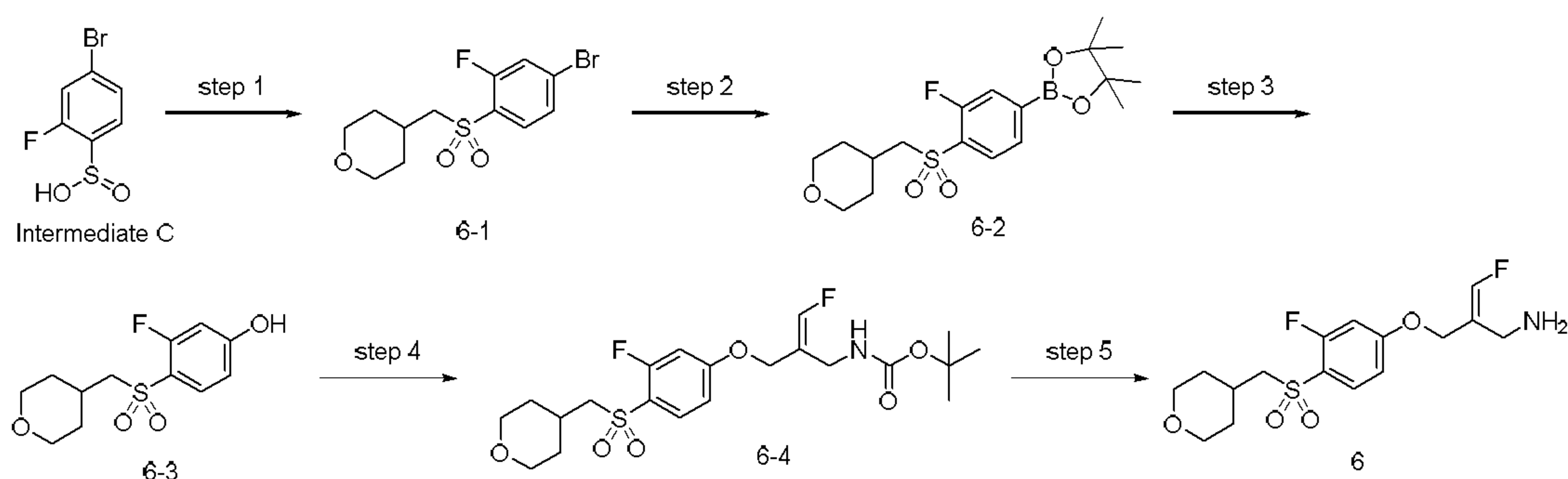
[00307] A mixture of **5-6** (0.7 g) and **Intermediate A** (138.85 mg, 517.86 μmol) in MeCN (20 mL) was added Cs_2CO_3 (2.53 g, 7.77 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **5-7** (120 mg, crude), which was used in the next step without purification. MS: $m/z = 457.5$ (M+1).

Step 7: Compound 5

[00308] A mixture of **5-7** (120 mg, 262.26 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 2-30% B; GT: 15 min; flow rate: 15 mL/min) to give **Compound 5** (22 mg, 61.55 μmol , 23.47% yield).

^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.99 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 80.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 4.77-4.67 (m, 2H), 3.80 (d, $J = 2.4$ Hz, 2H), 3.65 (dd, $J = 6.0, 4.6$ Hz, 4H), 3.26 (s, 2H), 1.79-1.75 (m, 2H), 1.59-1.45 (m, 2H), 1.32 (s, 3H). ppm; MS: $m/z = 358.7$ (M+1, ESI+).

5 Example 16: Synthesis of Compound 6



Step 1: 6-1

[00309] To a mixture of **Intermediate C** (1.0 g, 3.82 mmol) and 4-(bromomethyl)tetrahydropyran (751.61 mg, 4.20 mmol) in DMF (20 mL) was added Na_2CO_3 (1.21 g, 11.46 mmol). The reaction mixture was heated to 80 °C for 18 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether in ethyl acetate, 0 to 40%) to obtain **6-1** (970 mg, 2.88 mmol, 75.38% yield).

Step 2: 6-2

[00310] To a mixture of **6-1** (500 mg, 1.48 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (451.84 mg, 1.78 mmol) and KOAc (436.57 mg, 4.45 mmol) in Dioxane (12 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (108.50 mg, 148.28 μmol) at 20 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered, and concentrated. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 40%) to obtain **6-2** (350 mg, 910.82 μmol , 61.43% yield).

Step 3: 6-3

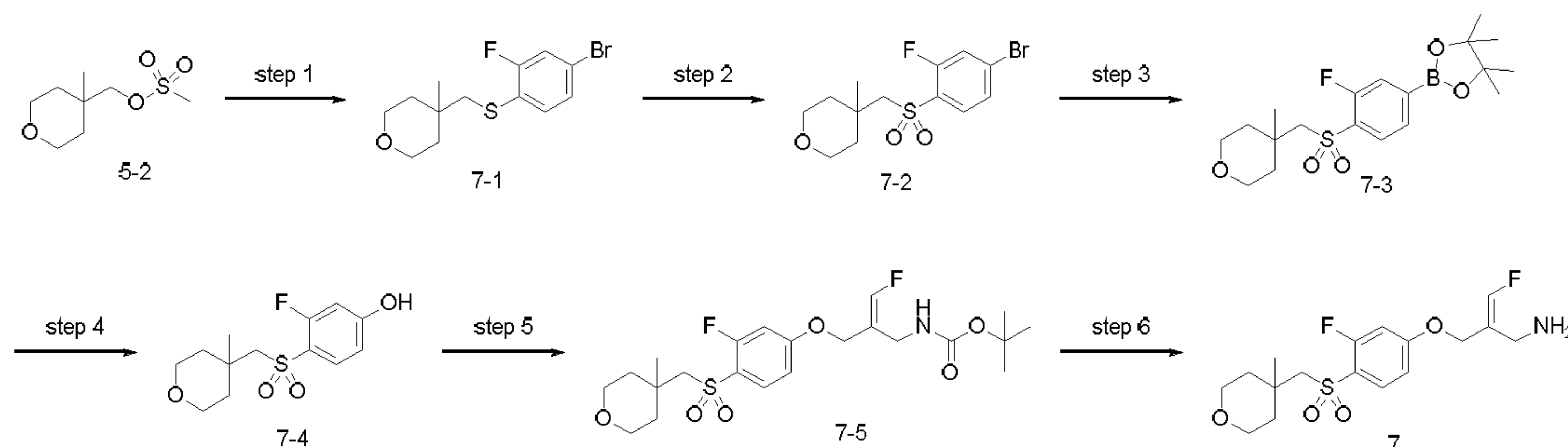
[00311] To a mixture of **6-2** (150 mg, 390.35 μmol), acetic acid (105.00 mg, 1.75 mmol, 0.1 mL) in THF (8 mL) was added hydrogen peroxide (0.2 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **6-3** (120 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 273$ (M-1).

Step 4: 6-4

[00312] To a mixture of **6-3** (120 mg, 437.46 μmol), **Intermediate A** (60 mg, 223.78 μmol) in MeCN (20 mL) was added Cs_2CO_3 (218.73 mg, 671.33 μmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **6-4** (110 mg, crude). The crude product was used for the next step without further purification. MS: $m/z = 462$ (M+1).

Step 5: Compound 6

[00313] To a mixture of **6-4** (110 mg, 238.34 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 2 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 6** (6.0 mg, 14.73 μmol , 6.18% yield, HCO_2H salt). MS: $m/z = 362$ (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.49 (s, 1H), 7.85 (t, $J = 8.7$ Hz, 1H), 7.23 (d, $J = 80.9$ Hz, 1H), 7.07-7.04 (m, 1H), 7.02 (d, $J = 2.6$ Hz, 1H), 4.71 (dd, $J = 3.5, 1.0$ Hz, 2H), 3.93-3.83 (m, 2H), 3.79 (d, $J = 2.3$ Hz, 2H), 3.37-3.32 (m, 3H), 3.28 (d, $J = 6.4$ Hz, 3H), 2.16 (dt, $J = 11.4, 6.5$ Hz, 1H), 1.79-1.70 (m, 2H), 1.50-1.36 (m, 2H). MS: $m/z = 362.1$ (M+1, ESI+).

Example 17: Synthesis of Compound 7*Step 1: 7-1*

[00314] To a mixture of 4-bromo-2-fluoro-benzenethiol (547.57 mg, 2.64 mmol) and NaH (202.66 mg, 5.29 mmol, 60% purity) in DMF (20 mL) was added **5-2** (550.78 mg, 2.64 mmol) at 0 °C. The reaction solution was stirred for 8 hr at 50 °C. To the mixture was added saturated aqueous ammonium chloride solution (100 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (80 mL $\times$ 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under

reduced pressure and the crude was purified by flash column chromatography (ethyl acetate in petroleum ether, 10% to 80%) to give **7-1** (189 mg, 592.05 μmol , 22.39% yield).

Step 2: 7-2

5 **[00315]** A mixture of **7-1** (150 mg, 469.88 μmol) and m-CPBA (286.18 mg, 1.41 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. Na_2SO_3 (0.3 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1-1/2, v/v) to obtain **7-2** (120 mg, 341.66 μmol , 72.71% yield). MS: $m/z = 351.2$ (M+1).

Step 3: 7-3

10 **[00316]** To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (108.45 mg, 427.07 μmol), **7-2** (100 mg, 284.71 μmol) and cyclopentyl(diphenyl)phosphane;dichloropalladium; iron (20.83 mg, 28.47 μmol) in Dioxane (20 mL) was added KOAc (83.83 mg, 854.14 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a
15 rotary evaporator and purified by column chromatography on silical gel (petroleum ether/ethyl acetate = 1/10 - 1/1) to obtain **7-3** (80 mg, 200.86 μmol , 70.55% yield). MS: $m/z = 398.3$ (M+1).

Step 4: 7-4

[00317] To a mixture of **7-3** (80 mg, 200.86 μmol) in THF (2 mL) and acetic acid (0.5 mL) was added H_2O_2 (0.5 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. Na_2SO_3 (0.2 g)
20 was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **7-4** (300 mg, crude), which was used in the next step without purification. MS: $m/z = 288.3$ (M+1).

Step 5: 7-5

[00318] To a mixture of **Intermediate A** (83.69 mg, 312.14 μmol) and **7-4** (300 mg) in
25 MeCN (50 mL) was added Cs_2CO_3 (1.02 g, 3.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **7-5** (209 mg, crude). MS: $m/z = 475.5$ (M+1).

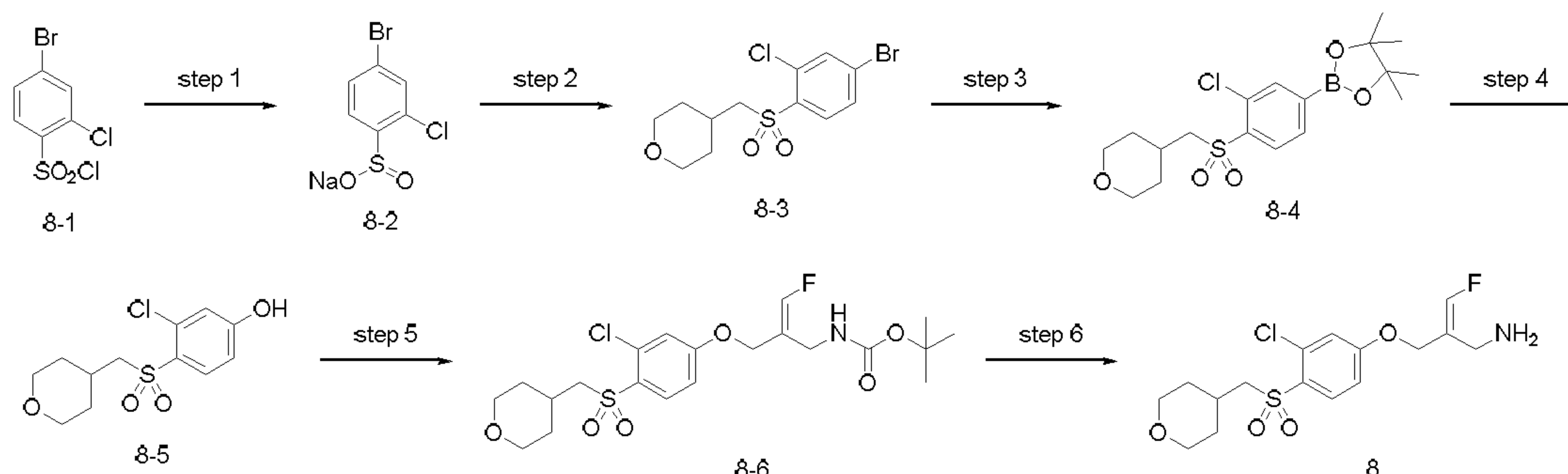
Step 6: Compound 7

[00319] A mixture of **7-5** (200 mg, 408.52 μmol) in HCl/Dioxane (4 M, 5.0 mL) was stirred at
30 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H

water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain

Compound 7 (20 mg, 51.35 μ mol, 12.57% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.84 (t, $J = 8.8$ Hz, 1H), 7.22 (d, $J = 80.0$ Hz, 1H), 7.04 (d, $J = 12.8$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.77 (s, 2H), 3.66 (t, $J = 5.4$ Hz, 4H), 3.39 (s, 2H), 1.87-1.73 (m, 2H), 1.54 (d, $J = 13.6$ Hz, 2H), 1.32 (s, 3H). ppm; MS: $m/z = 376.5$ (M+1, ESI+).

Example 18: Synthesis of Compound 8



Step 1: 8-2

[00320] A mixture of **8-1** (1 g, 3.45 mmol), Na_2SO_3 (812.87 mg, 6.45 mmol) and NaHCO_3 (533.08 mg, 6.35 mmol) in H_2O (20 mL) is heated at 100 $^\circ\text{C}$ for 1 hr. Then the mixture was concentrated to give **8-2** (2.5 g, crude). MS: $m/z = 277.5$ (M+1).

Step 2: 8-3

[00321] A mixture of **8-2** (1 g, 3.82 mmol) and 4-(bromomethyl)tetrahydropyran (684.72 mg, 3.82 mmol) in DMF (20 mL) was stirred at 20 $^\circ\text{C}$. The reaction solution was stirred for 8 hr at 100 $^\circ\text{C}$. Then ethyl acetate (100 mL) and H_2O (100 mL) were added, the organic was washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/1) to give **8-3** (300 mg, 848.27 μ mol, 22.18% yield). MS: $m/z = 353.6$ (M+1).

Step 3: 8-4

[00322] To a mixture of **8-3** (300.00 mg, 848.27 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (323.11 mg, 1.27 mmol) and cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (62.07 mg, 84.83 mmol) in Dioxane (10 mL) was added KOAc (254.88 mg, 2.54 mmol) at 30 $^\circ\text{C}$ under the nitrogen atmosphere. The reaction solution was stirred for 2 hr at 100 $^\circ\text{C}$. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethyl

acetate = 10/1-1:1, v/v) to obtain **8-4** (200 mg, 499.10 μmol , 58.84% yield). MS: m/z = 400.7(M+1).

Step 4: 8-5

[00323] To a mixture of **8-4** (150 mg, 344.69 μmol) in acetic acid (1 mL) and THF (4 mL) was added H_2O_2 (1 mL, 30% purity). The mixture was stirred at 20 $^\circ\text{C}$ for 1 hr. Na_2SO_3 (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **8-5** (700 mg, crude), which was used in the next step without purification. MS: $m/z = 290.7(\text{M}+1)$.

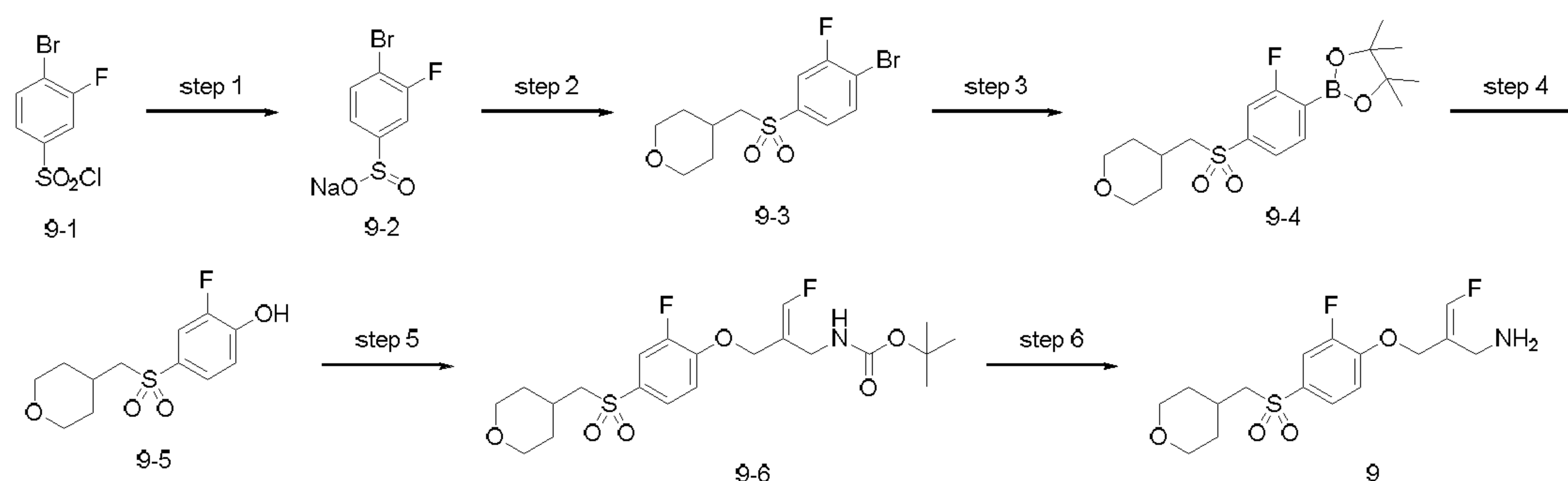
Step 5: 8-6

10 **[00324]** To a mixture of **8-5** (700 mg) and **Intermediate A** (193.65 mg, 722.24 μmol) in MeCN (30 mL) was added Cs_2CO_3 (705.96 mg, 2.17 mmol) at 20 $^\circ\text{C}$. The reaction solution was stirred for 1 hr at 80 $^\circ\text{C}$. Then, the solution was filtered and concentrated to obtain **8-6** (200 mg, crude), which was used in the next step without purification. MS: $m/z = 477.9$ (M+1).

Step 6: Compound 8

15 [00325] A mixture of **8-6** (100 mg, 195.15 μ mol) in HCl/Dioxane (4 M, 1.99 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 8** (21 mg, 50.93 μ mol, 26.10% yield). MS: m/z = 377.8 (M+1, ESI+). ¹H
20 NMR (400 MHz, Methanol-d₄) δ 8.05 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 80.0 Hz, 1H), 7.16 (d, J = 3.2 Hz, 1H), 4.72 (d, J = 3.6 Hz, 2H), 3.87 (d, J = 11.6 Hz, 2H), 3.82 (s, 2H), 3.40-3.35 (m, 4H), 2.14 (s, 1H), 1.74 (d, J = 13.2 Hz, 2H), 1.51-1.35 (m, 2H).ppm; MS: m/z = 378.7 (M+1, ESI+).

Example 19: Synthesis of Compound 9



Step 1: 9-2

[00326] A mixture of **9-1** (1 g, 3.66 mmol), Na₂SO₃ (861.77 mg, 6.84 mmol), and NaHCO₃ (565.15 mg, 6.73 mmol) in H₂O (30 mL) is heated at 100 °C for 1 hr. Then the mixture was concentrated to give **9-2** (4 g, crude). MS: m/z = 261(M+1).

Step 2: 9-3

5 [00327] A mixture of **9-2** (4 g, 15.32 mmol) and 4-(bromomethyl) tetrahydropyran (823.10 mg, 4.60 mmol) in DMF (50 mL) at 20 °C. The reaction solution was stirred for 8 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 - 3/1, v/v) to obtain **9-3** (400 mg, 1.19 mmol). MS: m/z = 337 (M+1).

10 *Step 3: 9-4*

[00328] A mixture of **9-3** (273.22 mg, 810.24 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (246.90 mg, 972.29 μmol) in Dioxane (10 mL) was added KOAc (206.75 mg, 2.43 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silical gel(ethyl acetate/petroleum ether = 1/10 - 1/1) to obtain **9-4** (200 mg, 520.47 μmol, 64.24% yield). MS: m/z = 384 (M+1).

Step 4: 9-5

[00329] To a mixture of **9-4** (200 mg, 520.47 μmol) in acetic acid (0.5 mL) and THF (2 mL) was added H₂O₂ (1 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. Na₂SO₃ (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **9-5** (0.8 g, crude), which was used in the next step without purification. MS: m/z = 274(M+1).

Step 5: 9-6

[00330] To a mixture of **9-5** (500 mg) and **Intermediate A** (146.62 mg, 546.83 μmol) in MeCN (80 mL) was added Cs₂CO₃ (1.78 g, 5.47 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **9-6** (200 mg, 433.35 μmol). MS: m/z = 461(M+1).

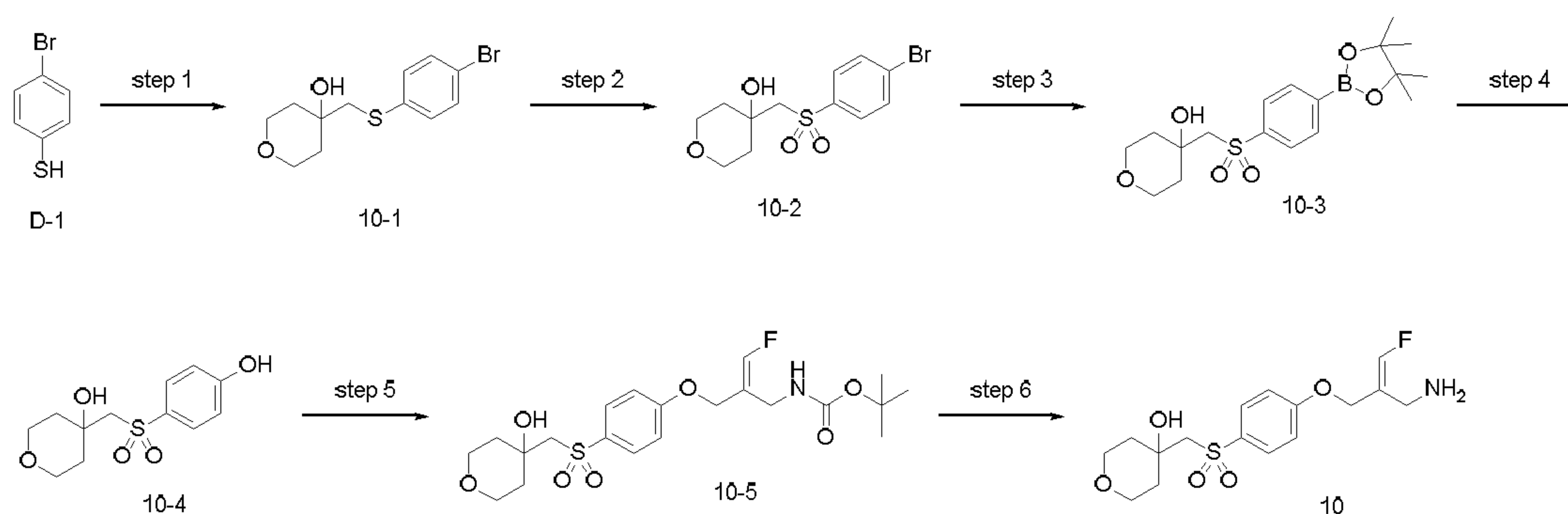
Step 6: Compound 9

[00331] A mixture of **9-6** (150 mg, 325.01 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H

water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain

Compound 9 (23 mg, 63.64 μ mol, 19.58% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 8.47 (s, 1H), 7.74 (t, $J = 8.4$ Hz, 2H), 7.40 (t, $J = 8.4$ Hz, 1H), 7.25 (d, $J = 80.0$ Hz, 1H), 4.79 (d, $J = 3.6$ Hz, 2H), 3.88 (d, $J = 11.2$ Hz, 2H), 3.84-3.75 (m, 2H), 3.38 (t, $J = 11.6$ Hz, 2H), 3.19 (d, $J = 6.4$ Hz, 2H), 2.13 (s, 1H), 1.76 (d, $J = 13.2$ Hz, 2H), 1.45-1.41 (m, 2H).ppm; MS: $m/z = 362.7$ (M+1, ESI+).

Example 20: Synthesis of Compound 10



Step 1: 10-1

- 10 [00332] A mixture of **D-1** (3 g, 15.87 mmol) and Cs_2CO_3 (7.75 g, 23.80 mmol) in MeCN (50 mL) was added 1,6-dioxaspiro[2.5]octane (1.81 g, 15.87 mmol) and the mixture was heated at 80 °C for 2 hr. After cooling to room temperature, the reaction mixture was filtered and concentrated to give a residue, which was purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/5, v/v) to give **10-1** (4 g, 13.19 mmol, 83.14% yield).
- 15 MS: $m/z = 303$ (M+1).

Step 2: 10-2

- [00333] To a mixture of **10-1** (500 mg, 1.65 mmol) and m-CPBA (1.00 g, 4.95 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. Na_2SO_3 (0.4 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 - 1/2, v/v) to obtain **10-2** (400 mg, 1.19 mmol, 72.36% yield). MS: $m/z = 335$ (M+1).
- 20

Step 3: 10-3

- [00334] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (454.52 mg, 1.79 mmol), **10-2** (400 mg, 1.19 mmol) in Dioxane (20 mL) was added cyclopentyl(diphenyl)phosphane; dichloropalladium;iron (87.31 mg, 119.33
- 25

μmol) and KOAc (351.33 mg, 3.58 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/1) to obtain **10-3** (300 mg, 784.77 μmol , 65.77% yield). MS: $m/z = 382.2$ (M+1).

5 Step 4: **10-4**

[00335] A mixture of **10-3** (300 mg, 784.77 μmol) in THF (2 mL) and acetic acid (0.5 mL) was added H_2O_2 (0.5 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. Na_2SO_3 (0.3 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **10-4** (0.6 g, crude), which was used in the next step without purification. MS: $m/z = 272$ (M+1).

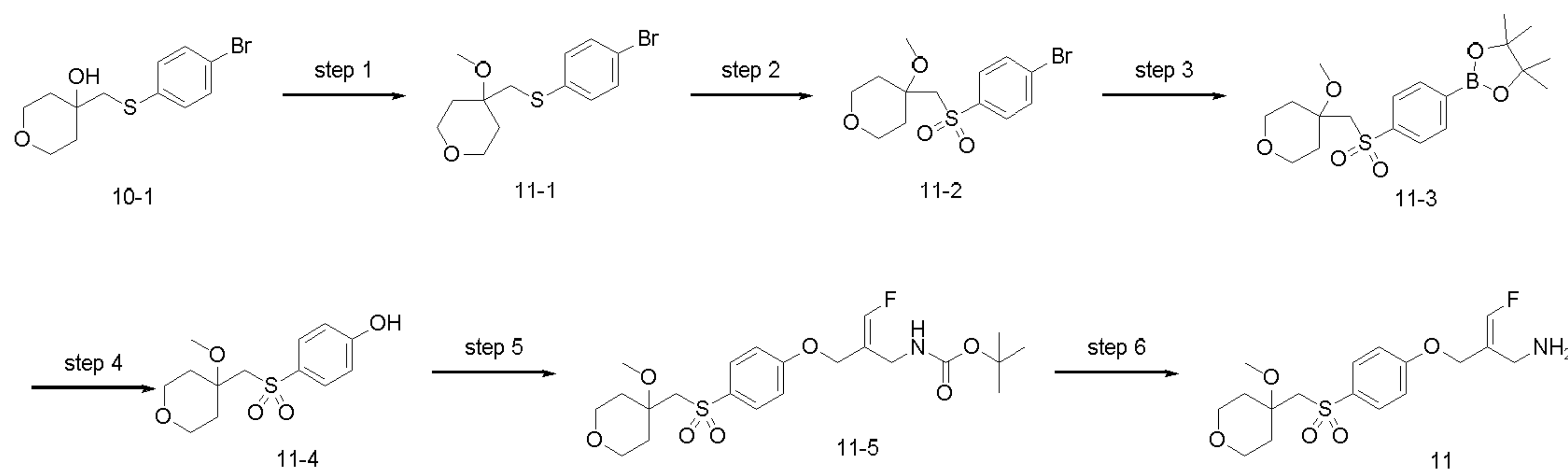
10 Step 5: **10-5**

[00336] To a mixture of **10-4** (0.5 g) and **Intermediate A** (147.69 mg, 550.83 μmol) in MeCN (20 mL) was added Cs_2CO_3 (1.79 g, 5.51 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **10-5** (280 mg, crude). MS: $m/z = 459$ (M+1).

15 Step 6: **Compound 10**

[00337] To a mixture of **10-5** (250 mg, 544.04 μmol) in HCl/Dioxane (4 M, 5 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-25% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 10** (19 mg, 52.86 μmol). ^1H NMR (400 MHz, Methanol- d_4) δ 7.89 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 80.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.84-3.79 (m, 2H), 3.78-3.71 (m, 2H), 3.69-3.65 (m, 2H), 3.40 (s, 2H), 1.95-1.84 (m, 2H), 1.72 (d, $J = 13.6$ Hz, 2H).ppm; MS: $m/z = 360.6$ (M+1, ESI+).

25 Example 21: Synthesis of **Compound 11**



Step 1: 11-1

[00338] A mixture of **10-1** (1 g, 3.30 mmol) in DMF (10 mL) was added NaH (197.86 mg, 4.95 mmol, 60% purity) at 0 °C and stirred for 1 hr. MeI (936.22 mg, 6.60 mmol) was added. The reaction solution was stirred at 50 °C for 4 hr. To the mixture was added saturated aqueous ammonium chloride solution (150 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate in petroleum ether, 10% to 80%) to give **11-1** (700 mg, 2.21 mmol, 66.91% yield). MS: m/z = 317 (M+1).

Step 2: 11-2

[00339] A mixture of **11-1** (700 mg, 2.21 mmol) and m-CPBA (1.34 g, 6.62 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. Na₂SO₃ (0.3 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 10/1 – 1/2, v/v) to obtain **11-2** (680 mg, 1.95 mmol, 88.24% yield). MS: m/z = 349 (M+1).

Step 3: 11-3

[00340] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (327.20 mg, 1.29 mmol), **11-2** (300 mg, 859.01 μmol) in Dioxane (20 mL) was added cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (62.85 mg, 85.90 μmol) and KOAc (252.91 mg, 2.58 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silica gel (petroleum ether/ethylacetate=1/10 - 1/1) to obtain **11-3** (200 mg, 504.66 μmol, 58.75% yield). MS: m/z = 396 (M+1).

Step 4: 11-4

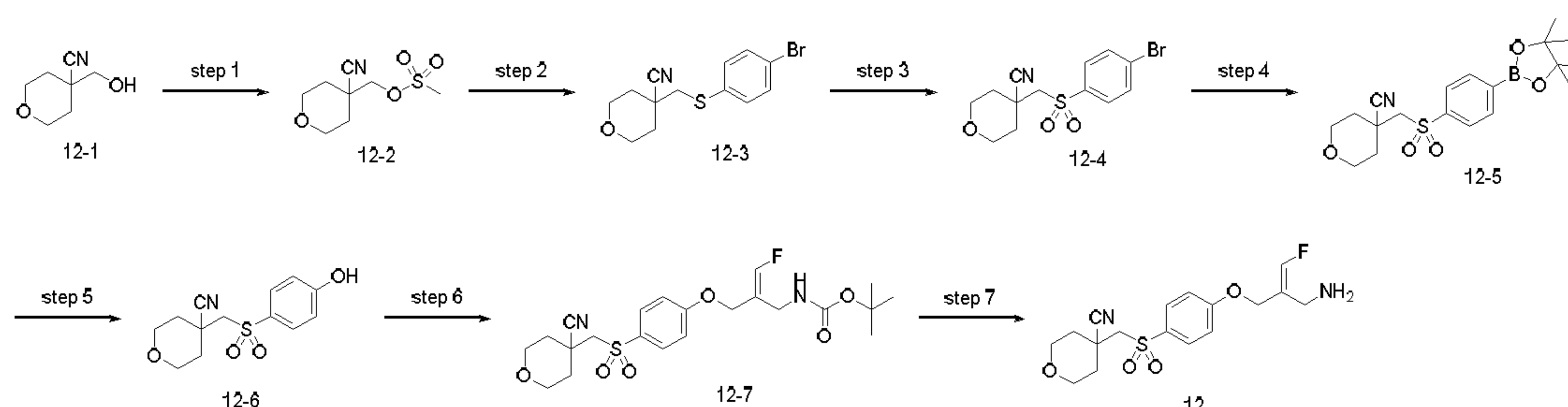
[00341] A mixture of **11-3** (200 mg, 504.66 μmol) in THF (2 mL) and acetic acid (0.5 mL) was added H₂O₂ (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. Na₂SO₃ (0.3 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **11-4** (0.6 g, crude), which was used in the next step without purification. MS: m/z = 286 (M+1).

Step 5: 11-5

[00342] To a mixture of **11-4** (0.5 g) and **Intermediate A** (140.46 mg, 523.85 μmol) in MeCN (50 mL) was added Cs_2CO_3 (568.93 mg, 1.75 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **11-5** (200 mg, crude). MS: $m/z = 473$ (M+1).

Step 6: Compound 11

[00343] A mixture of **11-5** (200 mg, 422.34 μmol) in HCl/Dioxane (4 M, 5 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 11** (25 mg, 66.95 μmol , 7.93% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 80.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.79 (d, $J = 2.4$ Hz, 2H), 3.73-3.57 (m, 4H), 3.50 (s, 2H), 2.95 (s, 3H), 1.98 (d, $J = 14.0$ Hz, 2H), 1.86-1.82 (m, 2H).ppm; MS: $m/z = 374.6$ (M+1, ESI+).

Example 22: Synthesis of Compound 12*Step 1: 12-2*

[00344] A mixture of **12-1** (1 g, 7.08 mmol), TEA (2.15 g, 21.25 mmol, 2.96 mL) in DCM (50 mL) was added MsCl (973.75 mg, 8.50 mmol) at 0 °C. The reaction solution was stirred for 1 hr at 0 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4/1, v/v) to obtain **12-2** (1.4 g, 6.39 mmol, 90.14% yield).

Step 2: 12-3

[00345] A mixture of 4-bromobenzenethiol (689.87 mg, 3.65 mmol), NaH (87.56 mg, 3.65 mmol) in DMF (10 mL) was added **12-2** (400 mg, 1.82 mmol) at 0 °C. The reaction solution was stirred for 12 hr at 50 °C. To the mixture was added saturated aqueous ammonium chloride solution (100 mL) and ethyl acetate (120 mL). The organic layer was separated and the aqueous

layer was further extracted with ethyl acetate (80 mL $\times$ 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (petroleum ether in ethyl acetate, 10% to 80%) to give **12-3** (150 mg, 480.42 μ mol, 26.33% yield). MS: m/z = 312 (M+1).

5 *Step 3: 12-4*

[00346] A mixture of **12-3** (100 mg, 320.28 μ mol) and m-CPBA (195.07 mg, 960.85 μ mol, 85% purity) in DCM (20 mL) was stirred at 25 °C for 1 hr. Na₂SO₃ (14 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 30/1 - 3/1, v/v) to obtain **12-4** (80 mg, 232.41 μ mol, 72.56% yield). MS: m/z = 344 (M+1).

10 *Step 4: 12-5*

[00347] A 30 mL microwave reaction tube was charged with **12-4** (80 mg, 232.41 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (88.53 mg, 348.61 μ mol), cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (170.05 mg, 232.41 μ mol) and KOAc (158.58 mg, 697.22 μ mol) in Dioxane (10 mL). After O₂ was purged by bubbling N₂ into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0-100%) to deliver **12-5** (75 mg, 191.67 μ mol, 82.47% yield). MS: m/z = 391(M+1).

15 *Step 5: 12-6*

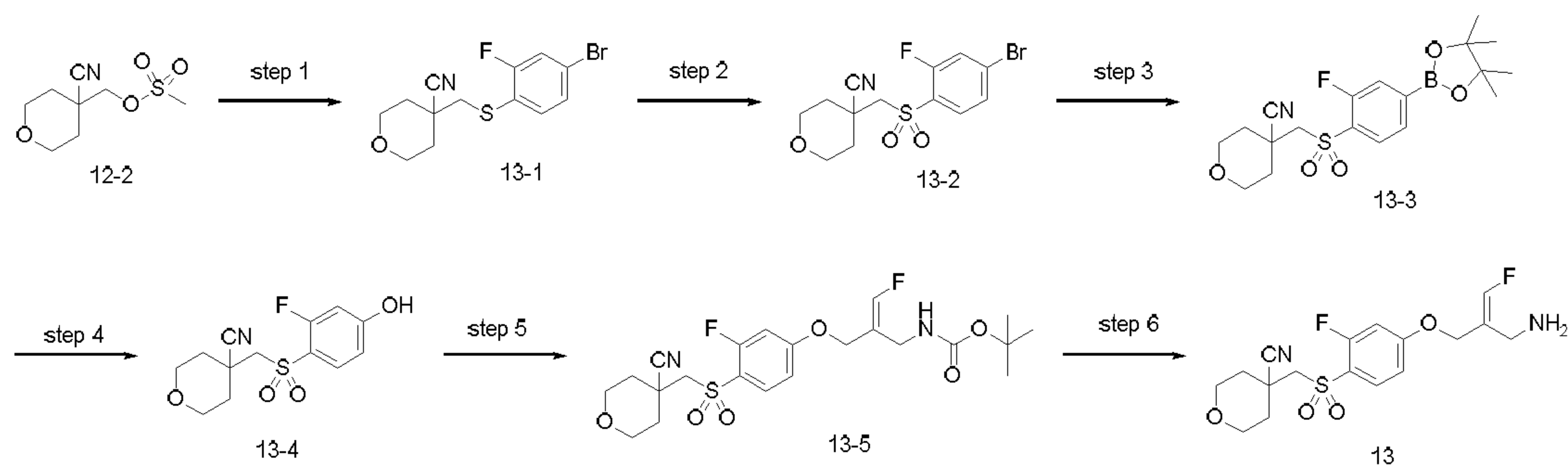
[00348] To a mixture of **12-5** (70 mg, 178.90 μ mol) in THF (1 mL) and acetic acid (0.25 mL) was added H₂O₂ (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. Na₂SO₃ (0.3 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and concentrated to give **12-6** (0.4 g, crude). MS: m/z = 281(M+1).

20 *Step 6: 12-7*

[00349] To a mixture of **12-6** (0.4 g) and **Intermediate A** (152.49 mg, 568.73 μ mol) in MeCN (50 mL) was added Cs₂CO₃ (1.39 g, 4.27 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered, concentrated and purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 5/1) to obtain **12-7** (70 mg, 149.40 μ mol, 10.51% yield). MS: m/z = 468 (M+1).

Step 7: Compound 12

[00350] A mixture of **12-7** (70 mg, 149.40 μmol) in HCl/Dioxane (4 M, 4.0 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-35% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 12** (12 mg, 32.57 μmol , 21.80% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 7.94 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 80.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 4.72 (d, J = 3.6 Hz, 2H), 3.98 – 3.88 (m, 2H), 3.82 (d, J = 2.4 Hz, 2H), 3.66 (d, J = 13.9 Hz, 4H), 2.07 (d, J = 13.6 Hz, 2H), 1.88-1.85 (m 2H).ppm; MS: m/z = 369.5 (M+1, ESI+).

Example 23: Synthesis of Compound 13*Step 1: 13-1*

[00351] A mixture of 4-bromo-2-fluorobenzenethiol (1 g, 4.83 mmol), NaH (370.10 mg, 9.66 mmol, 60% purity) in DMF (10 mL) was added **12-2** (423.56 mg, 1.93 mmol) at 0 °C. The reaction solution was stirred for 12 hr at 50 °C. To the mixture was added saturated aqueous ammonium chloride solution (100 mL) and ethyl acetate (100ml). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (50 ml $\times$ 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate in petroleum ether, 10% to 80%) to give **13-1** (200 mg, 605.67 μmol , 12.54% yield). MS: m/z = 330 (M+1).

Step 2: 13-2

[00352] To a mixture of **13-1** (200 mg, 605.67 μmol) and m-CPBA (368.88 mg, 1.82 mmol, 85% purity) in DCM (20 mL) was stirred at 25 °C for 1 hr. Na₂SO₃ (1 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and

purified by silica gel chromatography (petroleum ether/ethylacetate = 30/1-10/1, v/v) to obtain **13-2** (120 mg, 331.30 μ mol, 54.70% yield). MS: m/z = 362 (M+1).

Step 3: 13-3

[00353] To a mixture of **13-2** (110 mg, 303.69 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (115.68 mg, 455.53 μ mol) in Dioxane (4 mL) was added KOAc (158.58 mg, 911.06 μ mol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 2 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silical gel (petroleum ether/ethyl acetate = 1/10 - 1/1) to obtain **13-3** (90 mg, 219.90 μ mol, 72.41% yield). MS: m/z = 409 (M+1).

Step 4: 13-4

[00354] A mixture of **13-3** (90 mg, 219.90 μ mol) in THF (1 mL) and acetic acid (0.25 mL) was added H₂O₂ (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Na₂SO₃ (0.35 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and concentrated to give **13-4** (0.4 g, crude). MS: m/z = 299 (M+1).

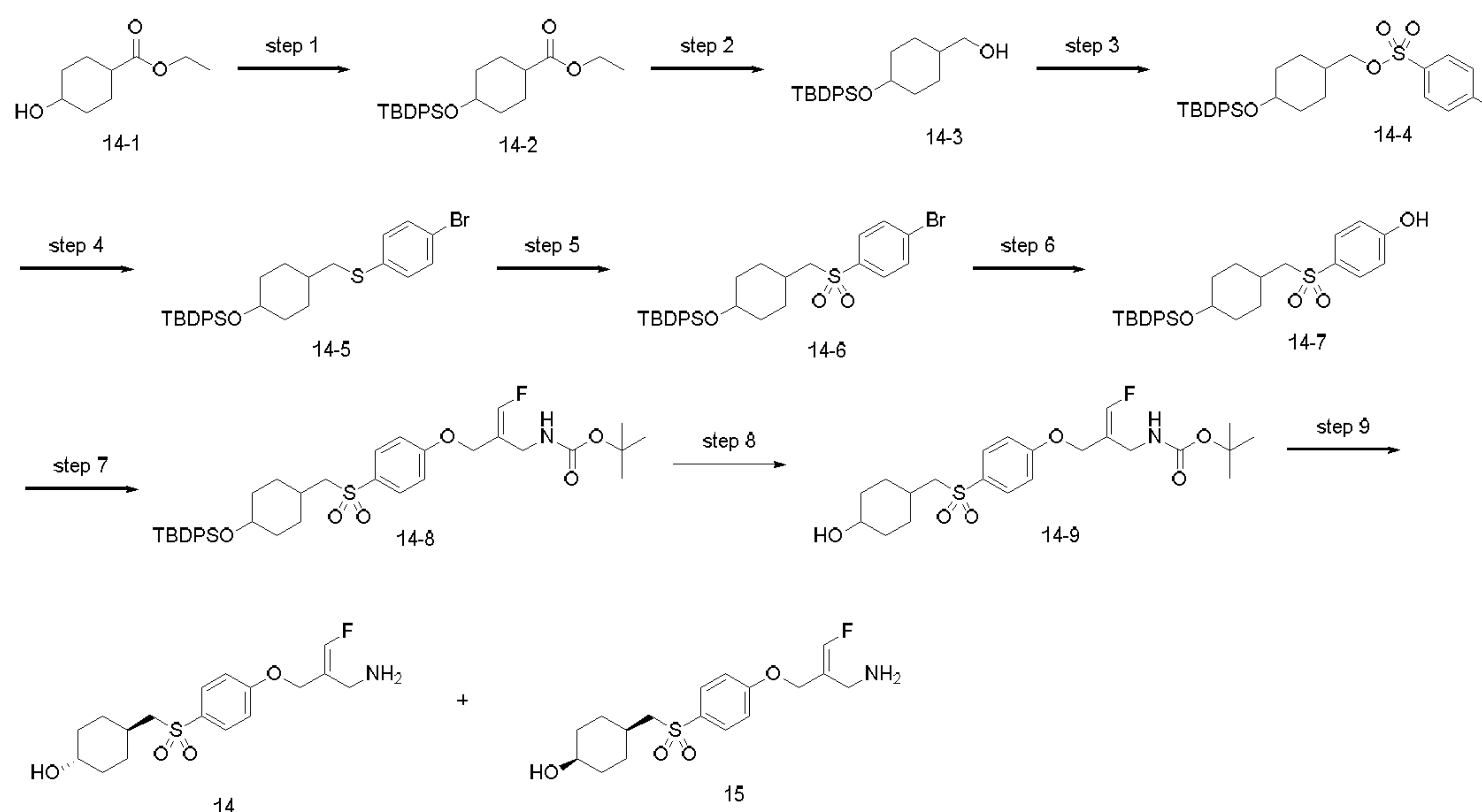
Step 5: 13-5

[00355] A mixture of **13-4** (0.4 g) and **Intermediate A** (143.33 mg, 534.55 μ mol) in MeCN (5 mL) was added Cs₂CO₃ (1.31 g, 4.01 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated and purified by column chromatography on silical gel (petroleum ether/ethyl acetate = 1/10 - 5/1) to obtain **13-5** (60 mg, 123.32 μ mol, 9.23% yield). MS: m/z = 486 (M+1).

Step 6: Compound 13

[00356] A mixture of **13-5** (60 mg, 123.32 μ mol) in HCl/Dioxane (4 M, 2.25 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 13** (5.3 mg, 13.72 μ mol, 11.12% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.50 (s, 1H), 7.89 (t, J = 8.8 Hz, 1H), 7.22 (d, J = 80.0 Hz, 1H), 7.10-7.00 (m, 2H), 4.72 (d, J = 3.6 Hz, 2H), 4.04-3.87 (m, 2H), 3.78 (d, J = 2.4 Hz, 2H), 3.74 (s, 2H), 3.63 (t, J = 12.4 Hz, 2H), 2.07 (d, J = 13.6 Hz, 2H), 1.90-1.86 (m, 2H).ppm; MS: m/z = 387.5 (M+1, ESI+).

Example 24: Synthesis of Compound 14 & 15



Step 1: 14-2

[00357] To a mixture of **14-1** (1.55 g, 9.00 mmol) in DCM (30 mL) was added *tert*-butylchlorodiphenylsilane (4.95 g, 18.0 mmol), Imidazole (1.53 g, 22.5 mmol). After stirred at 25 °C for 16 hr, the reaction mixture was poured into 50 mL water, extracted with DCM (50 mL × 3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (20/1) to afford **14-2** (2.8 g, 75.77% yield).

Step 2: 14-3

[00358] To a mixture of **14-2** (2.8 g, 6.82 mmol) in THF (30 mL) was added LiAlH₄ (518.24 mg, 13.64 mmol) at 0 °C. After addition, the mixture was warmed up to 25 °C and stirred at 25 °C for 2 hr. The resulting mixture was quenched with Na₂SO₄·10H₂O (2.0 g) and ice-water (20 mL). The aqueous mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (10/1) to afford **14-3** (2.3 g, 91.51% yield).

Step 3: 14-4

[00359] To a mixture of **14-3** (2.3 g, 6.24 mmol) in DCM (30 mL) was added 4-methylbenzenesulfonyl chloride (1.78 g, 9.36 mmol) and TEA (1.26 g, 12.48 mmol). After stirred at 25 °C for 16 hr, the resulting mixture was poured into ice-water (30 mL) and extracted

with DCM (50 mL $\times$ 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (50/1) to afford **14-4** (3.2 g, 98.10% yield).

5 *Step 4: 14-5*

[00360] To a mixture of **14-4** (3.2 g, 6.12 mmol) in MeCN (30 mL) was added 4-Bromothiophenol (1.39 g, 7.35 mmol) and K₂CO₃ (1.69 g, 12.24 mmol). The resulting mixture was stirred at 80 °C for 3 hr. After cooling to 25 °C, the reaction mixture was poured into ice-water (50 mL) and extracted with ethyl acetate (100 mL $\times$ 3). The combined organic layers were
10 washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (50/1) to afford **14-5** (3.2 g, 96.87% yield).

Step 5: 14-6

[00361] To a mixture of **14-5** (2.0 g, 3.71 mmol) in MeOH/H₂O (24 mL, 4/1) was added
15 Oxone (4.56 g, 7.41 mmol). After stirred at 25 °C for 2 hr, the resulting mixture was poured into ice-water (50 mL) and extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to afford **14-6** (2.05 g), which was used for next step directly without further purification.

20 *Step 6: 14-7*

[00362] To a mixture of **14-6** (2.05 g, 3.59 mmol) in Dioxane/H₂O (30 mL, 1/1) was added *t*-Buxphos (304.57 mg, 0.72 mmol), Pd₂(dba)₃ (328.14 mg, 0.36 mmol) and KOH (603.66 mg, 10.76 mmol). The resulting mixture was stirred at 100 °C for 1 hr under argon. After cooling to 25 °C, the reaction mixture was poured into ice-water (50 mL) and extracted with ethyl acetate
25 (50 mL $\times$ 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (5/1 to 2/1) to afford **14-7** (1.4 g, 76.74% yield). MS: *m/z* = 509.3 (M+H, ESI+).

Step 7: 14-8

30 [00363] To a mixture of **14-7** (254 mg, 0.5 mmol) in DMF (5 mL) was added **Intermediate A** (160.64 mg, 0.6 mmol) and K₂CO₃ (275.60 mg, 2.00 mmol). The resulting mixture was stirred at

80 °C for 5 hr. After cooling to 25 °C, the reaction mixture was poured into ice-water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (5/1) to afford **14-8** (330 mg, 94.97% yield). MS: m/z = 696.5 (M+H, ESI+).

Step 8: 14-9

[00364] To a mixture of **14-8** (330 mg, 0.47 mmol) in THF (10 mL) was added TABF (1 M in THF, 0.95 mL). The resulting mixture was stirred at 40 °C for 6 hr. After cooling to 25°C, the reaction mixture was poured into ice-water (30 mL) and extracted with ethyl acetate (30 mL × 3).

The combined organic layers were washed with water (30 mL), brine (30 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (1/1) to afford **14-9** (195 mg, 89.88% yield). MS: m/z = 458.2 (M+H, ESI+).

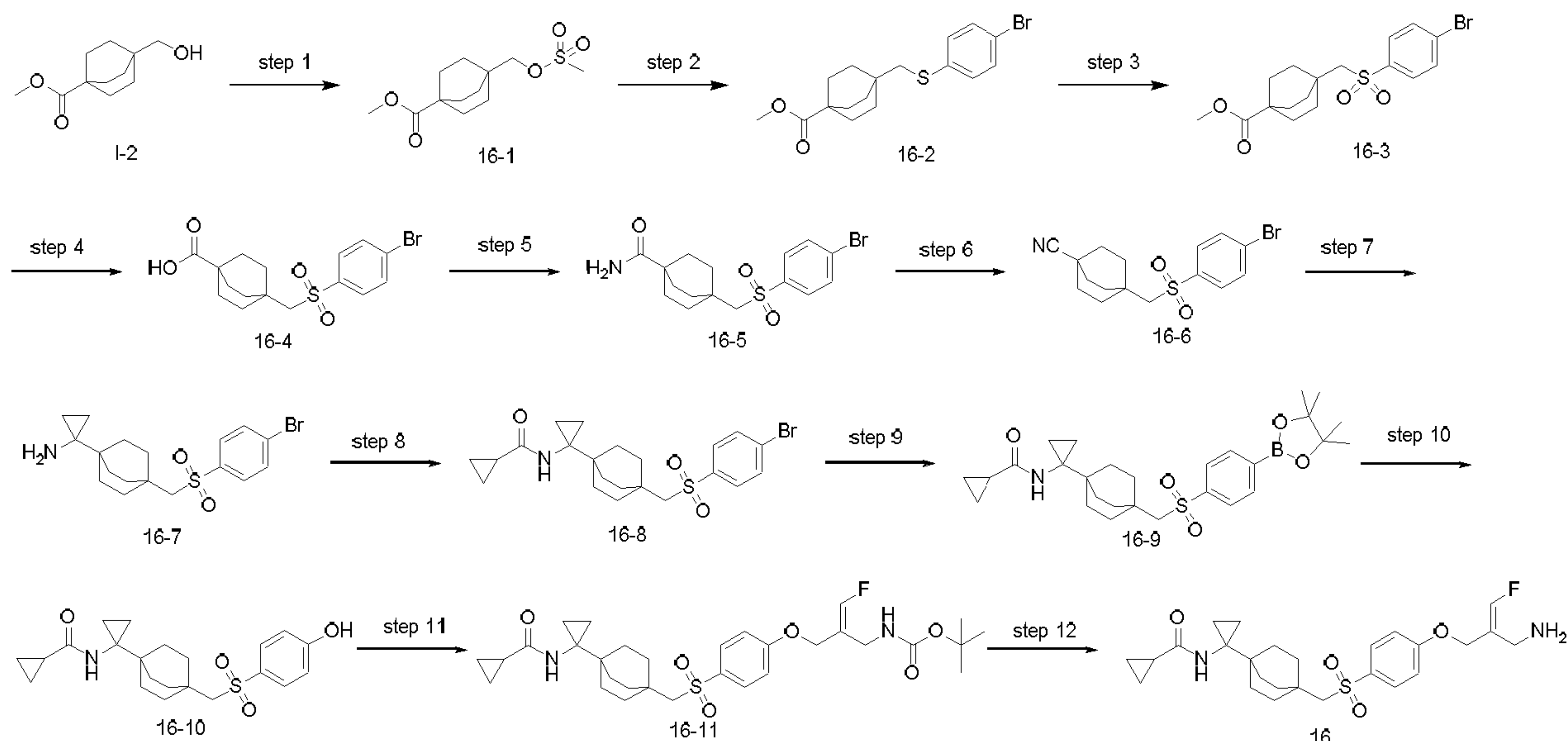
Step 9: Compound 14 & 15

[00365] To a mixture of **14-9** (195 mg, 0.43 mmol) in DCM (10 mL) was added HCl (4 M in Dioxane, 2.13 mL). After stirred at 25 °C for 3 hr, the solvent was removed under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire Prep C18 10 µm 19×250 mm; A: 0.05% HCl water, B: acetonitrile; gradient: 10-14% B; GT: 18 min; flow rate: 20 mL/min) to afford **Compound 15** (35 mg, 22.98% yield) and **Compound 14** (38 mg, 24.95% yield).

Compound 15: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (br, 3H), 7.84-7.82 (m, 2H), 7.45 (s, 1H), 7.24-7.22 (m, 2H), 4.78 (s, 2H), 3.27-3.13 (m, 3H), 1.77-1.75 (m, 4H), 1.61-1.43 (m, 2H), 1.07-1.05 (m, 4H) ppm; MS: m/z = 358.2 (M+H, ESI+).

Compound 14: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (br, 3H), 7.84-7.83 (m, 2H), 7.44 (s, 1H), 7.23-7.21 (m, 2H), 4.78 (s, 2H), 3.64-3.59 (m, 3H), 3.16 (d, *J* = 2.8 Hz, 2H), 1.78-1.36 (m, 9H) ppm; MS: m/z = 358.2 (M+H, ESI+).

Example 25: Synthesis of Compound 16



Step 1: 16-1

[00366] To a mixture of **I-2** (4 g, 20.18 mmol), Triethylamine (6.12 g, 60.53 mmol, 8.44 mL) in DCM (40 mL) was added Methanesulfonic anhydride (5.27 g, 30.26 mmol, 3.34 mL) at 0 °C.

5 The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0~30%, v/v) to obtain **16-1** (4.9 g, 17.73 mmol, 87.88% yield).

Step 2: 16-2

[00367] To a mixture of 4-bromobenzenethiol (5.03 g, 26.60 mmol), Potassium iodide (1.47 g, 8.87 mmol, 471.70 uL) in DMF (30 mL) was added **16-1** (4.9 g, 17.73 mmol) under the nitrogen atmosphere. The reaction mixture was heated at 55 °C for 8 hr. Ethyl acetate (150 mL) and H₂O (100 mL) were added, the organic layer was washed with brine (100 mL × 3), dried over Na₂SO₄, filtered and concentrated to a residue, which was purified by column chromatography on silical gel (ethyl acetate in petroleum ether, 0~20%, v/v) to give **16-2** (5.5 g, 14.89 mmol, 83.99%

15 yield).

Step 3: 16-3

[00368] To a mixture of **16-2** (5.5 g, 14.89 mmol) and m-CPBA (7.56 g, 37.23 mmol, 85% purity) in DCM (100 mL) was stirred at 20 °C for 2 hr. Na₂SO₃ (1 g) was added to the mixture and stirred for 20 min. Then, to the solution was added ethyl acetate (20 mL) and water (20 mL).

20 The organic layer was washed with aq. NaHCO₃ (30 mL × 3), brine (30 mL × 3), dried over Na₂SO₄, filtered, concentrated to give crude, which was purified by column chromatography on

silical gel (20 g, ethyl acetate in petroleum ether, 0~20%) to give **16-3** (4.5 g, 11.21 mmol, 75.29% yield).

Step 4: 16-4

5 [00369] A mixture of methyl **16-3** (1.5 g, 3.74 mmol) and lithium hydroxide monohydrate (784.24 mg, 18.69 mmol) in THF (10 mL) and water (10 mL) was stirred at 25 °C for 16 hr. Upon completion, the resulting mixture was concentrated to remove organic solvent. The residue was acidified with 1 M aqueous HCl to pH = 5 ~ 6 and filtered to give the filter cake as **16-4** (1.1 g, 2.84 mmol, 75.99% yield). MS: m/z = 387 (M+H)

Step 5: 16-5

10 [00370] To a mixture of **16-4** (1.1 g, 2.84 mmol), ammonium chloride (1.52 g, 28.42 mmol, 993.62 uL) and HATU (1.62 g, 4.26 mmol) in DMF (10 mL) was added DIPEA (1.10 g, 8.52 mmol, 1.48 mL). After addition, the mixture was stirred at 25 °C for 16 hr. Upon completion, the resulting mixture was diluted with H₂O (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with H₂O (20 mL × 3) and brine, dried over Na₂SO₄, filtered and
15 concentrated to give **16-5** (1 g, 2.59 mmol, 91.14% yield). MS: m/z = 386 (M+H)

Step 6: 16-6

[00371] A mixture of **16-5** (950 mg, 2.46 mmol) and Burgess Reagent (1.17 g, 4.92 mmol) in DCM (30 mL) was stirred at 25 °C for 3 hr. Upon completion, the resulting solution was concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 3/1) to
20 give **16-6** (900 mg, 2.44 mmol, 99.37% yield). MS: m/z = 368 (M+H)

Step 7: 16-7

[00372] To a mixture of **16-6** (500 mg, 1.36 mmol) and Ti(OiPr)₄ (3.09 g, 10.86 mmol) in THF (10 mL) was added bromo(ethyl)magnesium (1 M in THF, 13.6 mL) dropwise at 25 °C. After addition, the resulting mixture was stirred at 25 °C for 0.5 hr. Boron trifluoride diethyl
25 etherate (805.0 mg, 5.67 mmol, 700 uL) was added at 25 °C. After addition, the mixture was stirred at 25 °C for 0.5 hr. Upon completion, the resulting mixture was quenched with 10% aqueous NaOH and extracted with DCM (40 mL). The separated organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (silica gel, DCM/MeOH = 100/1 to 20/1) to give **16-7** (170 mg, 426.75 uL, 31.43% yield). MS: m/z =
30 398 (M+H)

Step 8: 16-8

[00373] To a mixture of **16-7** (170 mg, 426.75 μmol), DIPEA (275.77 mg, 2.13 mmol, 371.66 μL) in DCM (10 mL) was added cyclopropanecarbonyl chloride (134 mg, 1.28 mmol, 116.52 μL). After addition, the mixture was stirred at 25 °C for 2 hr. Upon completion, the resulting solution was quenched with water. The separated organic layer was concentrated. The residue was purified by FCC (silica gel, DCM/MeOH = 20/1) to give **16-8** (160 mg, 343.03 μmol , 80.38% yield). MS: m/z = 466 (M+H)

Step 9: 16-9

[00374] A mixture of **16-8** (160 mg, 343.03 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (131 mg, 515.87 μmol), Pd(dppf)Cl₂ (26 mg, 35.53 μmol) and KOAc (433 mg, 1.03 mmol) in Dioxane (5 mL) was microwaved at 120 °C for 30 min. Upon completion, the resulting mixture was cooled to room temperature, filtered and concentrated to give crude **16-9** (170 mg, 331.06 μmol , 96.51% yield).

Step 10: 16-10

[00375] A mixture of **16-9** (170 mg, 331.06 μmol), H₂O₂ (1 mL, 30% purity) and acetic acid (1 mL) in THF (4 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with Na₂SO₃, filtered and concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 1/1) to give **16-10** (120 mg, 297.37 μmol , 89.82% yield). MS: m/z = 404 (M+H)

Step 11: 16-11

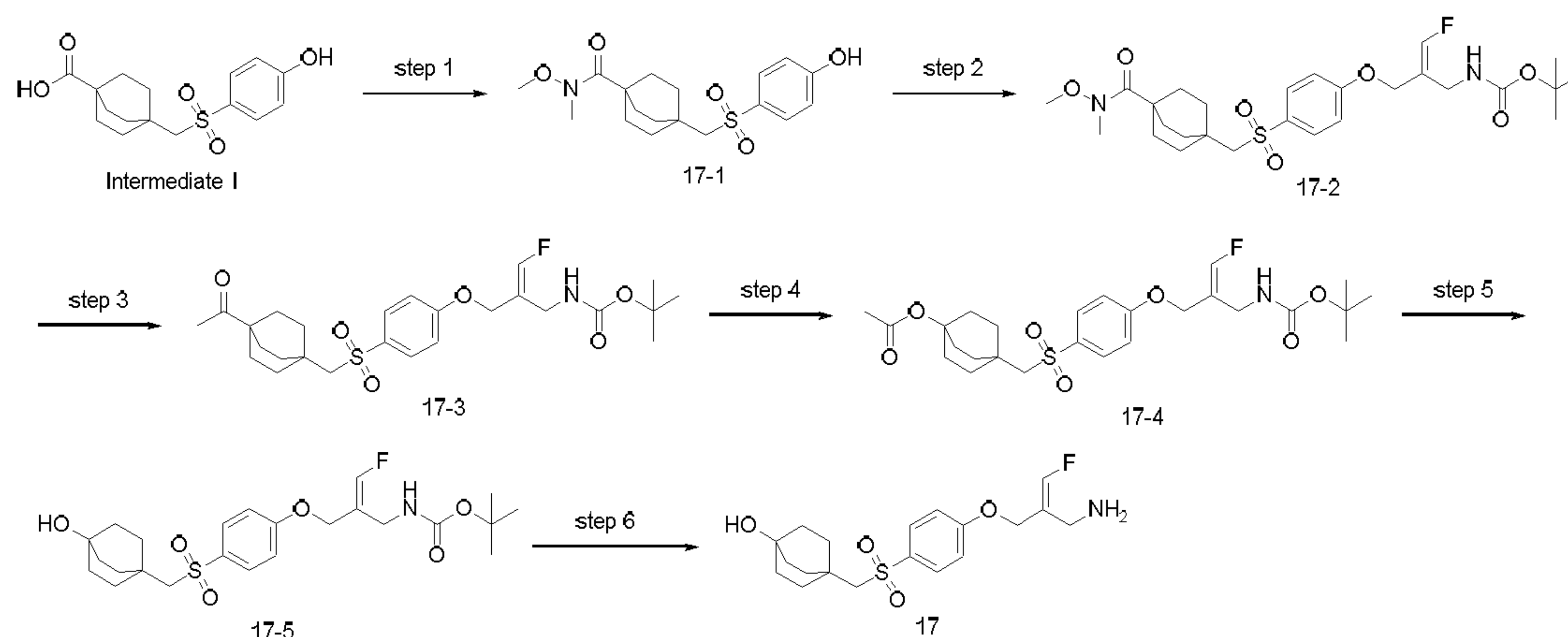
[00376] A mixture of **16-10** (120 mg, 297.37 μmol), **Intermediate A** (88 mg, 328.21 μmol) and Cs₂CO₃ (485 mg, 1.49 mmol) in MeCN (20 mL) was stirred at 95 °C for 1 hr. Upon completion, the resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 1/1 to 1/4) to give **16-11** (130 mg, 220.06 μmol , 74.00% yield). MS: m/z = 535 (M+H-56).

Step 12: Compound 16

[00377] A mixture of **16-11** (130 mg, 220.06 μmol) and HCl/Dioxane (4 M, 5.0 mL) in Dioxane (2 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was filtered to obtain the filter cake as **Compound 16** (70 mg, 132.80 μmol , 60.35% yield, HCl salt). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.77-7.72 (m, 2H), 7.24 (s, 0.5H), 7.12-7.09 (m, 2H), 7.08 (s, 0.5H), 4.62 (d, J = 3.4 Hz, 2H), 3.74 (d, J = 2.3 Hz, 2H), 2.94 (s, 2H), 1.60-1.50 (m, 6H),

1.43-1.30 (m, 7H), 0.74-0.64 (m, 4H), 0.58-0.53 (m, 2H), 0.51-0.40 (m, 2H). MS: $m/z = 491$ (M+1, ESI+).

Example 26: Synthesis of Compound 17



5 Step 1: 17-1

[00378] To a mixture of **Intermediate I** (900 mg, 2.77 mmol), N-methoxymethanamine (405.94 mg, 4.16 mmol, HCl salt) in DMF (10 mL) was added HATU (1.27 g, 3.33 mmol) and TEA (842.23 mg, 8.32 mmol, 1.16 mL) at 30 °C. The reaction solution was stirred for 1 hr at 30 °C. Then, ethyl acetate (100 mL) was added and the mixture reaction was washed with H₂O (100mL × 3), the organic phases were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1 - 1/1, v/v) to obtain **17-1** (220 mg, 598.71 μmol, 21.58% yield).

Step 2: 17-2

[00379] To a mixture of **17-1** (200 mg, 544.28 μmol) and **Intermediate A** (145.93 mg, 544.28 μmol) in MeCN (40 mL) was added Cs₂CO₃ (532.01 mg, 1.63 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to give a residue, which was purified by column chromatography on silical (ethyl acetate/petroleum ether = 5/1 - 1/1) to obtain **17-2** (220 mg, 396.63 μmol, 72.87% yield).

Step 3: 17-3

[00380] To a mixture of **17-2** (200 mg, 360.58 μmol) in THF (10 mL) was added bromo(methyl)magnesium (1 M in THF, 1.44 mL) at -40 °C. The reaction solution was stirred for 2 hr at 25 °C. Aq. NH₄Cl (10 mL) and ethyl acetate (100 mL) were added, the organic phases were dried over Na₂SO₄, filtered and concentrated with a rotary evaporator. The crude

product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4/1 – 1/1, v/v) to obtain **17-3** (160 mg, 313.95 μ mol, 87.07% yield).

Step 4: 17-4

5 [00381] A mixture of **17-3** (100 mg, 196.22 μ mol) and m-CPBA (79.67 mg, 392.44 μ mol, 85% purity) in DCM (5 mL) was stirred at 30 °C for 12 hr. Na₂SO₃ (4 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethylacetate = 5/1 – 1/1, v/v) to obtain **17-4** (20 mg, 37.90 μ mol, 19.32% yield). MS: m/z = 348.4 (M+1).

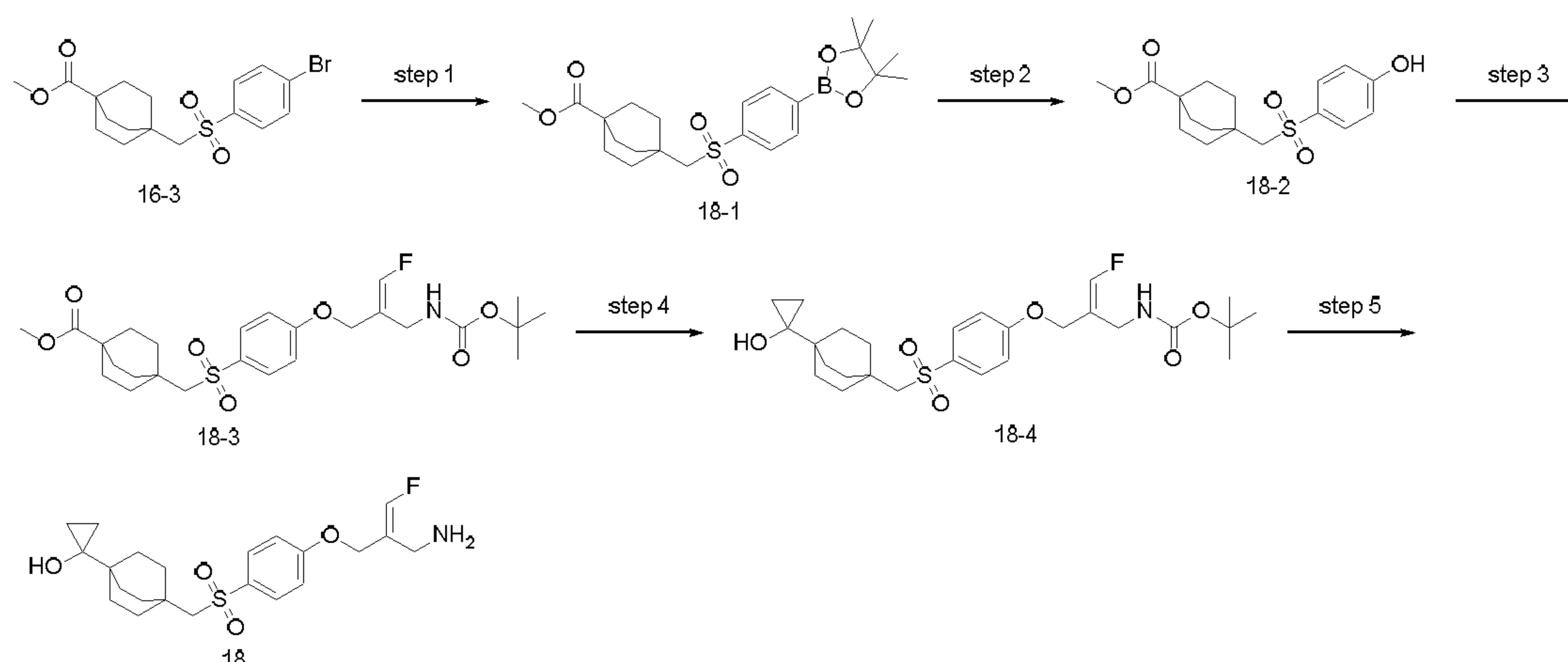
Step 5: 17-5

10 [00382] To a mixture of **17-5** (20 mg, 37.90 μ mol) in MeOH (5 mL) was added K₂CO₃ (15.72 mg, 113.71 μ mol) at 25 °C, and the reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4/1 - 1/1, v/v) to obtain **17-5** (18 mg, 37.07 μ mol, 97.79% yield). MS: m/z = 334.4 (M+1).

15 *Step 6: Compound 17*

[00383] A mixture of **17-5** (18 mg, 37.07 μ mol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-95% B; GT: 25 min; flow rate: 15 mL/min) to obtain
20 **Compound 17** (4 mg, 9.27 μ mol, 25.01% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-d₄) δ 8.51 (s, 1H), 7.90-7.82 (m, 2H), 7.24 (d, *J* = 80.0 Hz, 1H), 7.24-7.17 (m, 2H), 4.75-4.67 (m, 2H), 3.81 (d, *J* = 2.4 Hz, 2H), 3.07 (s, 2H), 1.84-1.80 (m, 6H), 1.66-1.63 (m, 6H). ppm; MS: m/z = 384.5 (M+1, ESI+).

Example 27: Synthesis of Compound 18



Step 1: 18-1

[00384] A mixture of **16-3** (590 mg, 1.47 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (560 mg, 2.21 mmol), Pd(dppf)Cl₂ (108 mg, 147.60 μmol) and KOAc (433 mg, 4.41 mmol) in Dioxane (5 mL) was microwaved at 120 °C for 30 min. The resulting mixture was cooled to room temperature, filtered and concentrated to give crude **18-1** (650 mg, 1.45 mmol, 98.61% yield. MS: m/z = 448 (M+H)

Step 2: 18-2

[00385] A mixture of **18-1** (650 mg, 1.45 mmol), H₂O₂ (1 mL, 30% purity) and acetic acid (1.45 mmol, 1 mL) in THF (4 mL) was stirred at 25 °C for 1 hr. The resulting solution was quenched with Na₂SO₃, filtered and concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 1/1) to give **18-2** (460 mg, 1.36 mmol, 93.76% yield). MS: m/z = 339 (M+H)

Step 3: 18-3

[00386] A mixture of **18-2** (200 mg, 590.99 μmol) and Cs₂CO₃ (963 mg, 2.96 mmol) in MeCN (20 mL) was stirred at 95 °C for 1 hr. The resulting mixture was filtered. The filtrate was concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 1/1 - 1/4) to give **18-3** (270 mg, 513.67 μmol, 86.92% yield). MS: m/z = 470 (M+H-56).

Step 4: 18-4

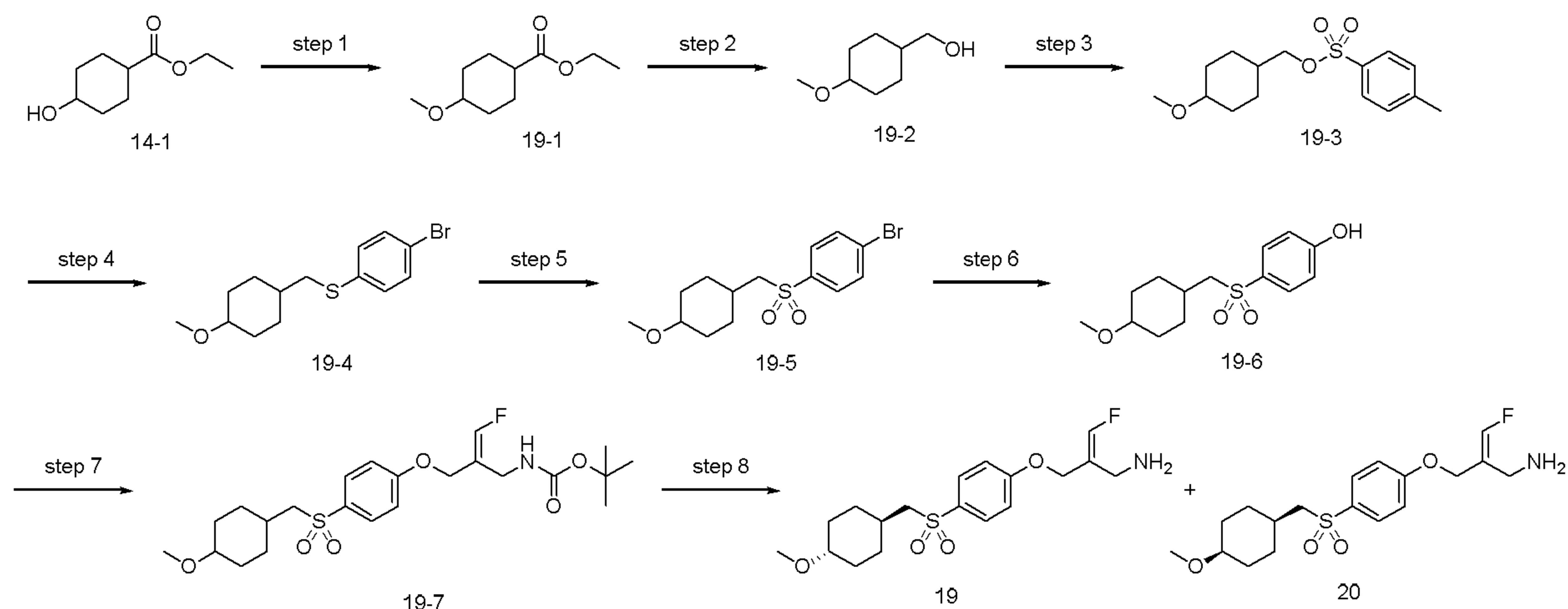
[00387] To a mixture of **18-3** (270 mg, 513.67 μmol) and Ti(OiPr)₄ (1.17 g, 4.11 mmol) in THF (20 mL) was added bromo(ethyl)magnesium (1 M in THF, 5.14 mL) dropwise at 25 °C. After addition, the resulting mixture was stirred at 25 °C for 2 hr. The resulting mixture was quenched with aqueous NH₄Cl and extracted with DCM (40 mL). The separated organic layer

was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by FCC (silica gel, petroleum ether/ethyl acetate = 1/1) to give **18-4** (100 mg, 190.97 μmol, 37.18% yield). MS: m/z = 468 (M+H-56)

Step 5: Compound 18

5 A mixture of **18-4** (100 mg, 190.97 μmol) and HCl/Dioxane (4 M, 3 mL) in Dioxane (1 mL) was stirred at 25 $^{\circ}\text{C}$ for 1 hr. The resulting mixture was concentrated and purified by prep. HPLC (gradient: 5 - 95% B, A: 0.2% HCO_2H , B: MeCN, GT: 18 min, flow rate: 15 mL/min) to give **Compound 18** (20 mg, 42.59 μmol , 22.30% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.53 (s, 1H), 7.90-7.82 (m, 2H), 7.31 (s, 0.5 H), 7.24-7.14 (m, 2H), 7.11 (s, 0.5
10 H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.78 (d, $J = 2.3$ Hz, 2H), 3.06 (s, 2H), 1.68 (dd, $J = 10.1, 5.7$ Hz, 6H), 1.47 (dd, $J = 10.0, 5.5$ Hz, 6H), 0.58-0.50 (m, 2H), 0.50-0.41 (m, 2H). MS: $m/z = 424$ ($\text{M}+\text{H}$, ESI+).

Example 28: Synthesis of Compound 19 & 20



15 *Step 1: 19-1*

[00388] To a mixture of **14-1** (10 g, 58.06 mmol) in DMF (100 mL) was added NaH (4.64 g, 116.13 mmol, 60% purity) while the internal temperature was kept below 20 °C. After addition, the resulting mixture was warmed up to 25 °C and stirred for 30 min, and then iodomethane (9.89 g, 69.68 mmol) was added. The reaction mixture was stirred at 25 °C for further 5 hr, poured into water (500 mL) and extracted with ethyl acetate (200 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate = 3/1 to give **19-1** (3 g, 27.74% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 4.12 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.33 (d, *J*

= 17.1 Hz, 3H), 3.13-3.09 (m, 1H), 2.25 (tt, $J = 11.7, 3.7$ Hz, 1H), 2.15-2.06 (m, 1H), 2.06-1.96 (m, 2H), 1.95-1.77 (m, 2H), 1.65 (dq, $J = 14.3, 5.1$ Hz, 1H), 1.57-1.40 (m, 2H), 1.25 (td, $J = 7.1, 4.7$ Hz, 3H) ppm.

Step 2: 19-2

5 [00389] To a mixture of **19-1** (2.5 g, 13.42 mmol) in THF (25 mL) was added LiAlH_4 (1.53 g, 40.27 mmol) while the internal temperature was kept below 0 °C. After addition, the resulting mixture was warmed up to 25 °C and stirred for 2 hr. The resulting mixture was quenched with ice water (300 mL) and filtered. The filtrate was extracted with ethyl acetate (100 mL $\times$ 3) and the combined organic layers were dried over Na_2SO_4 . After filtered, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel column eluted with petroleum ether/ethyl acetate = 2/1 to give **19-2** (1.5 g, 77.49% yield). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.35 (dt, $J = 17.4, 5.3$ Hz, 1H), 3.22 (s, 3H), 3.02-2.98 (m, 2H), 2.02-1.93 (m, 2H), 1.46-1.37 (m, 2H), 1.25-1.13 (m, 2H), 0.95-0.78 (m, 2H) ppm.

Step 3: 19-3

15 [00390] A mixture of **19-2** (500 mg, 3.47 mmol), 4-methylbenzenesulfonyl chloride (727.10 mg, 3.81 mmol) and TEA (701.68 mg, 6.93 mmol) in DCM (10 mL) was stirred at 25 °C for 5 hr. The resulting mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column eluting with petroleum ether/ethyl acetate = 3/1 to give **19-3** (760 mg, 70.52% yield). MS: $m/z = 299.1$ ($\text{M}+1$, ESI+).

Step 4: 19-4

25 [00391] A mixture of **19-3** (750 mg, 2.51 mmol), 4-bromobenzenethiol (570.27 mg, 3.02 mmol) and K_2CO_3 (1.04 g, 7.54 mmol) in MeCN (15 mL) was stirred at 100 °C for 2 hr. After cooling down to 25 °C, the resulting mixture was poured into water (100 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column (eluting with petroleum ether/ethyl acetate = 10/1) to give **19-4** (590 mg, 72.97% yield). MS: $m/z = 316.03$ ($\text{M}+1$, ESI+).

Step 5: 19-5

30 [00392] A mixture of **19-4** (590 mg, 1.83 mmol) and Oxone (2.25 g, 3.67 mmol) in MeOH/water (15 mL, 4/1) was stirred at 25 °C for 3 hr. The resulting mixture was diluted with

water (100 mL) and extracted with ethyl acetate (30 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give **19-5** (610 mg, 92.91% yield), which was used to next step without further purification. MS: m/z = 347.02 (M+1, ESI+).

Step 6: 19-6

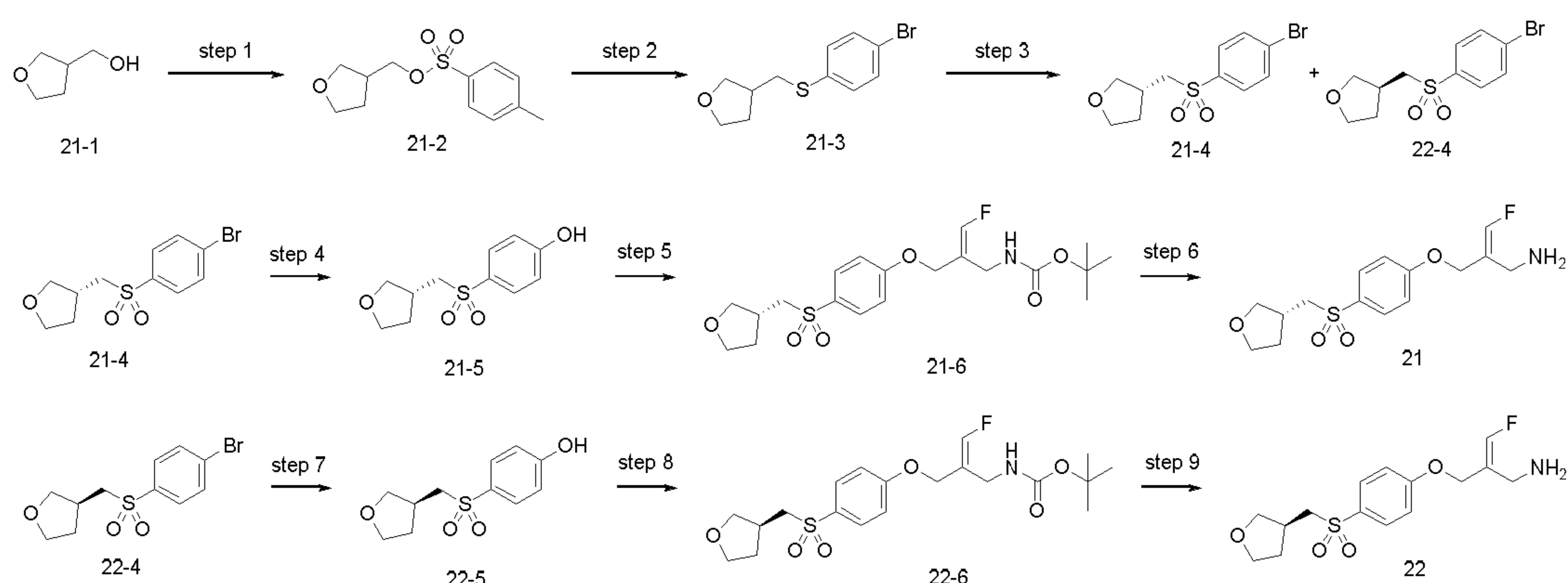
- 5 [00393] A mixture of **19-5** (600 mg, 1.68 mmol), Pd₂(dba)₃ (153.47 mg, 167.59 μ mol), *t*-BuXPhos (142.33 mg, 335.19 μ mol) and KOH (282.11 mg, 5.03 mmol) in Dioxane/water (12 mL, 1/1) was stirred at 100 °C for 2 hr under argon. After cooling down to 25 °C, the resulting mixture was diluted with water (100 mL) and extracted with EA (30 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue
- 10 was purified by silica gel column (eluting with DCM/MeOH = 20/1) to give **19-6** (500 mg, 92.91% yield). MS: m/z = 285.1 (M+1, ESI+).

Step 7: 19-7

- [00394] A mixture of **19-6** (300 mg, 1.05 mmol), **Intermediate A** (311.15 mg, 1.16 mmol) and K₂CO₃ (437.42 mg, 3.16 mmol) in DMF (6 mL) was stirred at 60 °C for 2 hr under argon.
- 15 After cooling down to room temperature, the resulting mixture was diluted with water (100 mL) and extracted with eluting with ethyl acetate (30 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give **19-7** (500 mg, 95.48% yield), which was used to next step without further purification. MS: m/z = 472.2 (M+1, ESI+).

Step 8: Compound 19 & 20

- 20 [00395] To a mixture of **19-7** (500 mg, 954.24 μ mol) in DCM (5 mL) was added HCl (3 M in ethyl acetate, 6.36 mL). After stirred at 25 °C for 3 hr, the excess of solvent was removed under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire Prep C18 10 μ m 19 $\times$ 250 mm; A: 0.05% HCl water, B: acetonitrile; gradient: 10 - 20% B; GT: 18 min; flow rate: 20 mL/min) to give **Compound 19** (90 mg, 25.14% yield) and **Compound 20** (100 mg, 27.65%
- 25 yield). **Compound 19**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.54 (s, 3H), 7.90-7.75 (m, 2H), 7.23 (d, J = 9.0 Hz, 3H), 4.81 (d, J = 3.6 Hz, 2H), 3.59 (d, J = 2.1 Hz, 2H), 3.37 (s, 2H), 3.18 (s, 4H), 3.16 (s, 1H), 1.93-1.87 (m, 2H), 1.86-1.77 (m, 2H), 1.73-1.61 (m, 1H), 1.13-0.95 (m, 4H) ppm; MS: m/z = 372.2 (M+1, ESI+). **Compound 20**: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.25 (s, 1H), 7.88-7.76 (m, 2H), 7.25-7.17 (m, 2H), 4.70 (d, J = 3.4 Hz, 2H), 3.46 (d, J = 2.3 Hz, 2H), 3.28-
- 30 3.23 (m, 1H), 3.17 (d, J = 4.7 Hz, 5H), 1.74 (dd, J = 47.4, 7.8 Hz, 3H), 1.55-1.22 (m, 6H) ppm; MS: m/z = 372.2 (M+1, ESI+).

Example 29: Synthesis of Compound 21 & 22**Step 1: 21-2**

[00396] To a mixture of **21-1** (4.65 g, 45.53 mmol) and TEA (7.37 g, 72.85 mmol) in DCM (100 mL) was added 4-methylbenzenesulfonyl chloride (10.42 g, 54.64 mmol) at 0 °C. After addition, the resulting mixture was warmed up to 10 °C and stirred for 18 hr. The reaction mixture was poured into ice water (100 mL) and extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (50 mL × 3) and dried over anhydrous sodium sulfate. The solvent was removed under *vacuum*. The residue was purified by flash chromatography over silica gel eluting with ethyl acetate in petroleum ether (30%) to afford **21-2** (10.0 g, 85.69%). ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 3.91-3.88 (m, 2H), 3.77-3.61 (m, 3H), 3.46 (dd, *J* = 9.1, 5.1 Hz, 1H), 2.60-2.49 (m, 1H), 2.42 (s, 3H), 2.01-1.90 (m, 1H), 1.57-1.46 (m, 1H) ppm.

Step 2: 21-3

[00397] To a mixture of **21-2** (3.1 g, 12.09 mmol) and 4-bromobenzenethiol (2.52 g, 13.30 mmol) in MeCN (50 mL) was added K₂CO₃ (5.01 g, 36.28 mmol). The resulting mixture was heated up to 100 °C and stirred for 4 hr. After that, the reaction mixture was cooled down to 10 °C and poured into water (100 mL). The aqueous mixture was extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column eluted with ethyl acetate in petroleum ether (8%) to afford **21-3** (3.0 g, 90.80%). ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.36 (m, 2H), 7.22-7.17 (m, 2H), 3.87-3.82 (m, 2H), 3.78-3.71 (m, 1H), 3.56 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.99-2.86 (m, 2H), 2.51-2.39 (m, 1H), 2.09-2.01 (m, 1H), 1.74-1.63 (m, 1H) ppm.

Step 3: 21-4 & 22-4

[00398] To a mixture of **21-3** (1.5 g, 5.49 mmol) in MeOH/H₂O (35 mL, 4/1) was added Oxone (6.75 g, 10.98 mmol). After stirred at 10 °C for 2 hr, the reaction mixture was poured into water (100 mL) and the methanol was removed under reduced pressure. To the residue was added water (50 mL) and the aqueous mixture was extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford racemic mixture (1.5 g, 89.52%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 - 7.76 (m, 2H), 7.75 - 7.70 (m, 2H), 3.94 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.85 (td, *J* = 8.4, 4.9 Hz, 1H), 3.73 (dd, *J* = 16.0, 7.6 Hz, 1H), 3.50 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.23 - 3.09 (m, 2H), 2.68 (dt, *J* = 14.3, 7.1 Hz, 1H), 2.18 (dtd, *J* = 12.7, 7.7, 4.9 Hz, 1H), 1.68 (ddd, *J* = 15.3, 12.7, 7.6 Hz, 1H) ppm. 300 mg of the racemic mixture was separated by SFC (column: Daicel chiralpak OD Prep C18 10 μm 25×250 mm; A: Supercritical CO₂, B: EtOH; GT: 6 min; flow rate: 70 mL/min) to afford **21-4 or 22-4** (145 mg, 48.33%) and **22-4 or 21-4** (140 mg, 46.67%).

Step 4/7: 21-5 or 22-5

[00399] Procedure for one isomer was shown. To a mixture of **21-4 or 22-4** (145 mg, 475.12 μmol), Pd₂(dba)₃ (43.49 mg, 47.49 μmol) and t-BuXphos (40.50 mg, 95.02 μmol) in Dioxane/H₂O (6 mL, 1/1) was added KOH (79.98 mg, 1.43 mmol). The resulting mixture was heated up to 100 °C and stirred for 1 hr under argon. After cooling down to 10 °C, the solvent was removed under reduced pressure. To the aqueous residue was added water (50 mL). The pH value of aqueous mixture was adjusted to 3 with HCl (1 M in water). The aqueous mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate. The solvent was removed under *vacuum*. The residue was purified by flash chromatography over silica gel eluted with MeOH in DCM (5%) to afford **21-5 or 22-5** (110 mg, 95.56%). MS: *m/z* = 243 (*M*+1, ESI+).

Step 5/8: 21-6 or 22-6

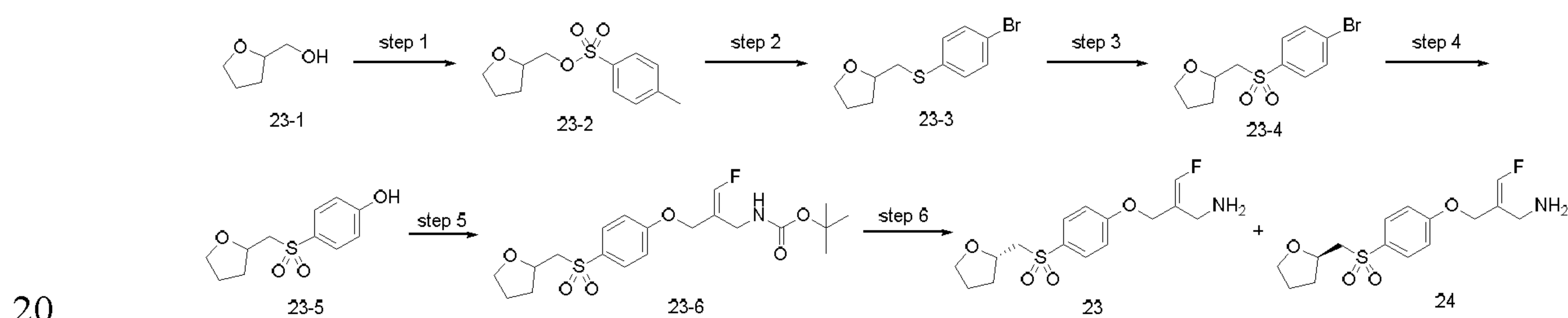
[00400] Procedure for one isomer was shown. To a mixture of **21-5 or 22-5** (55 mg, 227.0 μmol) and **Intermediate A** (60.86 mg, 227.0 μmol) in MeCN (5 mL) was added Cs₂CO₃ (147.91 mg, 454.0 μmol). The resulting mixture was heated up to 80 °C and stirred for 15 hr. After cooling down to 10 °C, the reaction mixture was poured into water (50 mL) and extracted with DCM (50 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried

over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford **21-6** or **22-6** (80 mg, 82.05%), which was used to next step without further purification. MS: $m/z = 448$ ($M+18$, ESI+).

Step 6/9: Compound 21 or 22

5 [00401] Procedure for one isomer was shown. To a mixture of **21-6** or **22-6** (80 mg, 186.26 μmol) in DCM (2 mL) was added HCl (2 mL, 3M in ethyl acetate). The resulting mixture was stirred at 10 °C for 1 hr. After that, the solvent was removed under reduced pressure. The residue was purified by prep-HPLC (column: Sunfire Prep C18 10 μm 19 $\times$ 250 mm; A: 0.05% HCl water, B: acetonitrile; gradient: 15 - 33% B; GT: 18 min; flow rate: 20 mL/min) to afford **Compound 21** or **22** (30 mg, 44.02%). ^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (s, 3H), 7.85 (d, $J = 8.9$ Hz, 2H), 7.47-7.20 (m, 3H), 4.78 (d, $J = 2.9$ Hz, 2H), 3.74 (dd, $J = 8.5, 7.4$ Hz, 1H), 3.67 (td, $J = 8.3, 5.0$ Hz, 1H), 3.63-3.53 (m, 3H), 3.39 (tt, $J = 7.5, 5.7$ Hz, 2H), 3.33-3.27 (m, 1H), 2.36 (dt, $J = 14.5, 7.4$ Hz, 1H), 1.96 (dtd, $J = 12.4, 7.6, 4.9$ Hz, 1H), 1.56-1.50 (m, 1H) ppm. MS: $m/z = 330$ ($M+1$, ESI+). The other isomer, **Compound 22** or **21** (35 mg) was obtained via the similar route. ^1H NMR (400 MHz, DMSO) δ 8.32 (s, 3H), 7.88-7.82 (m, 2H), 7.46-7.20 (m, 3H), 4.76 (d, $J = 3.2$ Hz, 2H), 3.75 (dd, $J = 8.5, 7.4$ Hz, 1H), 3.67 (td, $J = 8.2, 4.9$ Hz, 1H), 3.63-3.53 (m, 3H), 3.47-3.35 (m, 2H), 3.34-3.27 (m, 2H), 2.36 (dt, $J = 14.5, 7.4$ Hz, 1H), 1.97-1.92 (m, 1H), 1.61-1.51 (m, 1H) ppm. MS: $m/z = 330$ ($M+1$, ES+)

Example 30: Synthesis of Compound 23 & 24



Step 1: 23-2

25 [00402] To a mixture of **23-1** (10 g, 97.91 mmol) in DCM (80 mL) was added TEA (24.77 g, 244.78 mmol) and 4-methylbenzenesulfonyl chloride (17.26 g, 244.78 mmol). After stirred at 25 °C for 6 hr, the resulting mixture was concentrated. To the residue was added water (500 mL) and the aqueous mixture was extracted with ethyl acetate (500 mL $\times$ 2). The combined organic layers were washed with water (500 mL), brine (500 mL), dried over Na_2SO_4 . The solvent was removed under reduced pressure. The residue was purified by silica gel column

eluted with petroleum ether/ethyl acetate (4/1) to afford **23-2** (10 g, 39.85% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.25 (t, *J* = 15.6 Hz, 2H), 4.06-3.83 (m, 3H), 3.68-3.63 (m, 2H), 2.37 (s, 3H), 1.99-1.71 (m, 3H), 1.70-1.46 (m, 1H) ppm.

Step 2: 23-3

- 5 [00403] A mixture of **23-2** (2.56 g, 9.99 mmol), 4-bromobenzenethiol (2.27 g, 11.99 mmol) and K₂CO₃ (2.07 g, 14.98 mmol) in DMF (40 mL) was stirred at 100 °C for 16 hr. After cooling down to room temperature, the resulting mixture was poured into water (200 mL) and extracted with ethyl acetate (200 mL × 2). The combined organic layers were washed with water (200 mL), brine (100 mL), dried over Na₂SO₄. The solvent was removed under reduced pressure.
- 10 The residue was purified by silica gel column eluted with petroleum ether/ethyl acetate (10/1) to afford **23-3** (1.5 g, 54.98% yield). MS: *m/z* = 273 (M+1, ESI+).

Step 3: 23-4

- [00404] To a mixture of **23-3** (1 g, 3.66 mmol) in MeOH and H₂O (35 mL, 4:1) was added Oxone (4.50 g, 7.32 mmol). After stirred at 10 °C for 2 hr, the resulting mixture was poured into
- 15 water (100 mL) and the methanol was removed under reduced pressure. To the residue was added water (50 mL) and the aqueous mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford **23-4** (1.1 g, 98.47 %), which was used to the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.82-7.77
- 20 (m, 2H), 7.72-7.67 (m, 2H), 4.26 (m, *J* = 6.9, 5.4 Hz, 1H), 3.79-3.72 (m, 1H), 3.71-3.63 (m, 1H), 3.39 (dd, *J* = 14.3, 6.9 Hz, 1H), 3.22 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.20-2.09 (m, 1H), 1.92-1.84 (m, 2H), 1.70-1.59 (m, 1H) ppm.

Step 4: 23-5

- [00405] To a suspension of **23-4** (1.1 g, 3.60 mmol), t-BuXPhos (306.11 mg, 720.87
- 25 μmol) and Pd₂(dba)₃ (330.06 mg, 360.43 μmol) in Dioxane/H₂O (20 mL, 1/1) was added KOH (202.24 mg, 3.60 mmol). The resulting mixture was heated up to 100 °C and stirred for 1 hr under argon. After cooling down to 10 °C, the solvent was removed under reduced pressure. To the residue was added water (50 mL). The pH value of the resulting mixture was adjusted to 3 with HCl (1 M in water). The aqueous mixture was extracted with DCM (70 mL × 3). The
- 30 combined organic layers were washed with brine (30 mL × 3), dried over anhydrous sodium sulfate. The solvent was removed under *vacuum*. The residue was purified by flash

chromatography over silica gel eluted with MeOH in DCM (5%) to afford **23-5** (800 mg, 91.61 %). MS: $m/z = 243$ ($M + 1$, ESI+).

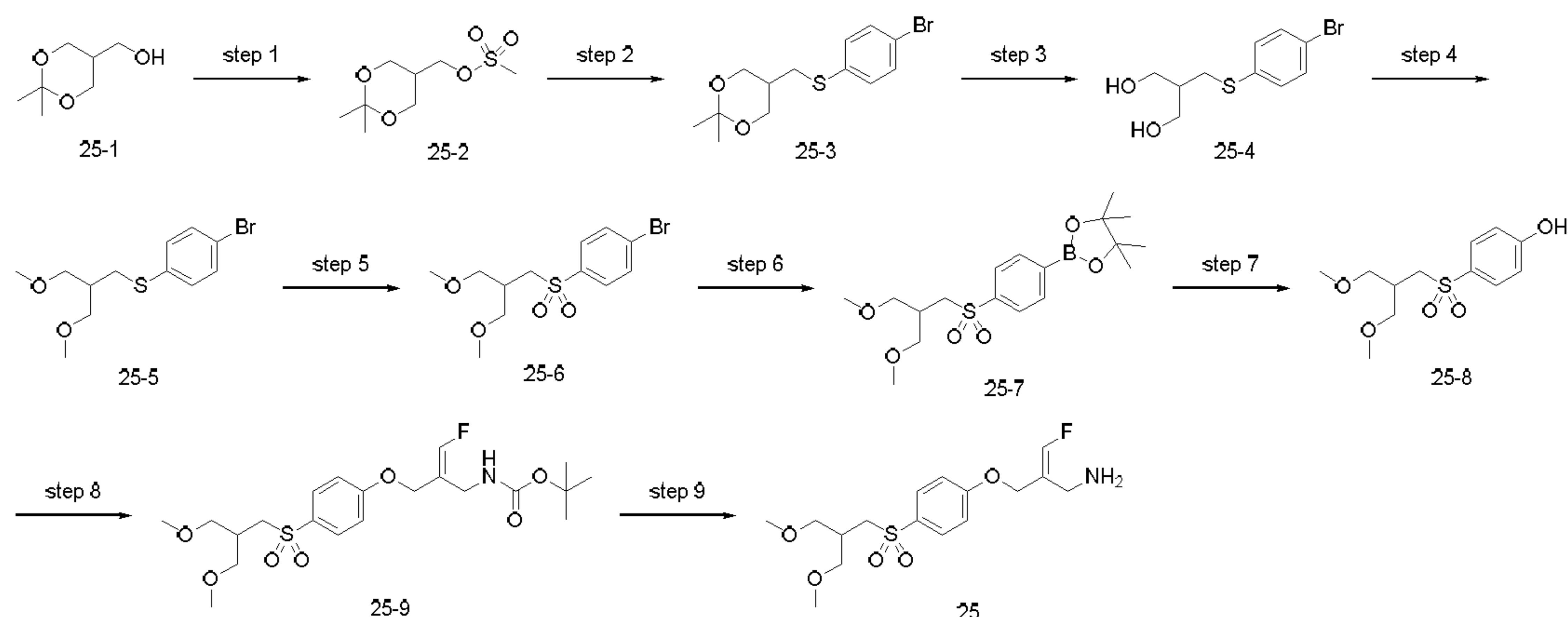
Step 5: 23-6

[00406] To a mixture of **23-5** (215 mg, 887.36 μmol), **Intermediate A** (261.71 mg, 976.10 μmol) in MeCN (5 mL) was added Cs_2CO_3 (722.80 mg, 2.22 mmol). The resulting mixture was heated up to 80 °C and stirred for 15 hr. After cooling down to 10 °C, the resulting mixture was poured into water (30 mL) and extracted with DCM (30 mL $\times$ 3). The combined organic layers were washed with brine (30 mL $\times$ 3), dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by silica gel column eluted with ethyl acetate in petroleum ether (10%) to afford **23-6** (300 mg, 78.71 %). ^1H NMR (400 MHz, CDCl_3) δ 7.88-7.80 (m, 2H), 7.04-6.98 (m, 2H), 6.88-6.64 (m, 1H), 4.75 (s, 1H), 4.51 (d, $J = 3.2$ Hz, 2H), 4.22 (p, $J = 6.4$ Hz, 1H), 3.98 (t, $J = 10.5$ Hz, 2H), 3.81-3.73 (m, 1H), 3.72-3.65 (m, 1H), 3.38 (dd, $J = 14.2, 6.3$ Hz, 1H), 3.18 (dd, $J = 14.2, 5.9$ Hz, 1H), 2.12 (m, 1H), 1.93-1.83 (m, 2H), 1.65-1.60 (m, 2H), 1.40 (s, 9H) ppm.

Step 6: Compound 23 & 24

[00407] To a mixture of **23-6** (300 mg, 698.48 μmol) in DCM (3 mL) was added HCl (3 mL, 3 M in ethyl acetate). After stirred at 10 °C for 4 hr, the solvent was removed under reduced pressure. The residue was purified by Prep-HPLC (column: Sunfire Prep C18 10 μm 19 $\times$ 250 mm; A: 0.05% HCl water, B: acetonitrile; gradient: 10 - 35% B; GT: 18 min; flow rate: 20 mL/min) and SFC (column: Daicel chiralpak OD Prep C18 10 μm 25 $\times$ 250 mm; A: Supercritical CO_2 , B: EtOH; GT: 14 min; flow rate: 70 mL/min) to afford **Compound 23 or 24** (41 mg, 16.04%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.09 (br, 3H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.36 (d, $J = 81.8$ Hz, 1H), 7.20 (d, $J = 8.9$ Hz, 2H), 4.71 (s, 2H), 4.04 (p, $J = 6.5$ Hz, 1H), 3.60 (dd, $J = 14.3, 7.7$ Hz, 3H), 3.55-3.43 (m, 3H), 1.94 (td, $J = 12.2, 7.5$ Hz, 1H), 1.84-1.69 (m, 2H), 1.55-1.51 (m, 1H) ppm. MS: $m/z = 330$ ($M+1$, ESI+). **Compound 24 or 23** (46 mg, 18.00%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.29 (s, 3H), 7.83 (d, $J = 5.8$ Hz, 2H), 7.35 (d, $J = 81.8$ Hz, 1H), 7.21 (d, $J = 8.9$ Hz, 2H), 4.75 (d, $J = 3.1$ Hz, 2H), 4.04 (p, $J = 6.5$ Hz, 1H), 3.60 (q, $J = 7.5$ Hz, 3H), 3.55-3.50 (m, 1H), 3.47 (dd, $J = 6.0, 4.2$ Hz, 2H), 2.01-1.89 (m, 1H), 1.84-1.67 (m, 2H), 1.55-1.50 (m, 1H) ppm. MS: $m/z = 330$ ($M+1$, ESI+).

Example 31: Synthesis of Compound 25



Step 1: 25-2

[00408] To a mixture of **25-1** (1.0 g, 6.84 mmol), Et₃N (1.38 g, 13.68 mmol) in DCM (45 mL) was added methanesulfonyl chloride (861.97 mg, 7.52 mmol, 582.41 μ L) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was filtered and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 50%, v/v) to obtain **25-2** (1.1 g, 4.90 mmol, 71.70% yield).

Step 2: 25-3

[00409] To a mixture of 4-bromobenzenethiol (400 mg, 2.12 mmol) in DMF (20 mL) was added NaH (110.0 mg, 2.75 mmol, 60% purity) at 25 °C. The reaction solution was stirred for 0.5 hr at 25 °C. Then, **25-2** (521.92 mg, 2.33 mmol) was added. The reaction solution was stirred for another 18 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 40%) to obtain **25-3** (410 mg, 1.29 mmol, 61.09% yield).

Step 3: 25-4

[00410] To a mixture of **25-3** (200 mg, 630.44 μ mol) in MeOH (15 mL) was added HCl/Dioxane (4 M, 4 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 2 hr. Then, the solution was concentrated with a rotary evaporator to obtain **25-4** (180 mg, crude).

Step 4: 25-5

[00411] To a mixture of **25-4** (180 mg, 649.40 μ mol) in DMF (10 mL) was added NaH (64.93 mg, 1.62 mmol, 60% purity) at 25 °C. The reaction solution was stirred for 0.5 hr at 25 °C. Then, iodomethane (276.53 mg, 1.95 mmol, 121.28 μ L) was added. The reaction solution was stirred further for 18 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator.

The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 50%) to obtain **25-5** (180 mg, 589.72 μ mol, 90.81% yield).

Step 5: 25-6

5 [00412] To a mixture of **25-5** (180 mg, 589.72 μ mol) in DCM (20 mL) was added m-CPBA (119.73 mg, 589.72 μ mol, 85% purity) at 25 °C. The mixture was stirred for 1 hr at 25 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL $\times$ 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **25-6** (210 mg, crude).

Step 6: 25-7

10 [00413] To a mixture of **25-6** (210 mg, 622.72 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (189.76 mg, 747.27 μ mol) and KOAc (183.35 mg, 1.87 mmol) in Dioxane (10 mL) was added Pd(dppf)Cl₂ (45.56 mg, 62.27 μ mol) at 25 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **25-7** (300 mg, crude).

15 *Step 7: 25-8*

[00414] To a mixture of **25-7** (300 mg, 780.65 μ mol), acetic acid (0.4 mL) in THF (15 mL) was added H₂O₂ (0.3 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, to the solution was added Na₂SO₃ (0.5 g), filtered and concentrated with a rotary evaporator to obtain **25-8** (250 mg, crude). MS: m/z = 273 (M-1).

20 *Step 8: 25-9*

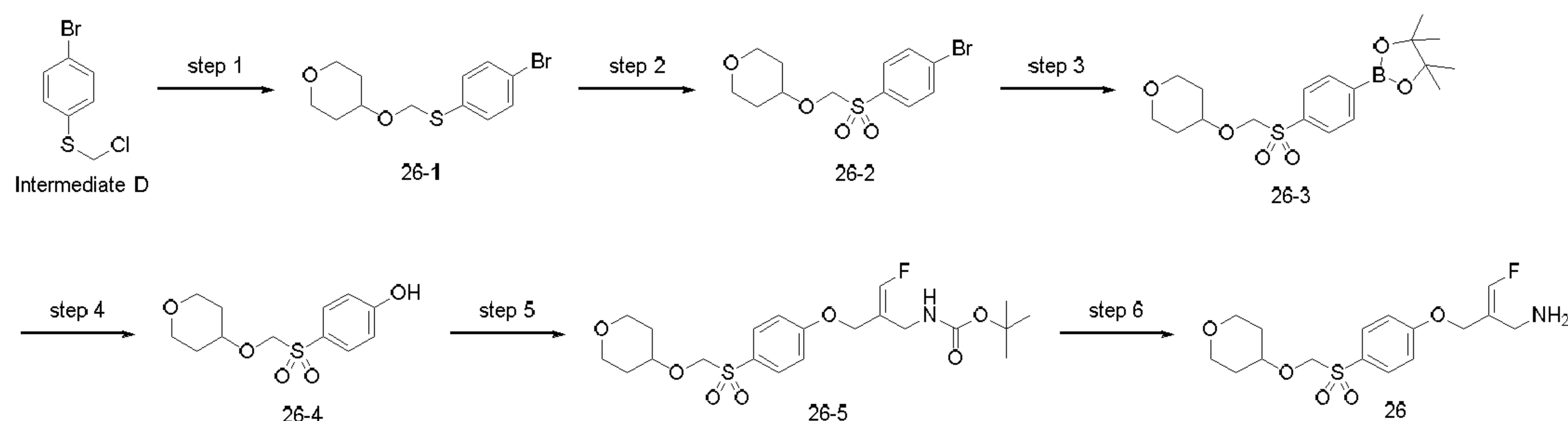
[00415] To a mixture of **25-8** (250 mg, 911.30 μ mol), **Intermediate A** (160 mg, 596.74 μ mol) in MeCN (30 mL) was added Cs₂CO₃ (890.76 mg, 2.73 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **25-9** (230 mg, crude). The crude product was
25 used for the next step without further purification. MS: m/z = 462 (M+1).

Step 9: Compound 25

[00416] To a mixture of **25-9** (230 mg, 498.33 μ mol) in DCM (15 mL) was added HCl/Dioxane (4 M, 4 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-
30 HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 25** (67 mg, 164.44

μmol , 33.0% yield, HCO_2H salt). MS: $m/z = 362$ ($M+1$). ^1H NMR (400 MHz, $\text{Methanol-}d_4$) δ 7.90 (d, $J = 8.9$ Hz, 2H), 7.29-7.21 (m, 2H), 7.28 (d, $J = 81.0$ Hz, 1H), 4.74 (dd, $J = 3.6, 1.1$ Hz, 2H), 3.92-3.81 (m, 2H), 3.47-3.37 (m, 4H), 3.26 (s, 6H), 3.25 (s, 2H), 2.34-2.31 (m, 1H).

Example 32: Synthesis of Compound 26



Step 1: 26-1

[00417] To a mixture of tetrahydropyran-4-ol (322.46 mg, 3.16 mmol) in DMF (10 mL) was added NaH (126.28 mg, 3.16 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (500 mg, 2.10 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **26-1** (300 mg, 989.40 μmol , 47.01% yield).

Step 2: 26-2

[00418] To a mixture of **26-1** (300 mg, 989.40 μmol) in DCM (20 mL) was added m-CPBA (602.60 mg, 2.97 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na_2SO_3 (10 mL), saturated aqueous NaHCO_3 (20 mL $\times$ 2) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator to obtain **26-2** (350 mg, crude).

Step 3: 26-3

[00419] To a mixture of **26-2** (350 mg, 1.04 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (318.17 mg, 1.25 mmol) and KOAc (188.10 mg, 3.13 mmol) in Dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (76.40 mg, 104.41 μmol) at 20 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered, and the filtrate was concentrated. The residual material was dissolved in DCM (15 mL), washed with H_2O (15 mL) and brine (15 mL) and concentrated with a rotary evaporator to obtain **26-3** (420 mg, crude).

Step 4: 26-4

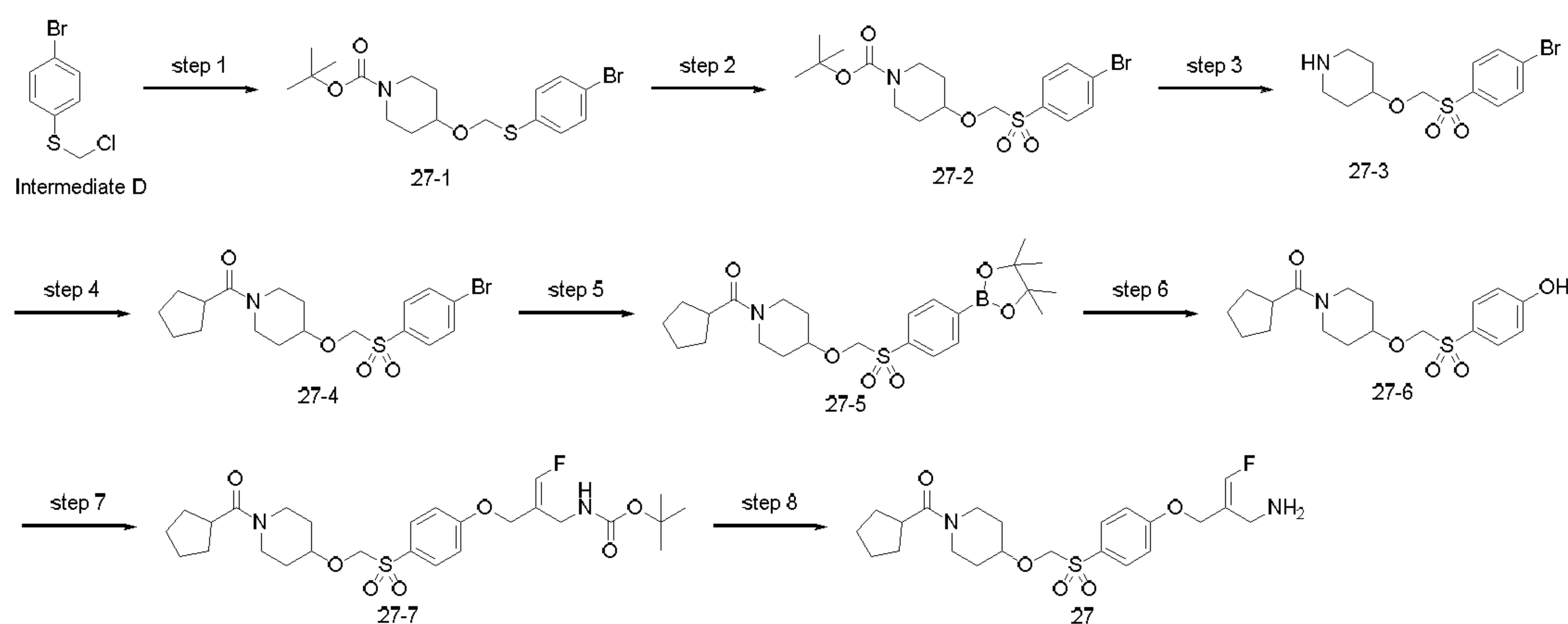
[00420] To a mixture of **26-3** (420 mg, 1.10 mmol), acetic acid (0.3 mL) in THF (10 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **26-4** (300 mg, crude). MS: $m/z = 271$ (M-1).

Step5: 26-5

[00421] To a mixture of **26-4** (300 mg, 1.10 mmol), **Intermediate A** (100 mg, 372.96 μ mol) in MeCN (30 mL) was added Cs₂CO₃ (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **26-5** (200 mg, crude). MS: $m/z = 460$ (M+1).

Step 6: Compound 26

[00422] To a mixture of **26-5** (200 mg, 435.23 μ mol) in DCM (15 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 10-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 26** (13 mg, 36.17 μ mol, 8.31% yield). MS: $m/z = 360$ (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.89-7.81 (m, 2H), 7.23-7.17 (m, 2H), 6.98 (d, $J = 82.9$ Hz, 1H), 4.69 (s, 2H), 3.88 (m, 1H), 3.80 (m, 2H), 3.52 (d, $J = 2.4$ Hz, 2H), 3.40 (m, 2H), 1.91-1.84 (m, 2H), 1.49 (m, 2H). MS: $m/z = 360.13$ (M+1)

Example 33: Synthesis of Compound 27*Step 1: 27-1*

[00423] To a mixture of tert-butyl 4-hydroxypiperidine-1-carboxylate (651.74 mg, 3.24 mmol) in DMF (20 mL) was added NaH (194.28 mg, 4.86 mmol, 60% purity) at 25 °C. The reaction

solution was stirred for 0.5 hr at 25 °C. Then, **Intermediate D** (1.0 g, 4.21 mmol) was added. The reaction solution was stirred for further 18 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **27-1** (800 mg, 1.99 mmol, 61.40% yield). MS: $m/z = 402$ (M+1).

Step 2: 27-2

[00424] To a mixture of **27-1** (200 mg, 497.09 μmol) in DCM (20 mL) was added m-CPBA (403.68 mg, 1.99 mmol, 85% purity) at 25 °C. The mixture was stirred for 1 hr at 25 °C. Then, the solution was washed with saturated aqueous Na_2SO_3 (10 mL), saturated aqueous NaHCO_3 (20 mL $\times$ 2) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator to obtain **27-2** (250 mg, crude). MS: $m/z = 434$ (M+1).

Step 3: 27-3

[00425] To a mixture of **27-2** (250 mg, 575.58 μmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 2 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **27-3** (220 mg, crude, HCl salt). The crude product was used for the next step without further purification. MS: $m/z = 334$ (M+1).

Step 4: 27-4

[00426] To a mixture of **27-3** (220 mg, 593.49 μmol), Et_3N (180.16 mg, 1.78 mmol) in DCM (20 mL) was added cyclopentanecarbonyl chloride (86.56 mg, 652.84 μmol) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was filtered and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 60%, v/v) to obtain **27-4** (180 mg, 418.26 μmol , 70.47% yield). MS: $m/z = 430$ (M+1).

Step 5: 27-5

[00427] To a mixture of **27-4** (180 mg, 418.26 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (127.45 mg, 501.91 μmol) and KOAc (123.15 mg, 1.25 mmol) in Dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (30.60 mg, 41.83 μmol) at 25 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **27-5** (220 mg, crude). MS: $m/z = 478$ (M+1).

Step 6: 27-6

[00428] To a mixture of **27-5** (220 mg, 460.81 μmol), acetic acid (0.5 mL) in THF (10 mL) was added H_2O_2 (0.2 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, to the solution was added Na_2SO_3 (0.5g), filtered and concentrated with a rotary evaporator to obtain **27-6** (230 mg, crude). MS: $m/z = 368$ (M+1).

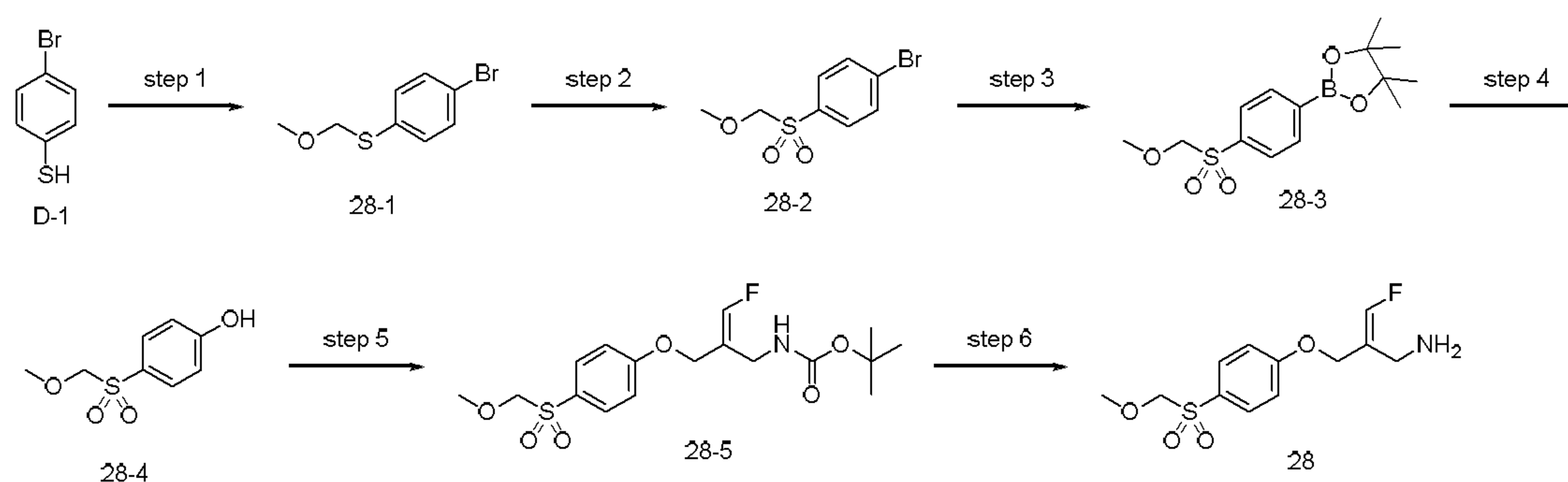
5 *Step 7: 27-7*

[00429] To a mixture of **27-6** (230 mg), **Intermediate A** (120 mg, 447.56 μmol) in MeCN (20 mL) was added Cs_2CO_3 (611.81 mg, 1.88 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **27-7** (250 mg, crude). MS: $m/z = 555$ (M+1).

10 *Step 8: Compound 27*

[00430] To a mixture of **27-7** (250 mg, 450.72 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 3 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 27** (85 mg, 169.80 μmol , 37.67% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.91 (d, $J = 8.9$ Hz, 2H), 7.29-7.22 (m, 2H), 7.27 (d, $J = 81.0$ Hz, 1H), 4.75 (s, 4H), 4.00-3.95 (m, 1H), 3.85 (d, $J = 2.3$ Hz, 2H), 3.78-3.64 (m, 3H), 3.40-3.32 (m, 2H), 3.10-2.98 (m, 1H), 2.00-1.40 (m, 12H). MS: $m/z = 455.74$ (M+1, ESI+).

Example 34: Synthesis of Compound 28



20 *Step 1: 28-1*

[00431] A mixture of **D-1** (1 g, 5.29 mmol) and chloro(methoxy)methane (511.0 mg, 6.35 mmol) in MeCN (10 mL) was added K_2CO_3 (2.19 g, 15.87 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 40 °C. Then, the solution was filtered and concentrated to obtain **28-1** (1 g, 4.29 mmol, 81.10% yield), which was used in the next step without purification.

25 *Step 2: 28-2*

[00432] A mixture of **28-1** (1 g, 4.29 mmol) and m-CPBA (2.37 g, 12.87 mmol, 85% purity) in DCM (50 mL) was stirred at 20 °C for 1 hr. Na₂SO₃ (6 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1 – 1/1, v/v) to obtain **28-2** (800 mg, 3.02 mmol, 70.34% yield). MS: m/z = 265 (M+1).

Step 3: 28-3

[00433] To a mixture of **28-2** (800 mg, 3.02 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (919.50 mg, 3.62 mmol) and cyclopentyl(diphenyl)phosphane; dichloropalladium; iron (220.79 mg, 301.75 μmol) in Dioxane (10 mL) was added KOAc (888.42 mg, 9.05 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (60 mL), washed with H₂O (100 mL × 3), dried over Na₂SO₄, filtered and concentrated to obtain **28-3** (300 mg, 960.96 μmol, 31.85% yield). MS: m/z = 312 (M+1).

Step 4: 28-4

[00434] To a mixture of **28-3** (300 mg, 960.96 μmol) in MeCN (4 mL) and acetic acid (1 mL) was added H₂O₂ (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. Na₂SO₃ (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **28-4** (300 mg, crude). MS: m/z = 202 (M+1, ESI+).

Step 5: 28-5

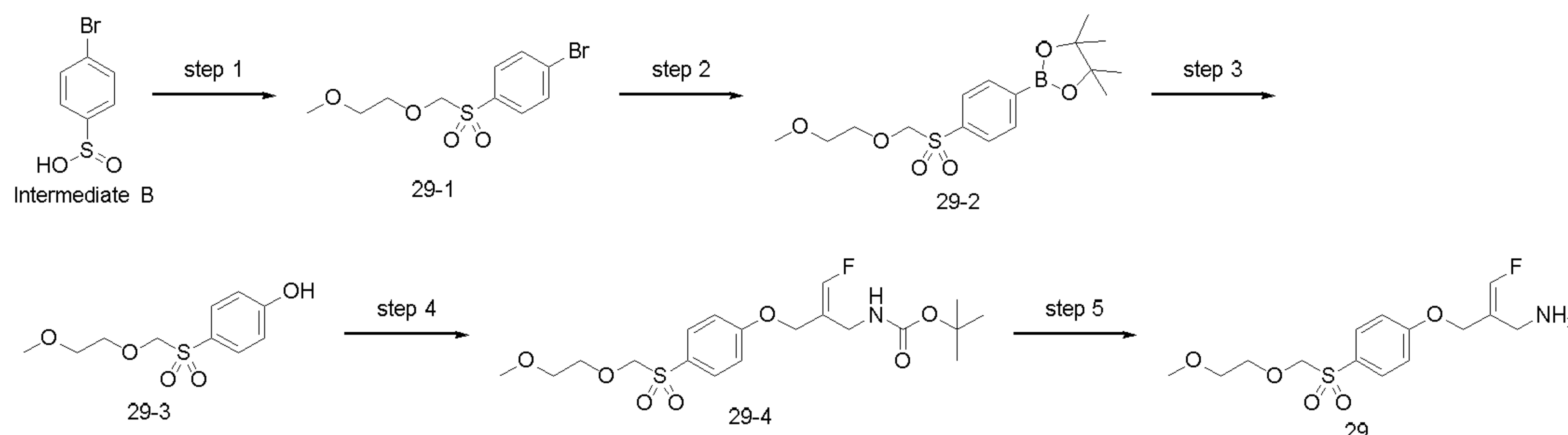
[00435] To a mixture of **28-4** (300 mg, 1.48 mmol) and **Intermediate A** (150 mg, 559.45 μmol) in MeCN (10 mL) was added Cs₂CO₃ (483.35 mg, 1.48 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **28-5** (400 mg, crude). MS: m/z = 389 (M+1, ESI+).

Step 6: Compound 28

[00436] A mixture of **28-5** (200 mg, 513.56 μmol) in HCl/Dioxane (4 M, 4 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 2 - 30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 28** (80 mg, 238.56 μmol, 46.45% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-d₄) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 80.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.72

(dd, $J = 3.6, 1.0$ Hz, 2H), 4.58 (s, 2H), 3.82 (d, $J = 2.3$ Hz, 2H), 3.57 (s, 3H).ppm; MS: $m/z = 420.93$ ($M+1$, ESI+).

Example 35: Synthesis of Compound 29



5 Step 1: 29-1

[00437] A mixture of **Intermediate B** (600 mg, 2.47 mmol) and 1-(chloromethoxy)-2-methoxy-ethane (369.0 mg, 2.96 mmol) in DMF (10 mL) was stirred at 20 °C. The reaction solution was stirred for 8 hr at 100 °C. Then ethyl acetate (100 mL) and H₂O (100 mL) were added, the organic phase was washed with brine (50 mL), dried over Na₂SO₄ and concentrated to give a residue, which was purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/1) to give **29-1** (230 mg, 743.91 μmol, 30.14% yield).

Step 2: 29-2

[00438] A mixture of **29-1** (200 mg, 646.88 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (197.12 mg, 776.26 μmol) in Dioxane (13 mL) was added KOAc (194.37 mg, 1.94 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/1) to obtain **29-2** (150 mg, 421.06 μmol, 65.09% yield). MS: $m/z = 309$ ($M+1$).

Step 3: 29-3

[00439] A mixture of **29-2** (120 mg, 336.85 μmol) in THF (1 mL) and acetic acid (0.25 mL) was added H₂O₂ (0.5 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. Na₂SO₃ (0.2 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **29-3** (350 mg, crude). MS: $m/z = 246$ ($M+1$).

Step 4: 29-4

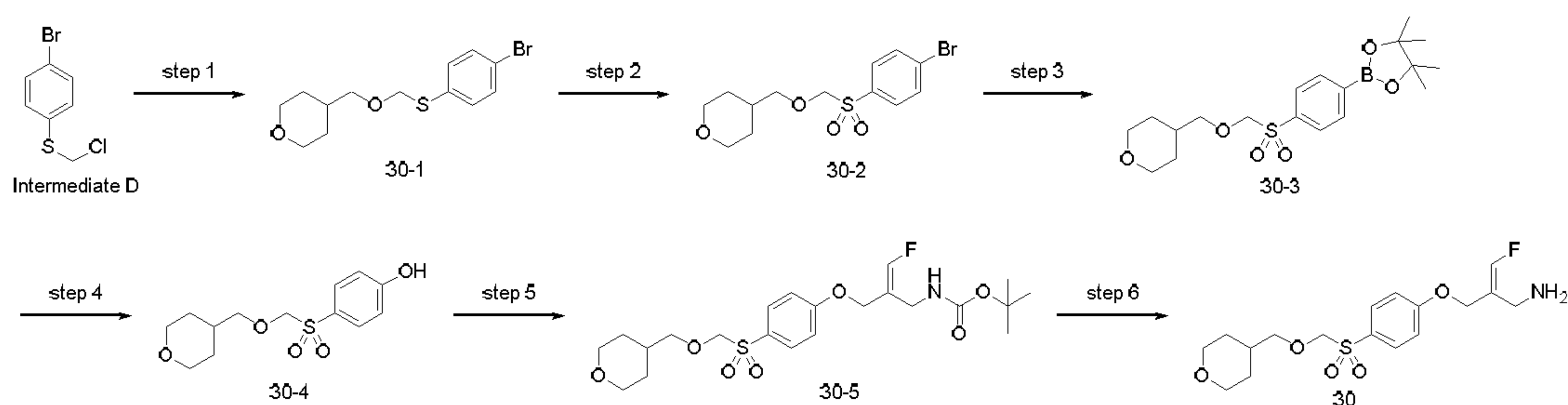
[00440] A mixture of **29-3** (350 mg, 1.42 mmol) and **Intermediate A** (114.31 mg, 426.34 μmol) in MeCN (50 mL) was added Cs₂CO₃ (1.39 g, 4.26 mmol) at 20 °C. The reaction solution

was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **29-4** (230 mg, crude). MS: $m/z = 433$ (M+1).

Step 5: Compound 29

[00441] A mixture of **29-4** (200 mg, 461.37 μmol) in HCl/Dioxane (4 M, 5 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 29** (42 mg, 125.98 μmol , 27.31% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 7.89 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 80.0$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 4.68 (s, 2H), 3.92 (t, $J = 4.4$ Hz, 2H), 3.82 (d, $J = 2.4$ Hz, 2H), 3.49 (t, $J = 4.4$ Hz, 2H), 3.31 (s, 3H). ppm; MS: $m/z = 334.6$ (M+1, ESI+).

Example 36: Synthesis of Compound 30



Step 1: 30-1

[00442] To a mixture of tetrahydropyran-4-ylmethanol (586.79 mg, 5.05 mmol) in DMF (15 mL) was added NaH (218.89 mg, 5.47 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (1.0 g, 4.21 mmol) was added. The reaction solution was stirred for further 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **30-1** (1.1 g, 3.47 mmol, 82.37% yield).

Step 2: 30-2

[00443] To a mixture of **30-1** (600 mg, 1.89 mmol) in DCM (20 mL) was added m-CPBA (1.15 g, 5.67 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL $\times$ 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **30-2** (660 mg, crude).

Step 3: 30-3

[00444] To a mixture of **30-2** (660 mg, 1.89 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (575.87 mg, 2.27 mmol) and KOAc (556.41 mg, 5.67 mmol, 354.40 μ L) in Dioxane (10 mL) was added Pd(dppf)Cl₂ (69.14 mg, 94.49 μ mol) at 20 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave.

5 The mixture was filtered and concentrated to obtain **30-3** (760 mg, crude).

Step 4: 30-4

[00445] To a mixture of **30-3** (760 mg, 1.92 mmol), acetic acid (0.5 mL) in THF (10 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **30-4** (600
10 mg, crude). MS: $m/z = 285$ (M-1).

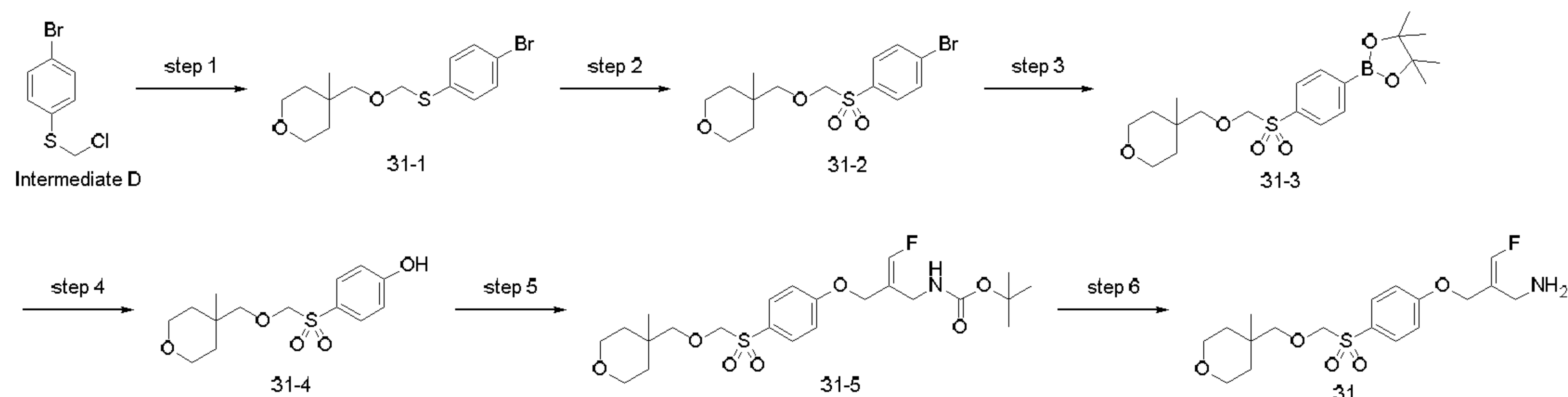
Step 5: 30-5

[00446] To a mixture of **30-4** (600 mg, 2.10 mmol), **Intermediate A** (250 mg, 932.41 μ mol) in Acetonitrile (30 mL) was added Cs₂CO₃ (682.72 mg, 2.10 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was
15 concentrated with a rotary evaporator to obtain **30-5** (620 mg, crude). MS: $m/z = 474$ (M+1).

Step 6: Compound 30

[00447] To a mixture of **30-5** (620 mg, 1.31 mmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 4.00 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC
20 (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 30** (56 mg, 133.50 μ mol, 10.20% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.51 (s, 1H), 7.89 (d, $J = 8.9$ Hz, 2H), 7.27-7.23 (m, 2H), 7.27 (d, $J = 81.0$ Hz, 1H), 4.75 (dd, $J = 3.6, 1.1$ Hz, 2H), 4.67 (s, 2H), 3.92-3.87 (m, 2H), 3.84 (d, $J = 2.2$ Hz, 2H), 3.65 (d, $J = 6.3$ Hz, 2H), 3.39-3.31 (m, 3H),
25 1.81-1.78 (m, 1H), 1.61-1.51 (m, 3H), 1.28 (dtd, $J = 13.5, 11.8, 4.6$ Hz, 3H). MS: $m/z = 374.6$ (M+1, ESI+).

Example 37: Synthesis of Compound 31



Step 1: 31-1

[00448] To a mixture of (4-methyltetrahydropyran-4-yl)methanol (822.06 mg, 6.31 mmol) in DMF (15 mL) was added NaH (269.40 mg, 6.74 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (1.0 g, 4.21 mmol) was added. The reaction solution was stirred for further 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **31-1** (410 mg, 1.24 mmol, 29.40% yield).

Step 2: 31-2

[00449] To a mixture of **31-1** (410 mg, 1.24 mmol) in DCM (20 mL) was added m-CPBA (1.01 g, 4.95 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **31-2** (510 mg, crude).

Step 3: 31-3

[00450] To a mixture of **31-2** (510 mg, 1.40 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (427.81 mg, 1.68 mmol) and KOAc (413.35 mg, 4.21 mmol) in Dioxane (10 mL) was added Pd(dppf)Cl₂ (102.73 mg, 140.39 μmol) at 20 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered and concentrated to obtain **31-3** (320 mg, crude).

Step 4: 31-4

[00451] To a mixture of **31-3** (320 mg, 779.86 μmol), acetic acid (0.4 mL) in THF (15 mL) was added H₂O₂ (0.3 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, to the solution was added Na₂SO₃ (0.5g), filtered and concentrated with a rotary evaporator to obtain **31-4** (180 mg, crude). MS: m/z = 299 (M-1).

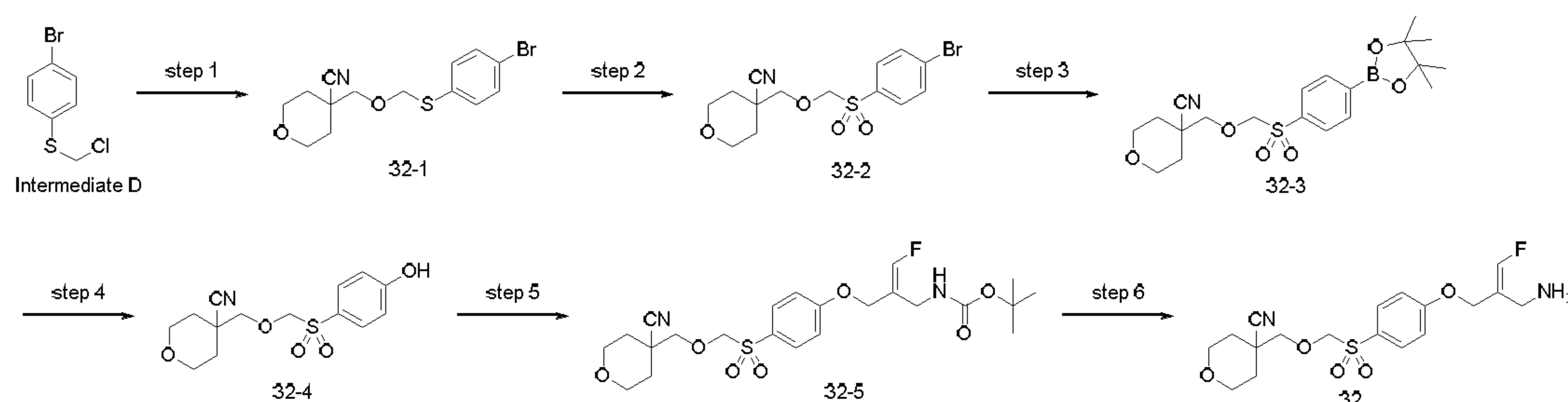
Step 5: 31-5

[00452] To a mixture of **31-4** (180 mg, 599.26 μmol), **Intermediate A** (150 mg, 559.45 μmol) in MeCN (30 mL) was added Cs_2CO_3 (585.75 mg, 1.80 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **31-5** (180 mg, crude). MS: $m/z = 488$ (M+1).

5 Step 6: **Compound 31**

[00453] To a mixture of **31-5** (180 mg, 369.17 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-35% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 31** (43 mg, 99.19 μmol , 26.87% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.90 (d, $J = 8.9$ Hz, 2H), 7.32-7.23 (m, 2H), 7.27 (d, $J = 8.9$ Hz, 1H), 4.75 (d, $J = 3.5$ Hz, 2H), 4.70 (s, 2H), 3.85 (d, $J = 2.2$ Hz, 2H), 3.71-3.54 (m, 6H), 1.54 (ddd, $J = 13.6, 9.0, 4.5$ Hz, 2H), 1.25-1.20 (m, 2H), 0.99 (s, 3H). MS: $m/z = 388.59$ (M+1, ESI+).

15 Example 38: Synthesis of **Compound 32**



Step 1: **32-1**

[00454] To a mixture of 4-(hydroxymethyl)tetrahydropyran-4-carbonitrile (800 mg, 5.67 mmol) in DMF (20 mL) was added NaH (252.56 mg, 6.31 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (1.0 g, 4.21 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 30%) to obtain **32-1** (810 mg, 2.37 mmol, 56.22% yield).

25 Step 2: **32-2**

[00455] To a mixture of **32-1** (400 mg, 1.17 mmol) in DCM (30 mL) was added m-CPBA (949.10 mg, 4.67 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then,

the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **32-2** (460 mg, crude).

Step 3: 32-3

- 5 [00456] To a mixture of **32-2** (400 mg, 1.07 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (325.69 mg, 1.28 mmol) and KOAc (314.68 mg, 3.21 mmol) in Dioxane (10 mL) was added Pd(dppf)Cl₂ (78.20 mg, 106.88 μmol) at 20 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **32-3** (380 mg, crude).

10 *Step 4: 32-4*

[00457] To a mixture of **32-3** (380 mg, 901.94 μmol), acetic acid (0.4 mL) in THF (15 mL) was added H₂O₂ (0.3 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, to the solution was added Na₂SO₃ (0.5g), filtered and concentrated with a rotary evaporator to obtain **32-4** (220 mg, crude). MS: m/z = 310 (M-1).

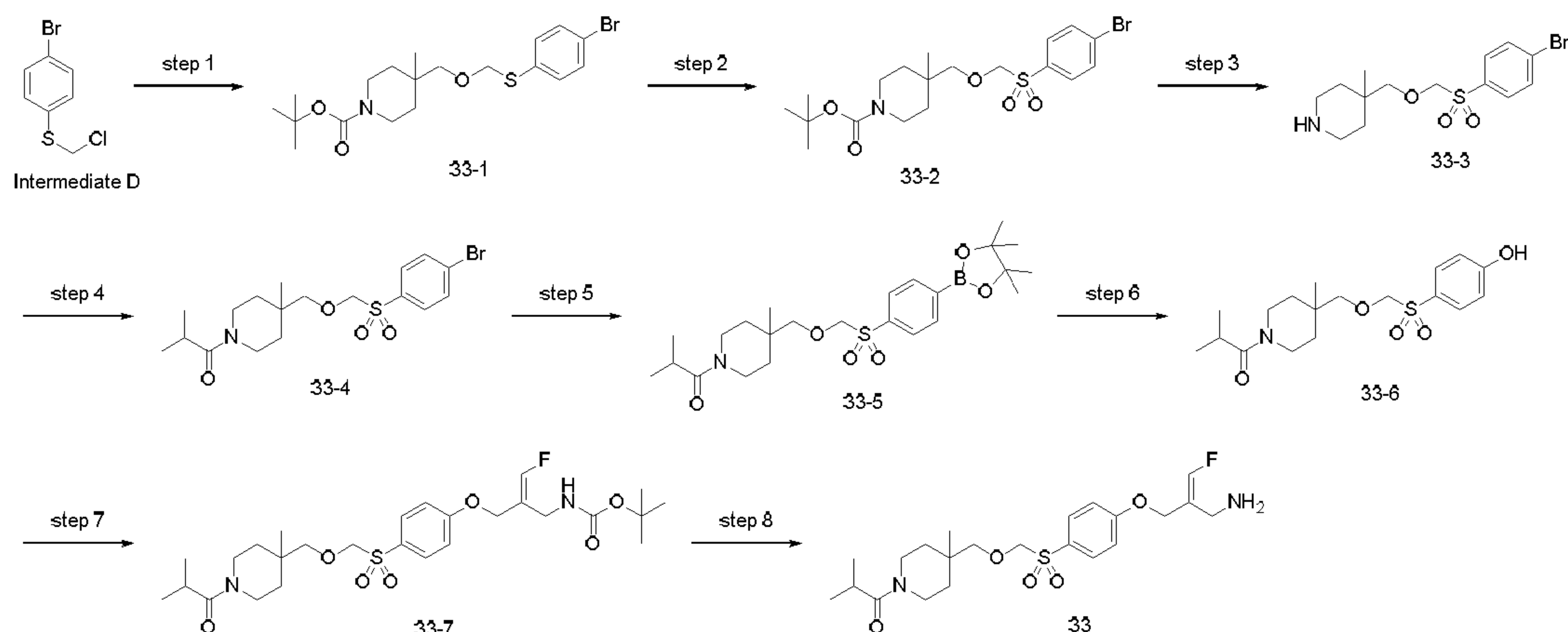
15 *Step 5: 32-5*

[00458] To a mixture of **32-4** (220 mg, 706.59 μmol), **Intermediate A** (120 mg, 447.56 μmol) in MeCN (30 mL) was added Cs₂CO₃ (690.66 mg, 2.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **32-5** (210 mg, crude). MS: m/z = 499 (M+1).

20 *Step 6: Compound 32*

- [00459] To a mixture of **32-5** (210 mg, 421.21 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 32** (86 mg, 193.49 μmol, 45.94% yield, HCO₂H salt).
25 ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.52 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 2H), 7.31-7.19 (m, 2H), 7.26 (d, *J* = 81.1 Hz, 1H), 4.78 (s, 2H), 4.76-4.73 (m, 2H), 3.94 (d, *J* = 10.0 Hz, 4H), 3.83 (d, *J* = 2.2 Hz, 2H), 3.63 (td, *J* = 12.1, 2.1 Hz, 2H), 1.93-1.76 (m, 2H), 1.66-1.60 (m, 2H), 1.22 (s, 2H). MS: m/z = 399.59 (M+1, ESI+).

30 **Example 39: Synthesis of Compound 33**



Step 1: 33-1

[00460] To a mixture of tert-butyl 4-(hydroxymethyl)-4-methyl-piperidine-1-carboxylate (1.74 g, 7.58 mmol) in DMF (15 mL) was added NaH (328.33 mg, 8.21 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, **Intermediate D** (1.5 g, 6.31 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **33-1** (420 mg, 975.84 μmol, 15.45% yield). MS: m/z = 430 (M+1).

Step 2: 33-2

[00461] To a mixture of **33-1** (420 mg, 975.84 μmol) in DCM (30 mL) was added m-CPBA (594.34 mg, 2.93 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **33-2** (510 mg, crude). The crude product was used for the next step without further purification. MS: m/z = 462 (M+1).

Step 3: 33-3

[00462] To a mixture of **33-2** (510 mg, 1.10 mmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 4 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **33-3** (450 mg, crude, HCl salt). MS: m/z = 362 (M+1).

Step 4: 33-4

[00463] To a mixture of **33-3** (200 mg, 501.58 μmol) and Et₃N (152.26 mg, 1.50 mmol) in DCM (20 mL) was added 2-methylpropanoyl chloride (58.79 mg, 551.73 μmol, 57.63 μL) at

20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was washed with H₂O (15 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 70%) to obtain **33-4** (180 mg, 416.31 μmol, 83.0% yield). MS: m/z = 432 (M+1).

Step 5: 33-5

[00464] To a mixture of **33-4** (180 mg, 416.31 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (126.86 mg, 499.57 μmol) and KOAc (122.57 mg, 1.25 mmol) in Dioxane (10 mL) was added Pd(dppf)Cl₂ (30.46 mg, 41.63 μmol) at 20 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **33-5** (220 mg, crude). MS: m/z = 480 (M+1).

Step 6: 33-6

[00465] To a mixture of **33-5** (220 mg, 458.87 μmol), acetic Acid (0.7 mL) in THF (20 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **33-6** (260 mg, crude). MS: m/z = 370 (M+1).

Step 7: 33-7

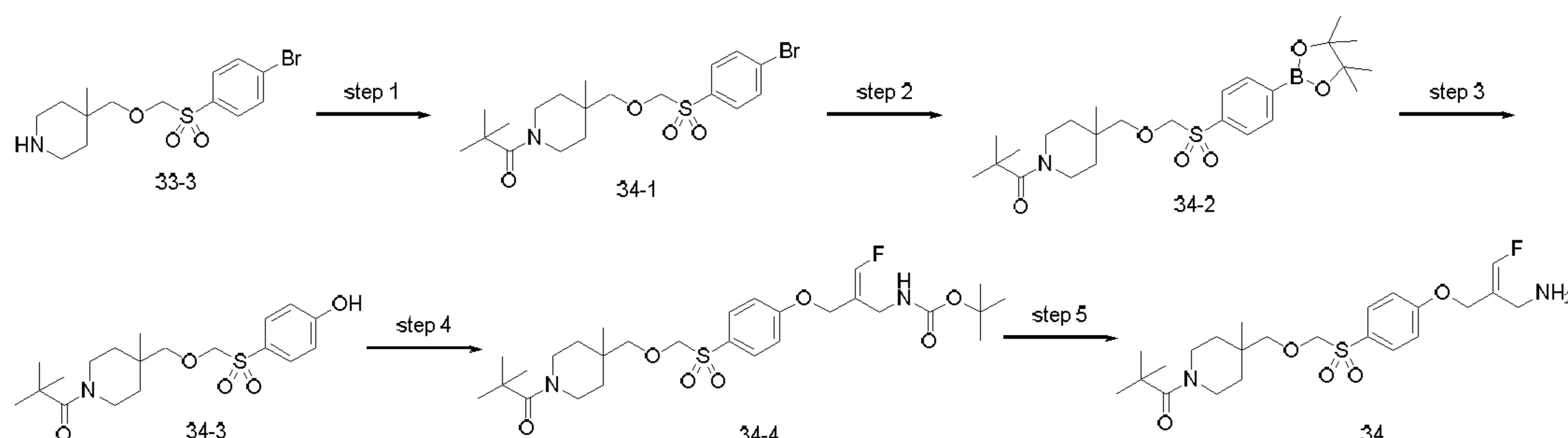
[00466] To a mixture of **33-6** 260 mg, 703.70 μmol), **Intermediate A** (188.68 mg, 703.70 μmol) in MeCN (30 mL) was added Cs₂CO₃ (687.84 mg, 2.11 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 100%) to obtain **33-7** (220 mg, 395.20 μmol, 56.16% yield). MS: m/z = 557 (M+1).

Step 8: Compound 33

[00467] To a mixture of **33-7** (220 mg, 395.20 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 4 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 33** (23 mg, 45.76 μmol, 11.58% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.49 (s, 1H), 7.88 (dd, *J* = 12.5, 8.8 Hz, 2H), 7.28 (d, *J* =

81.0 Hz, 1H), 7.23 (dd, $J = 17.5, 8.8$ Hz, 2H), 4.69 (d, $J = 5.3$ Hz, 2H), 4.13 (s, 1H), 3.84 (d, $J = 2.2$ Hz, 2H), 3.73-3.56 (m, 4H), 3.44 (t, $J = 12.1$ Hz, 2H), 3.26 (d, $J = 10.1$ Hz, 2H), 2.94-2.87 (m, 2H), 1.52 (d, $J = 9.8$ Hz, 1H), 1.46-1.30 (m, 2H), 1.09 (dd, $J = 6.7, 1.1$ Hz, 6H), 0.99 (s, 3H). MS: $m/z = 457.73$ ($M+1$, ESI+).

5 Example 40: Synthesis of Compound 34



Step 1: 34-1

[00468] To a mixture of **33-3** (250 mg, 626.97 μmol) and Et_3N (190.33 mg, 1.88 mmol) in DCM (20 mL) was added 2,2-dimethylpropanoyl chloride (83.16 mg, 689.67 μmol , 84.42 μL) at 20 $^\circ\text{C}$. The reaction solution was stirred for 1 hr at 20 $^\circ\text{C}$. Then, the solution was washed with H_2O (15 mL $\times$ 2) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 70%) to obtain **34-1** (210 mg, 470.43 μmol , 75.03% yield). MS: $m/z = 446$ ($M+1$).

15 Step 2: 34-2

[00469] To a mixture of **34-1** (210 mg, 470.43 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (143.35 mg, 564.52 μmol) and KOAc (138.51 mg, 1.41 mmol) in Dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (34.42 mg, 47.04 μmol) at 20 $^\circ\text{C}$. The reaction solution was heated at 120 $^\circ\text{C}$ for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **34-2** (300 mg, crude). MS: $m/z = 494$ ($M+1$).

Step 3: 34-3

[00470] To a mixture of **34-2** (300 mg, 607.95 μmol), acetic acid (0.5 mL) in THF (15 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 $^\circ\text{C}$. The reaction solution was stirred for 1 hr at 20 $^\circ\text{C}$. Then, the solution was concentrated with a rotary evaporator to obtain **34-3** (320 mg, crude). MS: $m/z = 384$ ($M+1$).

Step 4: 34-4

[00471] To a mixture of **34-3** (320 mg, 834.42 μ mol), **Intermediate A** (223.73 mg, 834.42 μ mol) in MeCN (30 mL) was added Cs_2CO_3 (815.61 mg, 2.50 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was

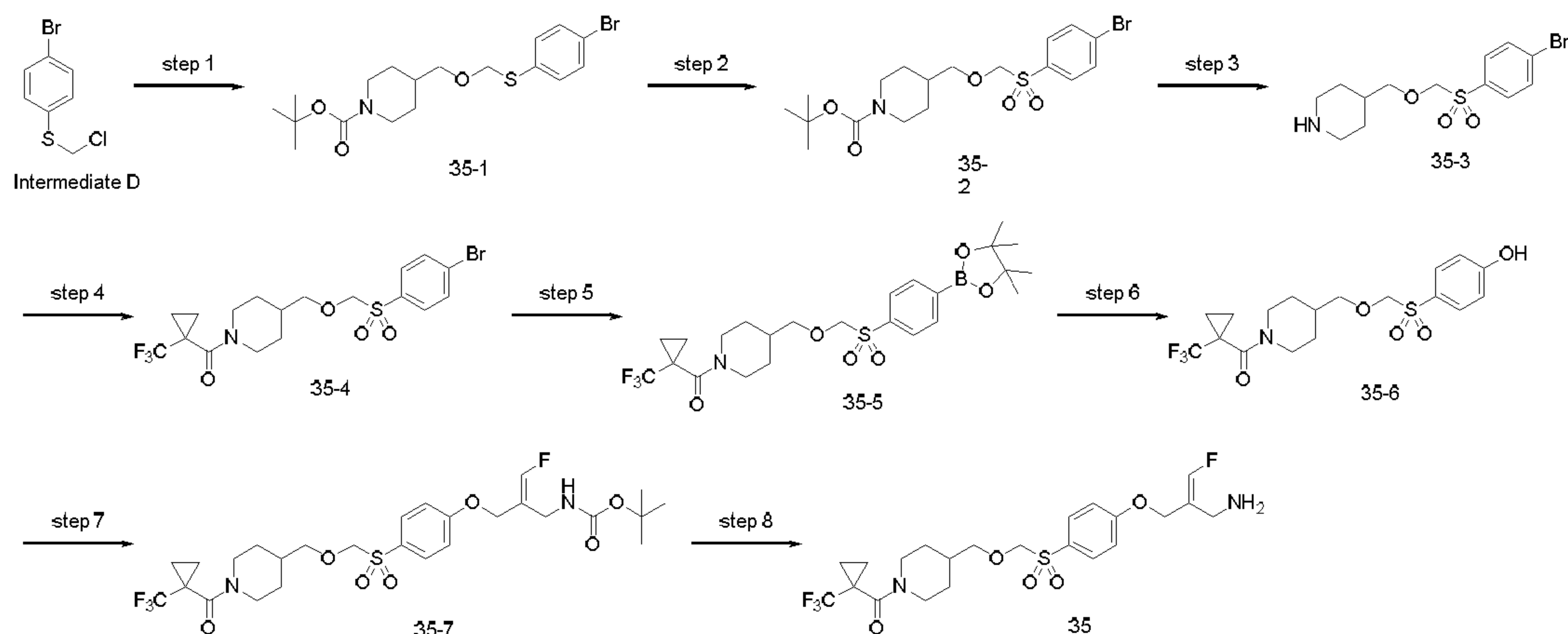
5 concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 100%) to obtain **34-4** (230 mg, 403.01 μ mol, 48.30% yield). MS: $m/z = 571$ (M+1).

Step 5: Compound 34

[00472] To a mixture of **34-4** (230 mg, 403.01 μ mol) in DCM (15 mL) was added

10 HCl/Dioxane (4 M, 4 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 10-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 34** (54 mg, 104.53 μ mol, 25.94% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.90 (d, $J = 8.9$ Hz, 2H), 7.28 (d, $J = 80.9$ Hz, 1H), 7.25 (d, $J = 8.9$ Hz, 2H), 4.75 (d, $J = 3.5$ Hz, 1H), 4.70 (s, 2H), 4.12 (d, $J = 7.6$ Hz, 1H), 3.84 (d, $J = 2.3$ Hz, 3H), 3.61 (d, $J = 4.7$ Hz, 2H), 1.54-1.42 (m, 2H), 1.28 (s, 9H), 0.99 (s, 3H). MS: $m/z = 471.68$ (M+1, ESI+).

15

Example 41: Synthesis of Compound 35*Step 1: 35-1*

[00473] A mixture of Tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (1.81 g, 8.42 mmol), NaH (241.95 mg, 6.31 mmol, 60% purity) in DMF (30 mL) was added **Intermediate D** (1 g, 4.21 mmol) at 0 °C. The reaction solution was stirred for 18 hr at 30 °C. To the mixture was added saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL).

The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (10 ml $\times$ 3). The combined organic extracts were dried over sodium sulfate. The solvent was evaporated under reduced pressure and the crude was purified by flash column chromatography (ethyl acetate in petroleum ether, 10% to 80%) to give **35-1** (500 mg, 1.20 mmol, 28.53% yield).

5 *Step 2: 35-2*

[00474] A mixture of **35-1** (400 mg, 960.68 μ mol) and m-CPBA (487.59 mg, 2.40 mmol, 85% purity) in DCM (50 mL) was stirred at 25 °C for 0.5 hr. Na₂SO₃ (14 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethylacetate = 10/1 – 3/1, v/v) to obtain **35-2** (400 mg, 892.12 μ mol, 92.86% yield).

Step 3: 35-3

[00475] A mixture of **35-2** (400 mg, 892.12 μ mol) in HCl/Dioxane (4 M, 5.0 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **35-3** (320 mg, crude).

15 *Step 4: 35-4*

[00476] A mixture of **35-3** (300 mg, 861.44 μ mol), 1-(trifluoromethyl)cyclopropanecarboxylic acid (132.74 mg, 861.44 μ mol) and TEA (261.51 mg, 2.58 mmol) in DCM (30 mL) was added HATU (491.32 mg, 1.29 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80 mL), washed with H₂O (100 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated to give **35-4** (280 mg, crude). MS: m/z = 384 (M+1).

Step 5: 35-5

[00477] A 30 mL microwave reaction tube was charged with **35-4** (250 mg, 516.18 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (196.62 mg, 774.27 μ mol) and cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (37.77 mg, 51.62 μ mol) and KOAc (151.98 mg, 1.55 mmol) in Dioxane (10 mL). After O₂ was purged by bubbling N₂ into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0-100%) to deliver **35-5** (300 mg, crude). MS: m/z = 531 (M+1).

Step 6: 35-6

[00478] To a mixture of **35-5** (300 mg, 564.56 μ mol) in THF (25 mL) and acetic acid (1 mL) was added H_2O_2 (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Na_2SO_3 (0.7 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and

5 concentrated to give **35-6** (1.2 g, crude). MS: $m/z = 421$ (M+1).

Step 7: 35-7

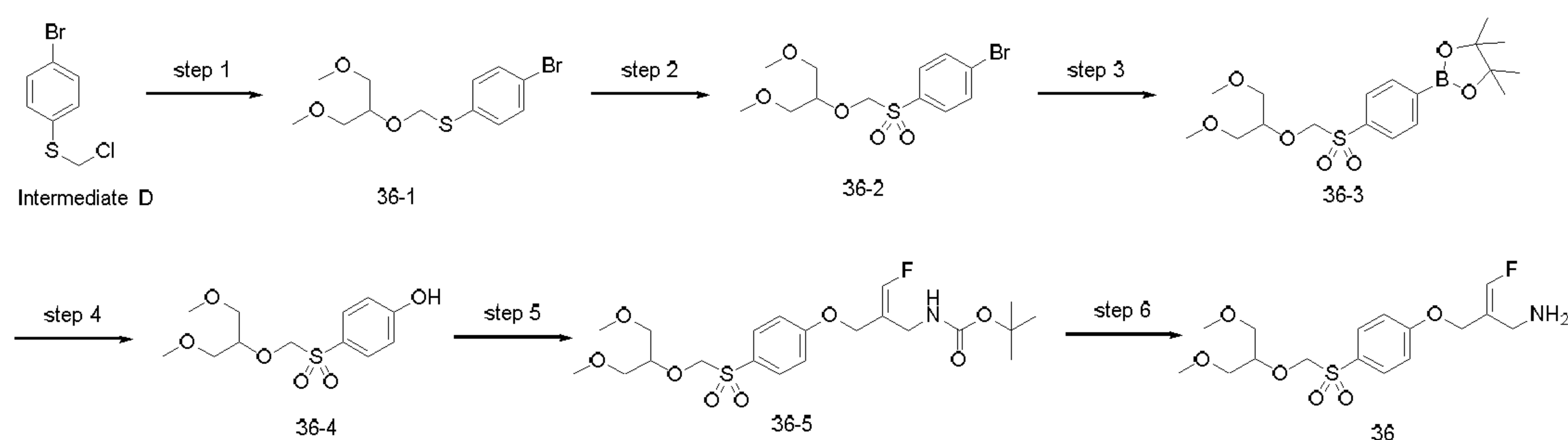
[00479] A mixture of **35-6** (1 g, crude) and **Intermediate A** (254.49 mg, 949.15 μ mol) in MeCN (50 mL) was added Cs_2CO_3 (2.32 g, 7.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **35-7** (300 mg,

10 crude). MS: $m/z = 608$ (M+1).

Step 8: Compound 35

[00480] A mixture of **35-7** (200 mg, 328.60 μ mol) in HCl/Dioxane (4 M, 4 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO_2H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 35** (43.2 mg, 84.95 μ mol, 25.85% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 80.0$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 4.65 (s, 2H), 4.36 (s, 2H), 3.78 (d, $J = 2.4$ Hz, 2H), 3.67 (d, $J = 6.0$ Hz, 2H), 3.10-3.06 (m, 2H), 1.84 (s, 1H), 1.70 (d, $J = 13.2$ Hz, 2H), 1.34 (s, 2H), 1.20-1.17 (s, 4H). ppm; MS: $m/z = 509.5$ (M+1, ESI+).

15

Example 42: Synthesis of Compound 36*Step 1: 36-1*

[00481] To a mixture of 1,3-dimethoxypropan-2-ol (400 mg, 3.33 mmol) in DMF (15 mL) was added NaH (159.79 mg, 4.00 mmol, 60% purity) at 25 °C. The reaction solution was

25 stirred for 0.5 hr at 25 °C. Then, **Intermediate D** (790.84 mg, 3.33 mmol) was added. The reaction solution was stirred further for 18 hr at 25 °C. Then, the solution was concentrated with

a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 40%) to obtain **36-1** (310 mg, 965.04 μ mol, 28.99% yield).

Step 2: 36-2

5 [00482] To a mixture of **36-1** (310 mg, 965.04 μ mol) in DCM (25 mL) was added m-CPBA (783.69 mg, 3.86 mmol, 85% purity) at 25 °C. The mixture was stirred for 1 hr at 25 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (10 mL), saturated aqueous NaHCO₃ (20 mL $\times$ 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **36-2** (360 mg, crude).

Step 3: 36-3

10 [00483] To a mixture of **36-2** (360 mg, 1.02 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (310.57 mg, 1.22 mmol) and KOAc (300.07 mg, 3.06 mmol) in Dioxane (9 mL) was added Pd(dppf)Cl₂ (74.57 mg, 101.92 μ mol) at 25 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **36-3** (360 mg, crude).

15 **Step 4: 36-4**

[00484] To a mixture of **36-3** (360 mg, 899.34 μ mol), acetic acid (0.3 mL) in THF (20 mL) was added H₂O₂ (0.3 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, to the solution was added Na₂SO₃ (0.5g), filtered and concentrated with a rotary evaporator to obtain **36-4** (330 mg, crude). MS: m/z = 289 (M-1).

20 **Step 5: 36-5**

[00485] To a mixture of **36-4** (330 mg, 1.14 mmol), **Intermediate A** (180 mg, 671.33 μ mol) in MeCN (30 mL) was added Cs₂CO₃ (1.11 g, 3.41 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **36-5** (220 mg, crude). MS: m/z = 478 (M+1).

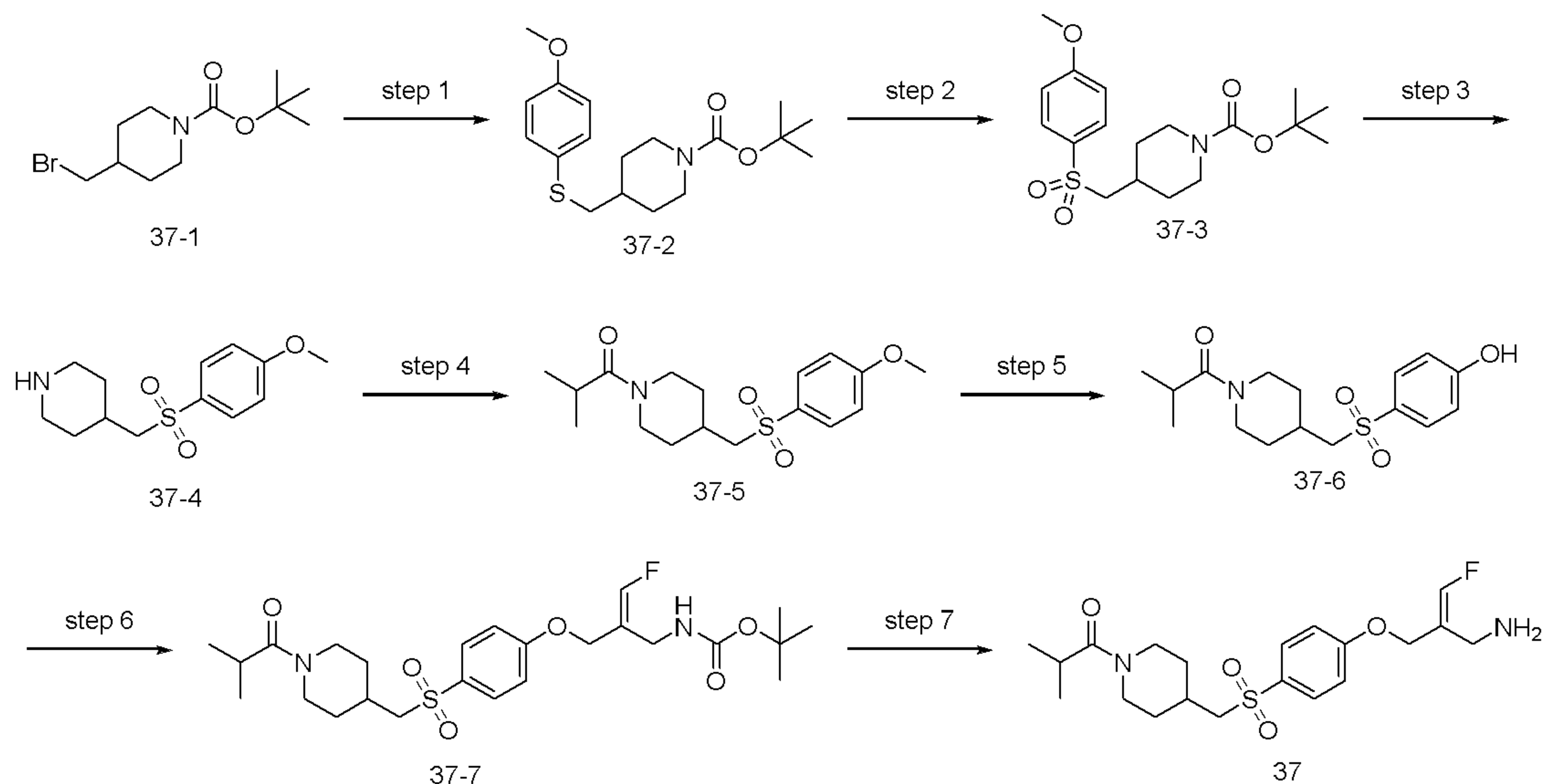
25 **Step 6: Compound 36**

[00486] To a mixture of **36-5** (220 mg, 460.69 μ mol) in DCM (20 mL) was added HCl/Dioxane (4 M, 3 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 36** (86 mg, 203.09 μ mol, 44.08% yield, HF). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.93 (d, *J* = 9.3 Hz, 2H), 7.26 (d, *J* = 81.0 Hz, 1H), 7.24 (d, *J* =

30

8.9 Hz, 2H), 4.83 (s, 2H), 4.75 (d, $J = 3.5$ Hz, 1H), 4.19-3.98 (m, 2H), 3.83 (d, $J = 2.3$ Hz, 2H), 3.53-3.39 (m, 7H), 3.33 (s, 6H). MS: $m/z = 378.63$ ($M+1$, ESI+).

Example 43: Synthesis of Compound 37



5 Step 1: 37-2

[00487] To a mixture of 4-methoxybenzenethiol (300 mg, 2.14 mmol, 263.16 μ L) and **37-1** (595.25 mg, 2.14 mmol) in MeCN (10 mL) was added Cs_2CO_3 (1.39 g, 4.28 mmol) at 30 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **37-2** (700 mg, crude).

10 Step 2: 37-3

[00488] To a mixture of **37-2** (700 mg, 2.07 mmol) and m-CPBA (1.43 g, 8.30 mmol) in DCM (10 mL) was stirred at 20 °C for 1 hr. Na_2SO_3 (4 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (petroleum ether/ethylacetate = 5/1 – 1/1, v/v) to obtain **37-3** (300 mg, 811.96 μ mol, 39.15% yield). MS: $m/z = 370$ ($M+1$).

15 Step 3: 37-4

[00489] To a mixture of **37-3** (300 mg, 811.96 μ mol) in HCl/Dioxane (4 M, 2.0 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **37-4** (290 mg, 948.27 μ mol, 116.79% yield, HCl salt). MS: $m/z = 270$ ($M+1$).

20 Step 4: 37-5

[00490] To a mixture of **37-4** (200 mg, 742.50 μ mol) and TEA (225.40 mg, 2.23 mmol) in DCM (5 mL) was added 2-methylpropanoyl chloride (94.94 mg, 891.00 μ mol) at 0 °C. The

reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80 mL), washed with H₂O (100 mL × 3), dried over Na₂SO₄, filtered and concentrated to obtain **37-5** (200 mg, crude). MS: m/z = 340 (M+1).

5 **Step 5: 37-6**

[00491] To a mixture of **37-5** (200 mg, 589.19 μmol) in DCM (10 mL) was added BBr₃ (442.82 mg, 1.77 mmol) was stirred at 0 °C under the nitrogen atmosphere. The mixture was stirred at 40 °C for 1 hr. MeOH (4 mL) was added and stirred for 15 min. The reaction mixture was concentrated to give **37-6** (300 mg, crude, HBr salt), which was used in the next step without purification. MS: m/z = 326 (M+1).

Step 6: 37-7

[00492] To a mixture of **37-6** (300 mg, 921.88 μmol) and **Intermediate A** (120 mg, 447.11 μmol) in MeCN (20 mL) was added Cs₂CO₃ (901.10 mg, 2.77 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **37-7** (300 mg, crude). MS: m/z = 513 (M+1).

Step 7: Compound 37

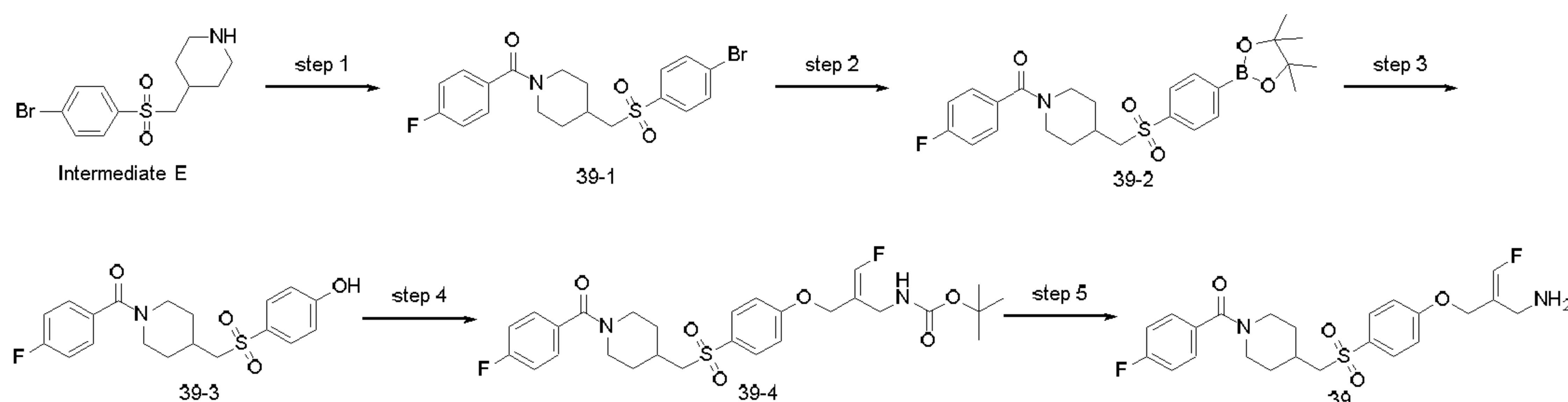
[00493] To a mixture of **37-7** (200 mg, 384.15 μmol) in HCl/Dioxane (4 M, 2.0 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 37** (18 mg, 42.80 μmol, 11.14% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.49 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 80.0 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 4.71 (d, *J* = 3.3 Hz, 2H), 4.44 (d, *J* = 12.8 Hz, 1H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.80 (d, *J* = 1.6 Hz, 2H), 3.17 (d, *J* = 6.4 Hz, 2H), 3.09 (t, *J* = 12.4 Hz, 1H), 2.91 (dt, *J* = 13.2, 6.7 Hz, 1H), 2.62 (t, *J* = 11.4 Hz, 1H), 2.16 (dd, *J* = 12.8, 9.0 Hz, 1H), 1.98 (d, *J* = 12.8 Hz, 1H), 1.83 (d, *J* = 13.2 Hz, 1H), 1.40-1.14 (m, 2H), 1.06 (t, *J* = 6.4 Hz, 6H) ppm; MS: m/z = 413.20 (M+1, ESI+).

[00494] The compounds of Formula (I') or (I) in Table 2 below were made according to **Example 43** of *Compound 37*.

Table 2

Cmpd No.	¹ H NMR and/or LC/MS data
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Cmpd No.	¹ H NMR and/or LC/MS data
38	¹ H NMR (400 MHz, Methanol-d ₄) δ 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.24 (d, <i>J</i> = 80.0 Hz, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 2H), 4.71 (d, <i>J</i> = 3.6 Hz, 2H), 3.81 (d, <i>J</i> = 2.4 Hz, 2H), 3.65 (dt, <i>J</i> = 12.4, 3.6 Hz, 2H), 3.19 (d, <i>J</i> = 6.3 Hz, 2H), 2.80 (s, 3H), 2.73 (td, <i>J</i> = 12.0, 2.4 Hz, 2H), 2.12-2.00 (m, 1H), 1.96 (d, <i>J</i> = 13.6 Hz, 2H), 1.47-1.37 (m, 2H) ppm; MS: <i>m/z</i> = 421.07 (M+1, ESI+).

Example 44: Synthesis of Compound 39**Step 1: 39-1**

- 5 **[00495]** To a mixture of **Intermediate E** (380 mg, 1.07 mmol, HC), Et₃N (433.64 mg, 4.29 mmol) in DCM (20 mL) was added 4-fluorobenzoyl chloride (169.87 mg, 1.07 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 60%) to obtain **39-1** (320 mg, 726.73 μmol, 67.83% yield). MS: *m/z* = 441 (M+1).

Step 2: 39-2

- 15 **[00496]** To a mixture of **39-1** (320 mg, 726.73 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (221.45 mg, 872.08 μmol) and KOAc (213.97 mg, 2.18 mmol) in Dioxane (8 mL) was added Pd(dppf)Cl₂ (53.18 mg, 72.67 μmol) at 20 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered, and the filtrate was concentrated. The residual material was dissolved in DCM (15 mL), washed with H₂O (15 mL) and brine (15 mL) and concentrated with a rotary evaporator to obtain **39-2** (410 mg, crude). MS: *m/z* = 488 (M+1).

Step 3: 39-3

[00497] To a mixture of **39-2** (410 mg, 841.21 μmol), acetic acid (0.2 mL) in THF (7 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **39-3** (420 mg, crude). MS: $m/z = 378$ (M+1).

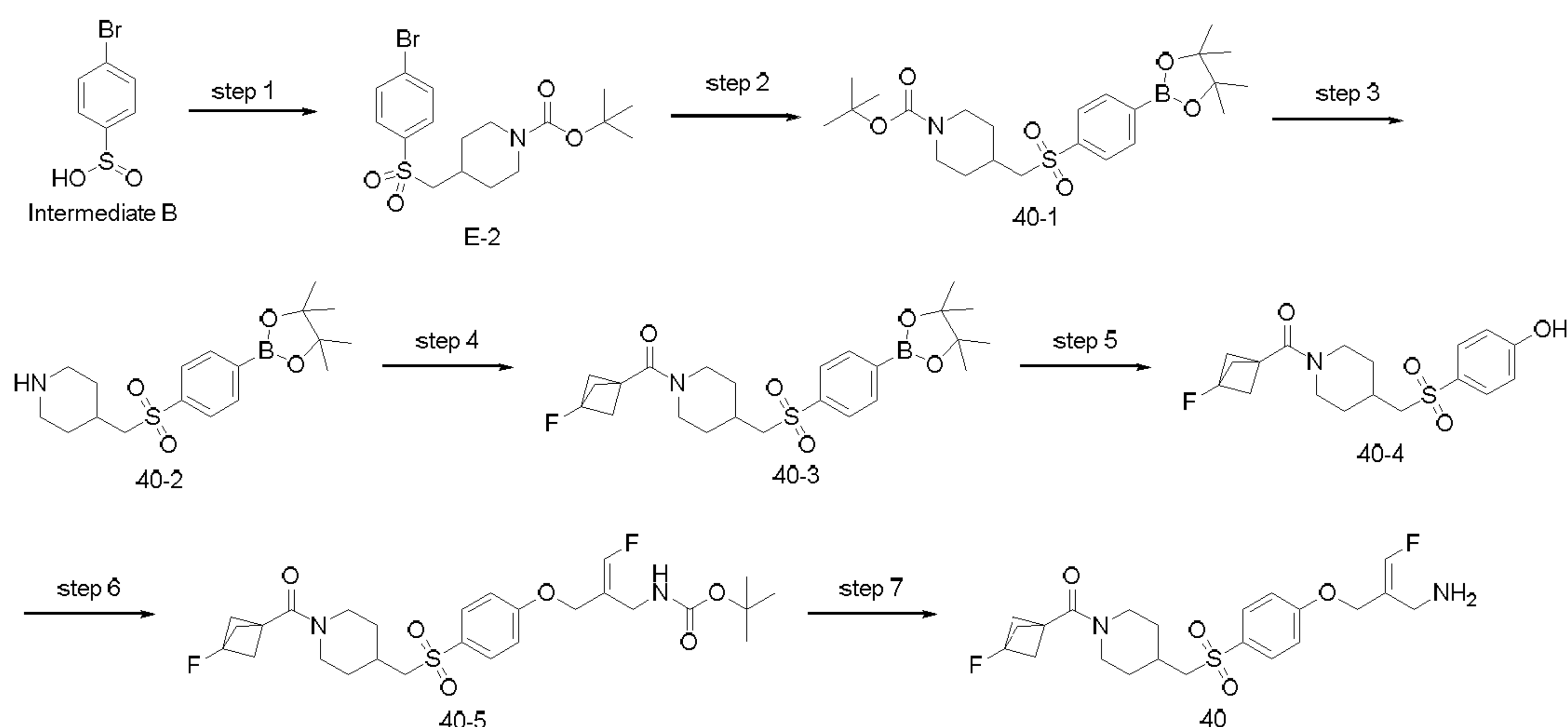
5 **Step 4: 39-4**

[00498] To a mixture of **39-3** (410 mg, 1.09 mmol), **Intermediate A** (100 mg, 372.96 μmol) in MeCN (20 mL) was added Cs_2CO_3 (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **39-4** (220 mg, crude). MS: $m/z = 565$ (M+1).

10 **Step 5: Compound 39**

[00499] To a mixture of **39-4** (220 mg, 389.63 μmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 2 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 39** (35 mg, 68.55 μmol , 17.59% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.49-7.39 (m, 2H), 7.26-7.14 (m, 4H), 7.22 (d, $J = 81.1$ Hz, 1H), 4.72 (d, $J = 3.5$ Hz, 2H), 4.51 (s, 1H), 3.80 (d, $J = 2.2$ Hz, 2H), 3.66 (s, 1H), 3.30-3.25 (m, 1H), 3.20 (d, $J = 6.3$ Hz, 2H), 3.11 (s, 1H), 2.96-2.79 (m, 1H), 2.19-2.14 (m, 1H), 1.89 (d, $J = 34.6$ Hz, 2H), 1.34 (d, $J = 19.0$ Hz, 2H). MS: $m/z = 464.90$ (M+1, ESI+).

Example 45: Synthesis of Compound 40



Step 1: E-2

[00500] To a mixture of **Intermediate B** (1 g, 4.52 mmol), tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (1.51 g, 5.43 mmol) in MeCN (20 mL) was added Cs₂CO₃ (4.42 g, 13.57 mmol) at 20 °C. The reaction solution was stirred for 4 hr at 80 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether/ethylacetate = 4/1, v/v) to obtain **E-2** (1.2 g, 2.87 mmol, 63.41% yield).

Step 2: 40-1

[00501] A 30 mL microwave reaction tube was charged with **E-2** (1.2 g, 2.87 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.09 g, 4.30 mmol) cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (209.89 mg, 286.84 µmol) and KOAc (844.55 mg, 8.61 mmol) in Dioxane (10 mL). After O₂ was purged by bubbling N₂ into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0-100%) to give **40-1** (1 g, 2.15 mmol, 74.91% yield). MS: m/z = 465 (M+1).

Step 3: 40-2

[00502] A mixture of **40-1** (1 g, 2.15 mmol) in HCl/Dioxane (4 M, 15 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated to obtain **40-2** (800 mg, crude, HCl salt). MS: m/z = 365 (M+1).

Step 4: 40-3

[00503] To a mixture of **40-2** (300 mg, 746.72 µmol), 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (97.16 mg, 746.72 µmol) in DCM (10 mL) was added TEA (226.68 mg, 2.24 mmol) and HATU (425.89 mg, 1.12 mmol) at 30 °C. The reaction solution was stirred for 1 hr at 30 °C. Then, ethyl acetate (100 mL) was added and the mixture was washed with H₂O (100 mL × 3), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel chromatography (petroleum ether/ethylacetate = 5/1 - 1/1, v/v) to obtain **40-3** (200 mg, 418.94 µmol, 56.10% yield). MS: m/z = 477 (M+1).

Step 5: 40-4

[00504] To a mixture of **40-3** (200 mg, 418.94 µmol) in THF (2 mL) and acetic acid (0.5 mL) was added H₂O₂ (1 mL, 30% purity). The mixture was stirred at 20 °C for 0.5 hr. Na₂SO₃

(0.3 g) was added to the mixture and stirred for 0.5 hr. The reaction mixture then filtered and concentrated to give **40-4** (0.5 g, crude). MS: $m/z = 367$ (M+1).

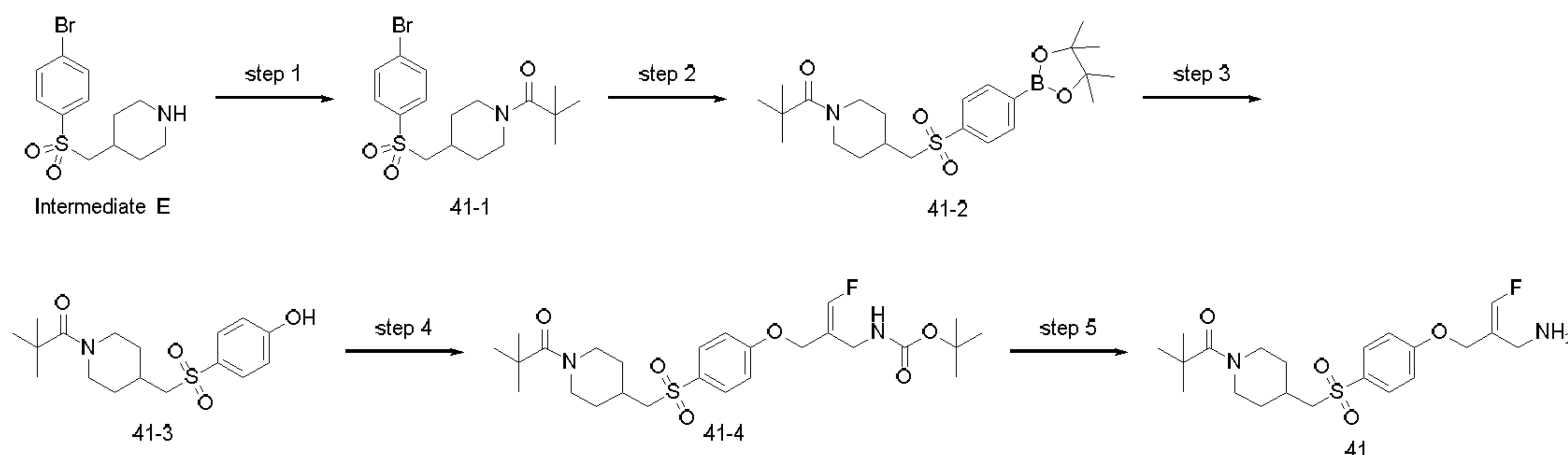
Step 6: 40-5

[00505] A mixture of **40-4** (0.5 g, crude) and **Intermediate A** (437.83 mg, 1.63 mmol) in MeCN (30 mL) was added Cs₂CO₃ (886.74 mg, 2.72 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **40-5** (400 mg, crude). MS: m/z = 554 (M+1).

Step 7: Compound 40

[00506] A mixture of **40-5** (400 mg, 721.18 μmol) in HCl/Dioxane (4 M, 8 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 40** (60 mg, 132.0 μmol , 18.30% yield). ¹H NMR (400 MHz, Methanol-d₄) δ 8.50 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 80.0 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 4.71 (d, J = 3.6 Hz, 2H), 4.38 (d, J = 13.6 Hz, 1H), 4.02 (d, J = 13.6 Hz, 1H), 3.80 (s, 2H), 3.17 (d, J = 6.0 Hz, 2H), 3.10 (t, J = 12.8 Hz, 1H), 2.67 (t, J = 12.8 Hz, 1H), 2.39 (t, J = 3.2 Hz, 5H), 2.23-2.12 (m, 1H), 1.97 (d, J = 13.6 Hz, 1H), 1.83 (d, J = 13.6 Hz, 1H), 1.28-1.22 (m, 3H) ppm; MS: m/z = 455.6 (M+1, ESI+).

Example 46: Synthesis of Compound 41



20 *Step 1: 41-1*

[00507] To a mixture of **Intermediate E** (340 mg, 1.07 mmol) and TEA (324.34 mg, 3.21 mmol, 446.75 μ L) in DCM (10 mL) was added 2,2-dimethylpropanoyl chloride (167.47 mg, 1.39 mmol) at 0 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80 mL), washed with H₂O (100 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated to obtain **41-1** (300 mg, 745.63 μ mol, 69.79% yield).

Step 2: 41-2

[00508] A mixture of **41-1** (300 mg, 745.63 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (227.21 mg, 894.75 μmol) and KOAc (351.22 mg, 2.24 mmol) in Dioxane (20 mL) was added cyclopentyl(diphenyl)phosphane; dichloropalladium;iron (54.56 mg, 74.56 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator to give a residue, which was purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/0) to give **41-2** (200 mg, 445.03 μmol , 59.68% yield). MS: $m/z = 449$ (M+1).

Step 3: 41-3

[00509] A mixture of **41-2** (200 mg, 445.03 μmol) in acetic acid (1 mL) and THF (5 mL) was added H_2O_2 (1 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. Na_2SO_3 (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered concentrated to give **41-3** (152 mg, 447.78 μmol , 100.62% yield). MS: $m/z = 339$ (M+1).

Step 4: 41-4

[00510] A mixture of **41-3** (120 mg, 353.51 μmol) and **Intermediate A** (94.79 mg, 353.51 μmol) in MeCN (10 mL) was added Cs_2CO_3 (345.55 mg, 1.06 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80°C. Then, the solution was filtered and concentrated to obtain **41-4** (180 mg, crude). MS: $m/z = 526$ (M+1).

Step 5: Compound 41

[00511] A mixture of **41-4** (150 mg, 284.81 μmol) in HCl/Dioxane (4 M, 4 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain

Compound 41 (20 mg, 46.89 μmol , 16.46% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 8.48 (s, 1H), 7.89 (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 80.0$ Hz, 1H), 7.22 (d, $J = 8.6$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 4.48 (d, $J = 13.2$ Hz, 1H), 4.02 (d, $J = 14.4$ Hz, 1H), 3.81 (d, $J = 2.4$ Hz, 2H), 3.17 (d, $J = 6.4$ Hz, 2H), 3.07 (d, $J = 13.2$ Hz, 1H), 2.61 (t, $J = 12.4$ Hz, 1H), 2.17-2.14 (m, 1H), 1.95 (d, $J = 13.2$ Hz, 1H), 1.83 (d, $J = 13.2$ Hz, 1H), 1.35-1.31 (m, 1H), 1.22-1.18 (m, 1H), 1.02 (s, 9H) ppm; MS: $m/z = 427.24$ (M+1, ESI+).

[00512] The compounds of Formula (I') or (I) in Table 3 below were made according to **Example 45** of *Compound 40*.

Table 3

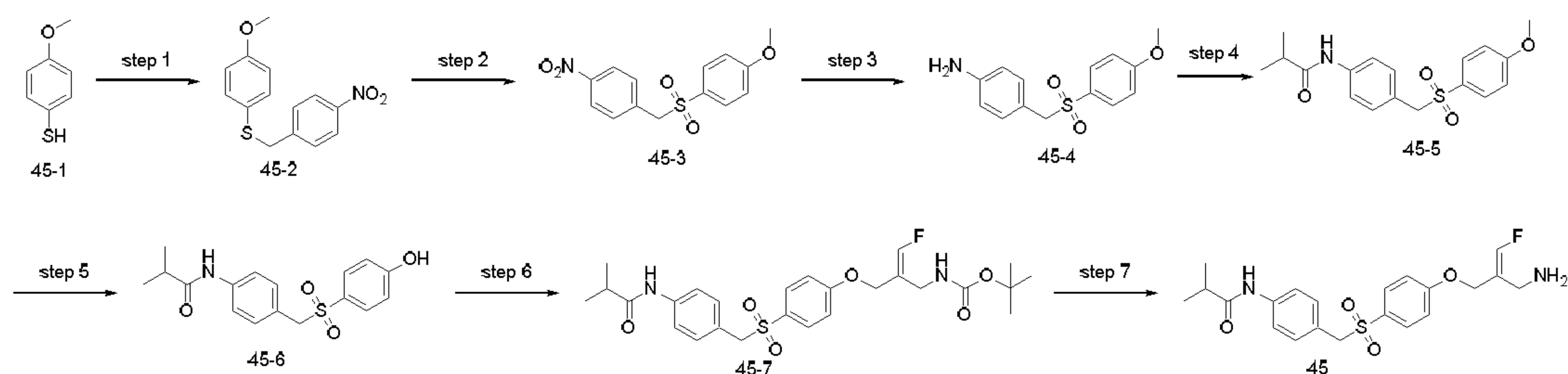
Cmpd No.	¹ H NMR and/or LC/MS data
42	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.50 (s, 1H), 7.91 (d, <i>J</i> = 8.9 Hz, 2H), 7.27 (d, <i>J</i> = 81.0 Hz, 1H), 7.25 (d, <i>J</i> = 8.9 Hz, 2H), 4.74 (d, <i>J</i> = 3.5 Hz, 2H), 4.51 (d, <i>J</i> = 13.4 Hz, 1H), 4.04 (d, <i>J</i> = 13.9 Hz, 1H), 3.84 (d, <i>J</i> = 2.2 Hz, 2H), 3.20 (dd, <i>J</i> = 6.3, 1.5 Hz, 3H), 3.11-3.03 (m, 2H), 2.64-2.59 (m, 1H), 2.44-2.25 (m, 3H), 2.17 (dd, <i>J</i> = 11.4, 6.3 Hz, 1H), 1.92 (dd, <i>J</i> = 46.2, 13.0 Hz, 3H), 1.40-1.15 (m, 3H), 1.04 (s, 9H). MS: <i>m/z</i> = 441.70 (M+1, ESI+).
43	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.43 (s, 1H), 7.79 (d, <i>J</i> = 8.9 Hz, 2H), 7.12 (d, <i>J</i> = 8.8 Hz, 2H), 7.05 (d, <i>J</i> = 81.7 Hz, 1H), 4.61 (d, <i>J</i> = 3.5 Hz, 2H), 4.34 (d, <i>J</i> = 13.5 Hz, 3H), 3.61 (s, 2H), 3.07 (dd, <i>J</i> = 6.3, 4.1 Hz, 3H), 2.75 (t, <i>J</i> = 12.9 Hz, 3H), 2.14-2.00 (m, 2H), 1.92 (s, 5H), 1.88 (d, <i>J</i> = 2.9 Hz, 9H), 1.84-1.75 (m, 4H), 1.67 (d, <i>J</i> = 3.0 Hz, 10H), 1.16-1.12 (m, 4H). MS: <i>m/z</i> = 505.73 (M+1, ESI+).

5 [00513] The compounds of Formula (I') or (I) in Table 4 below were made according to **Example 46** of *Compound 41*.

Table 4

Cmpd No.	¹ H NMR and/or LC/MS data
44	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.50 (s, 1H), 7.89 (d, <i>J</i> = 8.0 Hz, 2H), 7.23 (d, <i>J</i> = 80.0 Hz, 1H), 7.22 (d, <i>J</i> = 8.0 Hz, 2H), 4.71 (d, <i>J</i> = 3.6 Hz, 2H), 4.41-4.21 (m, 2H), 3.80 (d, <i>J</i> = 2.4 Hz, 2H), 3.18 (d, <i>J</i> = 6.4 Hz, 3H), 2.66 (t, <i>J</i> = 12.8 Hz, 1H), 2.19 (dd, <i>J</i> = 10.4, 5.2 Hz, 1H), 2.04-1.88 (m, 2H), 1.82 (d, <i>J</i> = 13.2 Hz, 1H), 1.36 (d, <i>J</i> = 12.8 Hz, 1H), 1.21 (d, <i>J</i> = 12.8 Hz, 1H), 0.86-0.70 (m, 4H) ppm; MS: <i>m/z</i> = 411.1 (M+1, ESI+).

Example 47: Synthesis of Compound 45

**Step 1: 45-2**

[00514] To a mixture of **45-1** (500 mg, 3.57 mmol) in DMF (10 mL) was added NaH (156.90 mg, 3.92 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, 1-(bromomethyl)-4-nitro-benzene (785.83 mg, 3.64 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 10%) to give **45-2** (850 mg, 3.09 mmol, 86.57% yield).

Step 2: 45-3

[00515] To a mixture of **45-2** (500 mg, 1.82 mmol) in DCM (30 mL) was added m-CPBA (1.11 g, 5.45 mmol, 85% purity) at 20 °C. The mixture was stirred for 2 hr at 20 °C. Then, the solution was washed with saturated aqueous Na₂SO₃ (15 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator to obtain **45-3** (550 mg, crude).

Step 3: 45-4

[00516] To a mixture of **45-3** (550 mg, 1.79 mmol) in MeOH (20 mL) was added Pd/C (217.35 mg, 178.97 μmol, 10% purity) at 20 °C. The reaction solution was stirred for 18 hr at 20 °C under H₂ atmosphere. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **45-4** (510 mg, crude). MS: m/z = 278 (M+1).

Step 4: 45-5

[00517] To a mixture of **45-4** (510 mg, 1.84 mmol), Et₃N (558.23 mg, 5.52 mmol) in DCM (40 mL) was added 2-methylpropanoyl chloride (195.94 mg, 1.84 mmol) at 20 °C. The reaction solution was stirred for 2 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 60%) to obtain **45-5** (330 mg, 949.84 μmol, 51.65% yield). MS: m/z = 348 (M+1).

Step 5: 45-6

[00518] To a mixture of **45-5** (330 mg, 949.84 μmol) in DCM (15 mL) was added BBr_3 (0.5 mL, 5.29 mmol) at 0 °C. The reaction mixture was stirred for 1 hr at 20 °C. Then, the solution was quenched with MeOH (20 mL) at 0 °C, and stirred for 0.25 hr at 20 °C. The solution was concentrated with a rotary evaporator to obtain **45-6** (330 mg, crude). MS: $m/z = 332$ ($M+1$).

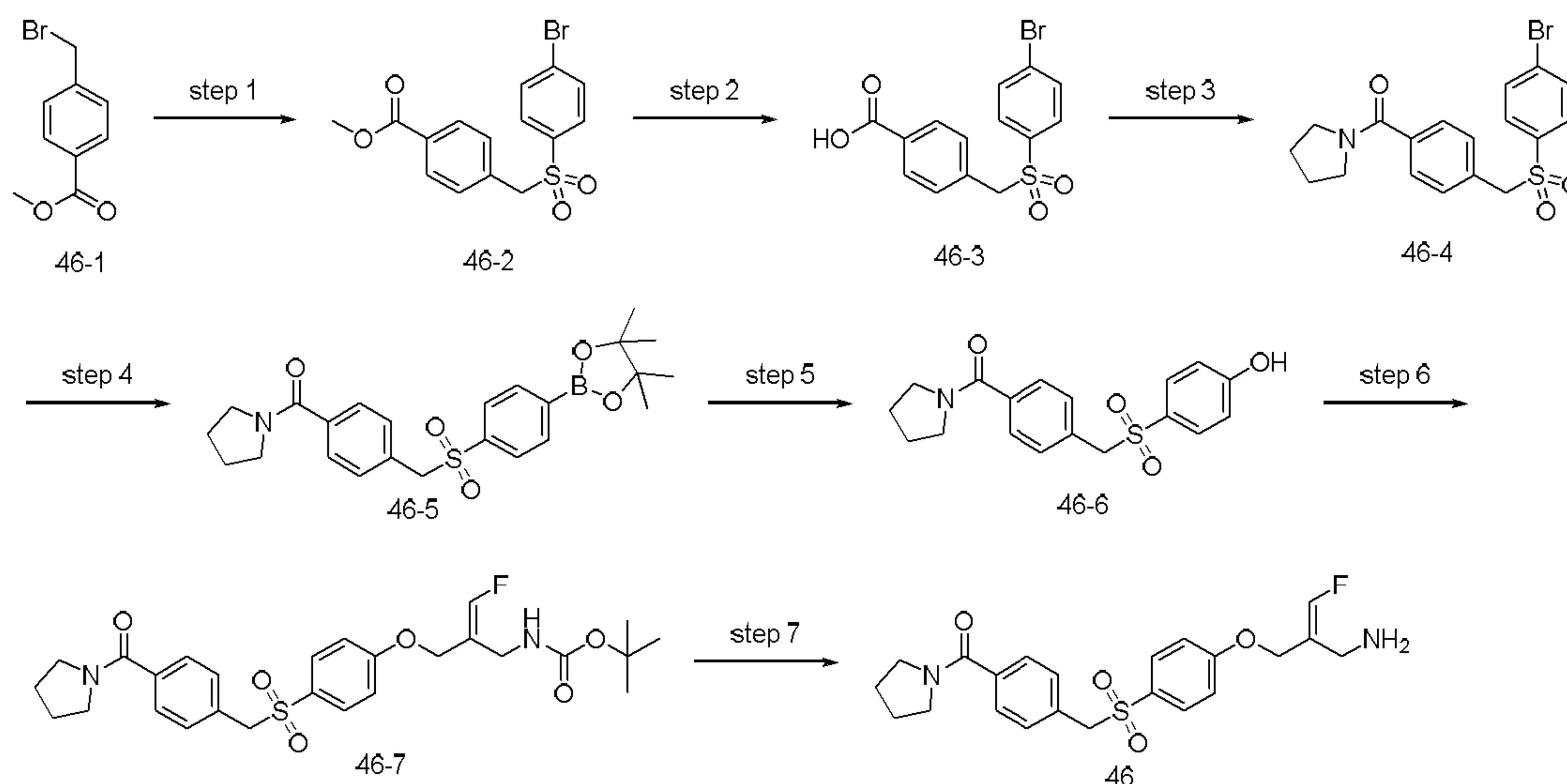
5 **Step 6: 45-7**

[00519] To a mixture of **45-6** (330 mg, 989.80 μmol), **Intermediate A** (100 mg, 372.96 μmol) in MeCN (30 mL) was added Cs_2CO_3 (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **45-7** (220 mg, crude). MS: $m/z = 521$ ($M+1$).

10 **Step 7: Compound 45**

[00520] To a mixture of **45-7** (220 mg, 422.58 μmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 3.0 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO_2H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 45** (44 mg, 94.32 μmol , 22.32% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.58 (d, $J = 8.7$ Hz, 2H), 7.50-7.42 (m, 2H), 7.23 (d, $J = 81.1$ Hz, 1H), 7.14-7.06 (m, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 4.67 (d, $J = 3.5$ Hz, 2H), 4.41 (s, 2H), 3.76 (d, $J = 2.2$ Hz, 2H), 2.60-2.56 (m, 1H), 1.18 (d, $J = 6.8$ Hz, 6H) ppm. MS: $m/z = 420.96$ ($M+1$, ESI+).

20 **Example 48: Synthesis of Compound 46**



Step 1: 46-2

[00521] To a mixture of **46-1** (1.2 g, 5.24 mmol) and 4-bromobenzenesulfinic acid (1.51 g, 6.81 mmol) was added K_2CO_3 (1.45 g, 10.48 mmol) and stirred at 120 °C for 0.5 hr under microwave. Water (20 mL) was added, extracted with DCM (30 mL), the organic layer was washed with water, brine and dried with Na_2SO_4 . The organic layer was concentrated and the residue was purified by column chromatography on silcal gel (ethyl acetate/petroleum ether = 1/10 - 1/1, v/v) to give **46-2** (1.4 g, 3.79 mmol, 72.38% yield).

Step 2: 46-3

[00522] To a mixture of **46-2** (0.4 g, 1.08 mmol) in MeOH (5 mL) was added NaOH (4 M in water, 8.13 mL) and the mixture was stirred at 90 °C for 5 hr. HCl (1 M in water) was added to adjusted pH to 3. H_2O (20 mL) was then added, and the mixture was extracted with ethyl acetate (150 mL), washed with H_2O , brine. The organic layer was dried over Na_2SO_4 , concentrated and the residue was purified by column chromatography on silcal gel (ethyl acetate/petroleum ether = 1/10 - 1/1, v/v) to give **46-3** (0.35 g, 985.35 μ mol, 90.96% yield).

Step 3: 46-4

[00523] A mixture of **46-3** (0.35 g, 985.35 μ mol), HATU (561.99 mg, 1.48 mmol), DIPEA (382.05 mg, 2.96 mmol, 514.89 μ L) in DMF (8 mL) was added pyrrolidine (91.10 mg, 1.28 mmol, 106.43 μ L) and stirred at 20 °C for 8 hr. H_2O (30 mL) was added, and the mixture was extracted with ethyl acetate (100 mL), washed with H_2O , brine. The organic layer was dried over Na_2SO_4 , concentrated and the residue was purified by column chromatography on silcal gel (ethyl acetate/petroleum ether = 1/10 - 1/1, v/v) to give **46-4** (0.38 g, 930.67 μ mol, 94.45% yield). MS: m/z = 408.0 (M+1).

Step 4: 46-5

[00524] A mixture of **46-4** (0.38 g, 930.67 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (354.50 mg, 1.40 mmol), potassium acetate (182.68 mg, 1.86 mmol) and cyclopentyl(diphenyl)phosphane; dichloromethane; dichloropalladium; iron (38.0 mg, 46.53 μ mol) in Dioxane (8 mL) was stirred at 120 °C for 0.7 hr under microwave. The reaction mixture was filtered, the filtrate was concentrated to give **46-4** (crude, 0.4 g). MS: m/z = 456.2 (M+1).

Step 5: 46-6

[00525] To a mixture of **46-5** (0.4 g, 878.40 μ mol) in THF (4 mL) and acetic acid (1 mL) was added H_2O_2 (0.5 mL, 30% purity). The reaction was stirred at 20 °C for 1 hr. Na_2SO_3 (1.0 g) was

added to quench the reaction, and the reaction mixture was filtered and concentrated to give **46-6** (crude, 0.3 g). MS: $m/z = 346.1$ ($M+1$).

Step 6: 46-7

[00526] To a mixture of **46-6** (0.3 g, 868.53 μmol) in MeCN (20 mL) was added Cs_2CO_3 (848.95 mg, 2.61 mmol) and **Intermediate A** (302.73 mg, 1.13 mmol). The mixture was stirred at 95 °C for 1 hr. The reaction mixture was concentrated and the residue was purified by flash chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 5/1, v/v) to give **46-7** (0.3 g, 563.25 μmol , 64.85% yield). MS: $m/z = 533.2$ ($M+1$).

Step 7: Compound 46

[00527] A mixture of **46-7** (0.3 g, 563.25 μmol) in HCl/Dioxane (4 M, 4.22 mL) was stirred at 20 °C for 0.5 hr. Then, the solution was concentrated and the residue was purified by Prep-HPLC (prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 46** (0.2 g, 417.94 μmol , 74.20% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.68-7.53 (m, 2H), 7.43 (d, $J = 8.2$ Hz, 2H), 7.33 (s, 0.5 H), 7.24 (d, $J = 8.2$ Hz, 2H), 7.11 (d, $J = 9.0$ Hz, 2.5H), 4.69 (d, $J = 3.4$ Hz, 2H), 4.54 (s, 2H), 3.81 (d, $J = 2.1$ Hz, 2H), 3.58 (t, $J = 6.9$ Hz, 2H), 3.42 (t, $J = 6.6$ Hz, 2H), 2.16-1.80 (m, 4H). MS: $m/z = 433.2$ ($M+1$, ESI+).

[00528] The compounds of Formula (I') or (I) in Table 5 below were made according to **Example 48** of *Compound 46*.

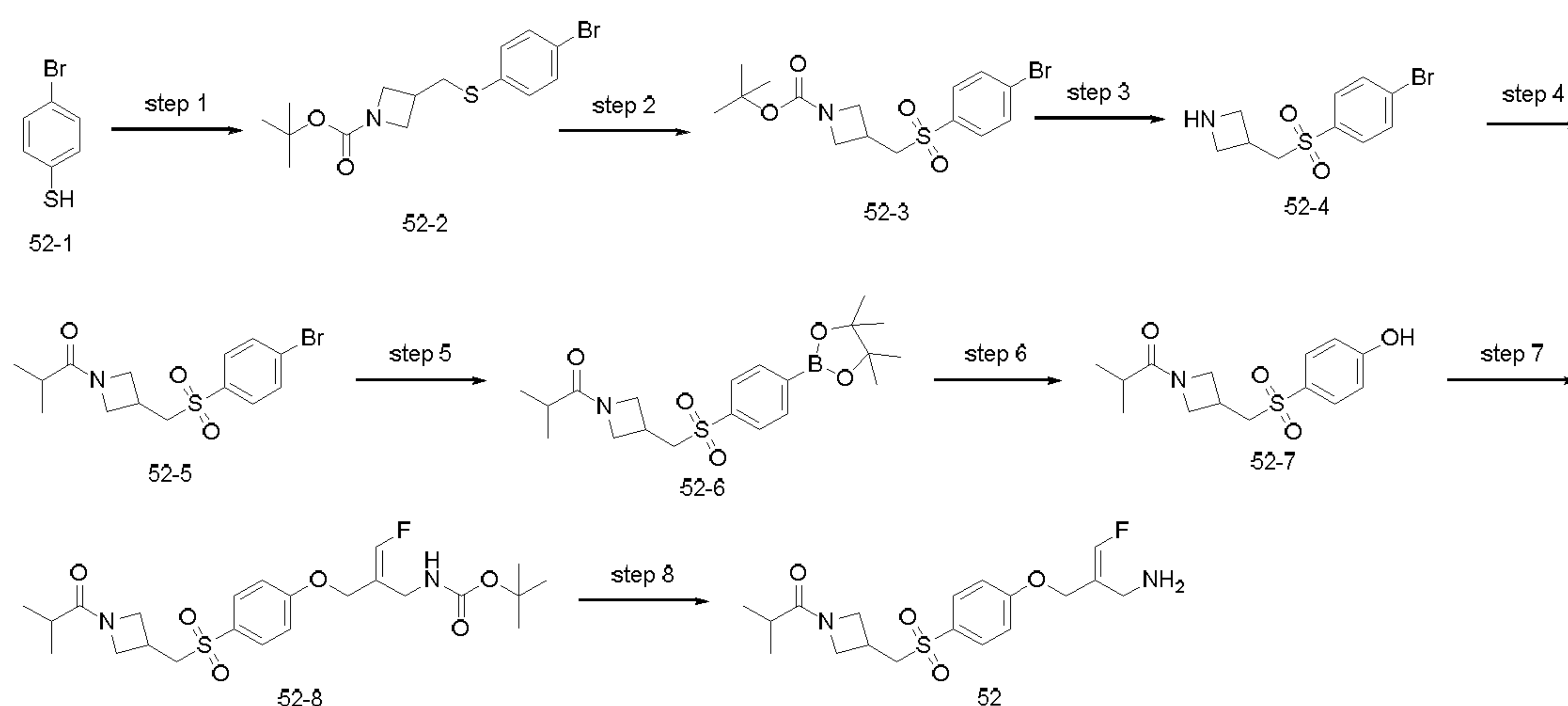
Table 5

Cmpd No.	^1H NMR and/or LC/MS data
47	^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.65-7.54 (m, 2H), 7.47-7.45 (m, 1H), 7.44-7.34 (m, 1H), 7.33 (s, 0.5H), 7.28 (dd, $J = 4.7, 2.8$ Hz, 2H), 7.17-7.03 (m, 2.5H), 4.69 (d, $J = 3.4$ Hz, 2H), 4.55 (s, 2H), 3.82 (d, $J = 2.2$ Hz, 2H), 3.55 (t, $J = 7.0$ Hz, 2H), 3.29 (t, $J = 7.0$ Hz, 3H), 2.06-1.75 (m, 4H) ppm. MS: $m/z = 433.2$ ($M+1$, ESI+).

[00529] The compounds of Formula (I') or (I) in Table 6 below were made according to **Example 44** of *Compound 39*.

Table 6

Cmpd No.	¹ H NMR and/or LC/MS data
48	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.52 (s, 1H), 7.65-7.54 (m, 2H), 7.47-7.45 (m, 1H), 7.44-7.34 (m, 1H), 7.33 (s, 0.5H), 7.28 (dd, <i>J</i> = 4.7, 2.8 Hz, 2H), 7.17-7.03 (m, 2.5H), 4.69 (d, <i>J</i> = 3.4 Hz, 2H), 4.55 (s, 2H), 3.82 (d, <i>J</i> = 2.2 Hz, 2H), 3.55 (t, <i>J</i> = 7.0 Hz, 2H), 3.29 (t, <i>J</i> = 7.0 Hz, 3H), 2.06-1.75 (m, 4H) ppm. MS: <i>m/z</i> = 433.2 (M+1, ESI+).
49	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.72 (d, <i>J</i> = 8.9 Hz, 2H), 7.05 (d, <i>J</i> = 8.9 Hz, 2H), 6.97 (s, 1H), 4.55 (d, <i>J</i> = 3.5 Hz, 2H), 4.32-4.22 (m, 2H), 3.79-3.69 (m, 2H), 3.65 (d, <i>J</i> = 2.3 Hz, 2H), 3.00 (t, <i>J</i> = 5.7 Hz, 3H), 2.97-2.85 (m, 2H), 2.46 (td, <i>J</i> = 12.8, 3.0 Hz, 2H), 2.12 (d, <i>J</i> = 6.8 Hz, 3H), 2.04-1.91 (m, 2H), 1.83-1.62 (m, 3H), 1.22-0.98 (m, 3H), 0.79-0.71 (m, 2H) ppm. MS: <i>m/z</i> = 425.67 (M+1, ESI+).
50	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.51 (s, 1H), 7.92 (d, <i>J</i> = 8.9 Hz, 2H), 7.26 (d, <i>J</i> = 81.0 Hz, 1H), 7.25 (d, <i>J</i> = 8.9 Hz, 2H), 4.74 (d, <i>J</i> = 3.6 Hz, 2H), 4.66-4.58 (m, 1H), 4.35 (s, 3H), 4.13 (d, <i>J</i> = 2.4 Hz, 1H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.20 (t, <i>J</i> = 5.8 Hz, 4H), 2.29-2.11 (m, 2H), 1.95 (d, <i>J</i> = 12.0 Hz, 3H), 1.40-1.24 (m, 6H), 1.21 (q, <i>J</i> = 2.7, 1.9 Hz, 3H) ppm. MS: <i>m/z</i> = 479.64 (M+1, ESI+).
51	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.49 (s, 1H), 7.96-7.88 (m, 2H), 7.30-7.21 (m, 2H), 7.27 (d, <i>J</i> = 81.0 Hz, 1H), 4.74 (d, <i>J</i> = 3.5 Hz, 2H), 4.62 (dd, <i>J</i> = 3.6, 1.0 Hz, 1H), 4.42 (d, <i>J</i> = 13.7 Hz, 2H), 4.13 (d, <i>J</i> = 2.4 Hz, 1H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.80 (s, 1H), 3.21-3.16 (m, 3H), 2.88-2.72 (m, 7H), 2.23-2.10 (m, 2H), 2.02-1.80 (m, 4H), 1.40-1.14 (m, 4H) ppm. MS: <i>m/z</i> = 461.72 (M+1, ESI+).

Example 49: Synthesis of Compound 52**Step 1: 52-2**

[00530] To a mixture of **52-1** (687.17 mg, 3.63 mmol) in DMF (15 mL) was added NaH (159.90 mg, 4.0 mmol, 60% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, tert-butyl 3-(bromomethyl)azetidine-1-carboxylate (1.0 g, 4.00 mmol) was added. The reaction solution was stirred further for 18 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 10%) to obtain **52-2** (1.1 g, 3.07 mmol, 84.47% yield). MS: $m/z = 358$ (M+1).

Step 2: 52-3

[00531] To a mixture of **52-2** (1.1 g, 3.07 mmol) in DCM (40 mL) was added m-CPBA (2.49 g, 12.28 mmol, 85% purity) at 20 °C. The mixture was stirred for 2 hr at 20 °C. Then, the solution was washed with saturated aqueous Na_2SO_3 (10 mL), saturated aqueous NaHCO_3 (20 mL $\times$ 2) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator to obtain **52-3** (1.0 g, crude). MS: $m/z = 390$ (M+1).

Step 3: 52-4

[00532] To a mixture of **52-3** (1.0 g, 2.56 mmol) in DCM (30 mL) was added HCl/Dioxane (4 M, 4 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **52-4** (800 mg, crude, HCl salt). MS: $m/z = 290$ (M+1).

Step 4: 52-5

[00533] To a mixture of **52-4** (400 mg, 1.22 mmol), Et₃N (495.67 mg, 4.90 mmol) in DCM (30 mL) was added 2-methylpropanoyl chloride (143.53 mg, 1.35 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 60%) to obtain **52-5** (300 mg, 832.72 μmol, 68.00% yield). MS: m/z = 360 (M+1).

Step 5: 52-6

[00534] To a mixture of **52-5** (300 mg, 832.72 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (253.75 mg, 999.26 μmol) and KOAc (245.17 mg, 2.50 mmol) in Dioxane (8 mL) was added Pd(dppf)Cl₂ (60.93 mg, 83.27 μmol) at 20 °C. The reaction solution was stirred for 0.667 hr at 120 °C under microwave. The mixture was filtered and the filtrate was evaporated to **52-6** (330 mg, crude). MS: m/z = 408 (M+1).

Step 6: 52-7

[00535] To a mixture of **52-6** (330 mg, 810.15 μmol), acetic acid (0.2 mL) in THF (10 mL) was added hydrogen peroxide (0.4 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was filtered and concentrated with a rotary evaporator to obtain **52-7** (200 mg, crude). MS: m/z = 296 (M+1).

Step 7: 52-8

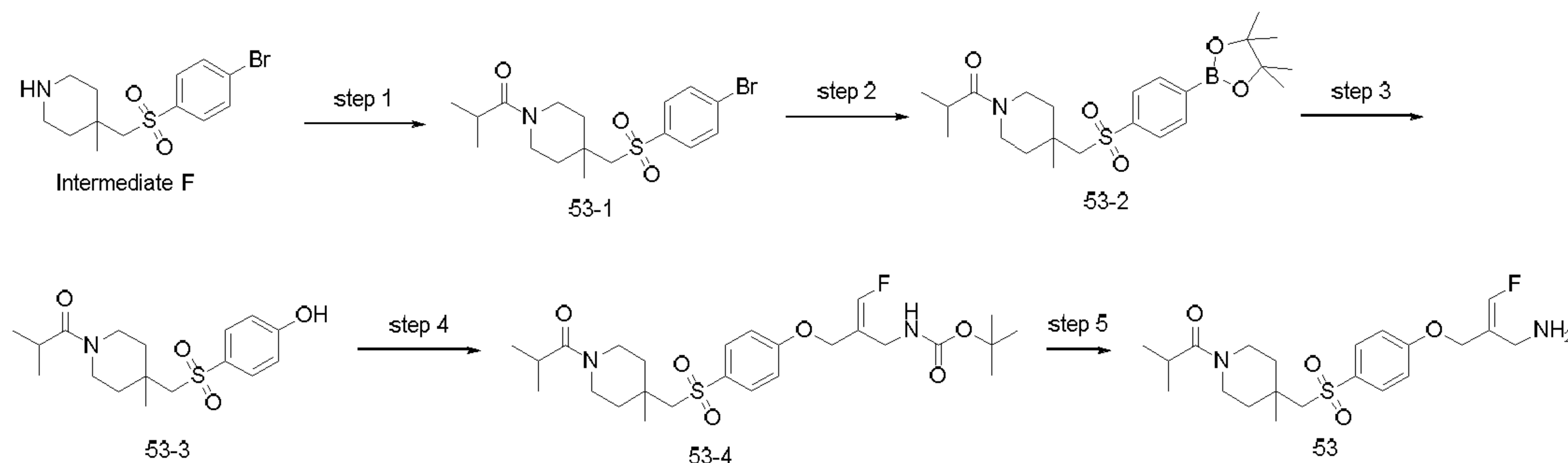
[00536] To a mixture of **52-7** (200 mg, 672.56 μmol), **Intermediate A** (100 mg, 372.96 μmol) in MeCN (20 mL) was added Cs₂CO₃ (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **52-8** (150 mg, crude). MS: m/z = 485 (M+1).

Step 8: Compound 52

[00537] To a mixture of **52-8** (150 mg, 309.55 μmol) in DCM (10 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 52** (22 mg, 51.10 μmol, 16.51% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.47 (s, 1H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.28 (d, *J* = 81.1 Hz, 1H), 7.26 (d, *J* = 8.9 Hz, 2H), 4.75 (d, *J* = 3.5 Hz, 1H), 4.35 (q, *J* = 8.5 Hz, 2H), 4.13 (d, *J* = 2.4 Hz, 2H), 3.66 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.05-3.00 (m, 3H),

2.48 (p, $J = 6.8$ Hz, 2H), 1.30-1.23 (m, 2H), 1.06 (d, $J = 1.8$ Hz, 6H). MS: $m/z = 385.24$ (M+1, ESI+).

Example 50: Synthesis of Compound 53



5 Step 1: 53-1

[00538] To a mixture of **Intermediate F** (80 mg, 216.97 μmol) and TEA (65.87 mg, 650.91 μmol) in DCM (10 mL) was added 2-methylpropanoyl chloride (46.24 mg, 433.94 μmol) at 0 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80 mL), washed with H₂O (100 mL $\times$ 3), dried over Na₂SO₄, filtered and concentrated to obtain **53-1** (80 mg, 198.83 μmol , 91.64% yield). MS: $m/z = 402$ (M+1).

Step 2: 53-2

[00539] To a mixture of **53-1** (80 mg, 198.83 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (60.59 mg, 238.60 μmol) and cyclopentyl(diphenyl)phosphane; dichloropalladium; iron (145.49 mg, 198.83 μmol) in Dioxane (5 mL) was added KOAc (304.87 mg, 596.50 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silical gel (ethyl acetate/petroleum ether = 1/10 - 1/1) to obtain **53-2** (60 mg, 133.51 μmol , 67.15% yield). MS: $m/z = 449$ (M+1).

20 Step 3: 53-3

[00540] To a mixture of **53-2** (60 mg, 133.51 μmol) in THF (5 mL) and acetic acid (1 mL) was added H₂O₂ (1 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. Na₂SO₃ (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **53-3** (600 mg, crude). MS: $m/z = 339$ (M+1).

25 Step 4: 53-4

[00541] To a mixture of **53-3** (600 mg, crude) and **Intermediate A** (94.79 mg, 353.51 μmol) in MeCN (10 mL) was added Cs_2CO_3 (575.91 mg, 1.77 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **53-4** (60 mg, 113.93 μmol , 6.45% yield). MS: $m/z = 526$ (M+1).

5 **Step 5: Compound 53**

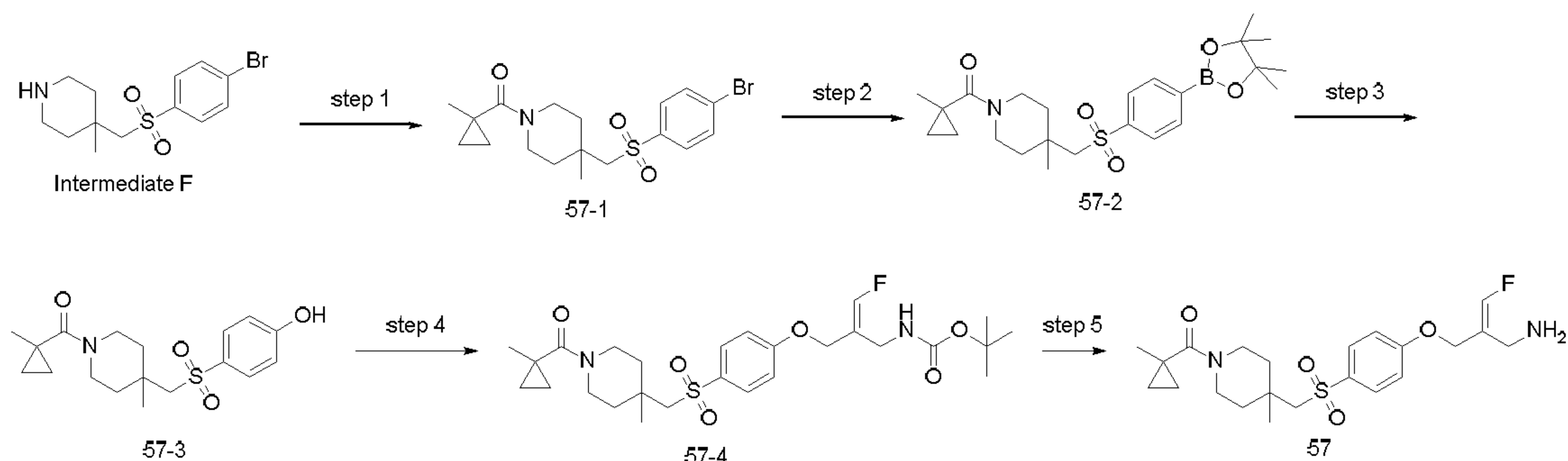
[00542] A mixture of **53-4** (60 mg, 113.93 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, B: acetonitrile; gradient: 10-40% B; GT: 15 min; flow rate: 15 mL/min) to give

10 **Compound 53** (20 mg, 42.32 μmol , 37.15% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.90 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 80.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 2H), 4.71 (s, 2H), 3.33-3.29 (m, 2H), 3.66-3.62 (m, 2H), 3.56-3.37 (m, 2H), 3.28 (s, 2H), 2.99-2.85 (m, 1H), 1.86-1.82 (s, 1H), 1.67-1.61 (s, 2H), 1.52-1.45 (m, 1H), 1.32 (s, 3H), 1.07 (d, $J = 6.8$ Hz, 6H) ppm; MS: $m/z = 427.27$ (M+1, ESI+).

15 [00543] The compounds of Formula (I') or (I) in Table 7 below were made according to **Example 50 of Compound 53**.

Table 7

Cmpd No.	^1H NMR and/or LC/MS data
54	MS: $m/z = 441.70$ (M+1, ESI+).
55	^1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 80.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.85-3.69 (m, 4H), 3.61-3.57 (m, 2H), 1.79-1.76 (m, 2H), 1.62-1.56 (m, 2H), 1.33 (s, 5H), 1.19 (s, 2H) ppm; MS: $m/z = 493.6$ (M+1, ESI+).
56	^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.89 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 80.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.77 (d, $J = 2.4$ Hz, 2H), 3.39-3.34 (m, 4H), 3.27 (s, 2H), 2.49-2.44 (m, 2H), 2.04-1.94 (m, 1H), 1.88-1.84 (m, 3H), 1.69 (d, $J = 10.4$ Hz, 2H), 1.57-1.53 (m, 2H), 1.41 (s, 3H), 1.32 (s, 3H) ppm; MS: $m/z = 453.7$ (M+1, ESI+).

Example 51: Synthesis of Compound 57**Step 1: 57-1**

[00544] To a mixture of **Intermediate F** (50 mg, 150.49 μmol), 1-

5 methylcyclopropanecarboxylic acid (18.08 mg, 180.58 μmol) in DCM (10 mL) was added TEA (45.68 mg, 451.46 μmol , 62.92 μL) and HATU (85.83 mg, 225.73 μmol) at 30 °C. The reaction solution was stirred for 1 hr at 30 °C. Then, ethyl acetate (100 mL) was added and the mixture reaction was washed with H_2O (100 mL $\times$ 3), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1 –

10 1/1, v/v) to obtain **57-1** (55 mg, 132.74 μmol , 88.20% yield).

Step 2: 57-2

[00545] A 30 mL microwave reaction tube was charged with **57-1** (55 mg, 132.74 μmol),

4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (50.56 mg, 199.10 μmol), cyclopentyl(diphenyl)phosphane;dichloropalladium;iron (9.71 mg, 13.27

15 μmol) and KOAc (39.08 mg, 398.21 μmol) in Dioxane (5 mL). After O_2 was purged by bubbling N_2 into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0-100%) to deliver **57-2** (40 mg, 86.69 μmol , 65.31% yield). MS: m/z

20 = 461 (M+1).

Step 3: 57-3

[00546] A mixture of **57-2** (40 mg, 86.69 μmol) in THF (1 mL) and H_2O (0.25 mL) was added H_2O_2 (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Na_2SO_3 (0.6 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and

25 concentrated in vacuo to give **57-3** (0.5 g, crude). MS: m/z = 351 (M+1).

Step 4: 57-4

[00547] A mixture of **57-3** (0.5 g, crude) and **Intermediate A** (152.58 mg, 569.06 μmol) in MeCN (50 mL) was added Cs_2CO_3 (1.39 g, 4.27 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **57-4** (80 mg, crude). MS: $m/z = 538$ (M+1).

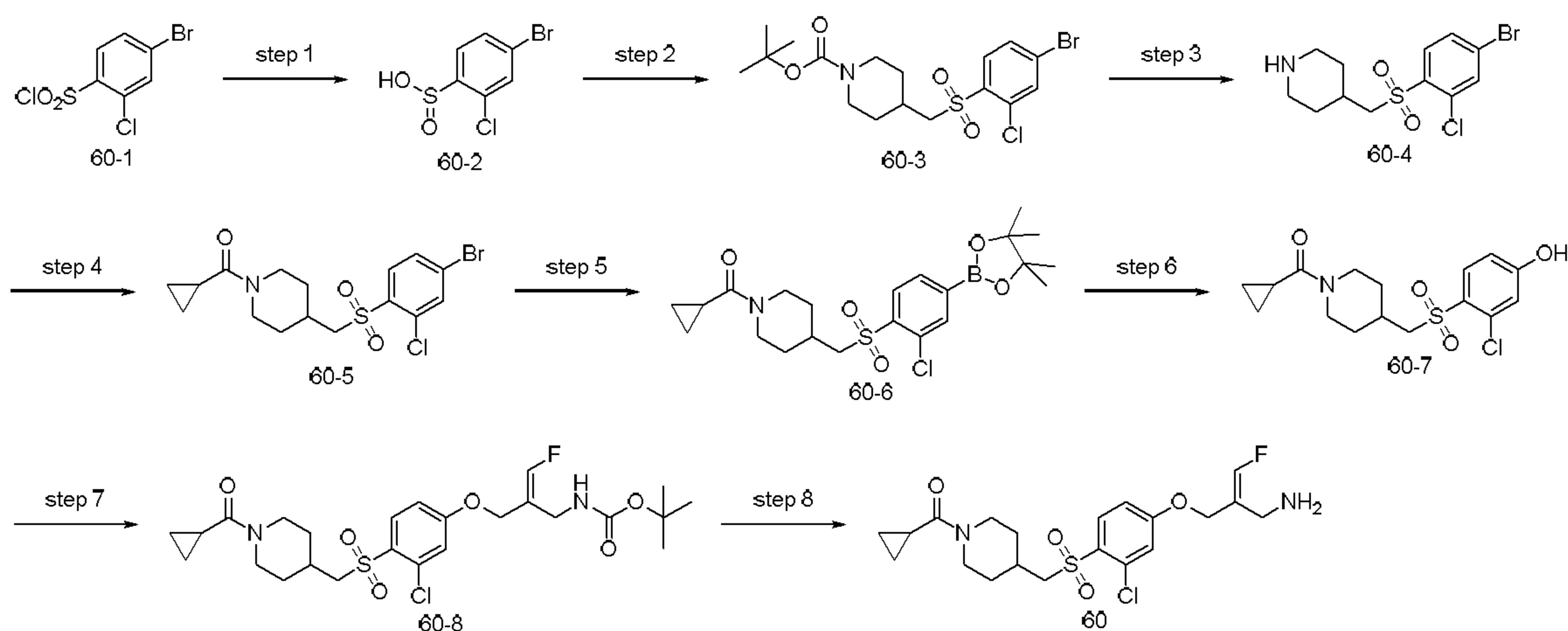
5 **Step 5: Compound 57**

[00548] A mixture of **57-4** (80 mg, 148.51 μmol) in HCl/Dioxane (4 M, 3.26 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, GT: 15 min; flow rate: 15 mL/min) to afford **Compound 57** (4.2 mg, 8.67 μmol , 5.84% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 80.0$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.93-3.78 (m, 2H), 3.75-3.70 (m, 2H), 3.58-3.54 (m, 2H), 3.31-3.28 (m, 2H), 1.78-1.74 (m, 2H), 1.58-1.54 (m, 2H), 1.33 (s, 3H), 1.28 (s, 3H), 0.86 (d, $J = 5.0$ Hz, 2H), 0.61 (t, $J = 3.2$ Hz, 2H) ppm; MS: $m/z = 439.6$ (M+1, ESI+).

15 [00549] The compounds of Formula (I') or (I) in Table 8 below were made according to **Example 51** (starting from **Intermediate G**) of **Compound 57**.

Table 8

Cmpd No.	^1H NMR and/or LC/MS data
58	^1H NMR (400 MHz, Methanol- d_4) δ 7.86 (t, $J = 8.4$ Hz, 1H), 7.25 (d, $J = 80.0$ Hz, 1H), 7.04 (d, $J = 10.4$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 4.45 (d, $J = 13.2$ Hz, 1H), 4.05 (d, $J = 14.0$ Hz, 1H), 3.84-3.81 (m, 2H), 3.31-3.27 (m, 2H), 3.15-2.94 (m, 2H), 2.62 (t, $J = 12.8$ Hz, 1H), 2.22 (d, $J = 12.4$ Hz, 1H), 1.97 (d, $J = 13.2$ Hz, 1H), 1.84 (d, $J = 13.2$ Hz, 3H), 1.72-1.68 (m, 4H), 1.62-1.58 (m, 2H), 1.32 (t, $J = 13.2$ Hz, 1H), 1.26-1.22 (m, 1H) ppm; MS: $m/z = 457.6$ (M+1, ESI+).
59	^1H NMR (400 MHz, Methanol- d_4) δ 8.48 (s, 1H), 7.86 (t, $J = 8.8$ Hz, 1H), 7.24 (d, $J = 80.0$ Hz, 1H), 7.09-6.92 (m, 2H), 4.71 (d, $J = 3.2$ Hz, 2H), 4.45 (d, $J = 13.6$ Hz, 1H), 3.88 (d, $J = 14.0$ Hz, 1H), 3.80 (s, 2H), 3.48-3.44 (m, 2H), 3.13 (t, $J = 13.2$ Hz, 1H), 2.68 (t, $J = 12.8$ Hz, 1H), 2.22 (s, 1H), 2.00-1.96 (m, 1H), 1.87 (d, $J = 13.2$ Hz, 1H), 1.40-1.16 (m, 3H) ppm; MS: $m/z = 471.6$ (M+1, ESI+).

Example 52: Synthesis of Compound 60**Step 1: 60-2**

[00550] To a mixture of **60-1** (1.0 g, 3.08 mmol) in water (20 mL) was added Na_2SO_3 (777.07 mg, 6.17 mmol) and NaHCO_3 (517.91 mg, 6.17 mmol) in one portion, and the mixture was then stirred at 100 °C for 1 hr. After the temperature was cooled to 25 °C, HCl (con.) was added to adjust the pH to 3. Then, the suspension was filtered, the cake was dried to give **60-2** (0.89 g, 3.07 mmol, 99.57% yield).

Step 2: 60-3

[00551] To a mixture of **60-2** (300 mg, 1.17 mmol), tert-butyl 4-(bromomethyl)piperidine-1-carboxylate (359.28 mg, 1.29 mmol) in DMF (15 mL) was added Na_2CO_3 (373.32 mg, 3.52 mmol) at 25 °C. The reaction solution was stirred for 18 hr at 100 °C. Then, the solution was quenched with H_2O (20 mL), and extracted by ethyl acetate (15 mL $\times$ 2). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 to 80%) to obtain **60-3** (100 mg, 220.85 μmol , 18.81% yield).

Step 3: 60-4

[00552] To a mixture of **60-3** (100 mg, 220.85 μmol) in DCM (15 mL) was added HCl /Dioxane (4 M, 2 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **60-4** (100 mg, crude, HCl salt). MS: $m/z = 352$ ($M+1$).

Step 4: 60-5

[00553] To a mixture of **60-4** (100 mg, 256.98 μmol), Et_3N (78.01 mg, 770.94 μmol) in DCM (20 mL) was added cyclopropanecarbonyl chloride (29.55 mg, 282.68 μmol) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was filtered and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 60%, v/v) to obtain **60-5** (73 mg, 173.50 μmol , 67.52% yield). MS: $m/z = 420$ (M+1).

Step 5: 60-6

[00554] To a mixture of **60-5** (73 mg, 173.50 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (52.87 mg, 208.20 μmol) and KOAc (51.08 mg, 520.50 μmol) in Dioxane (6 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (12.70 mg, 17.35 μmol) at 25 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **60-6** (100 mg, crude). MS: $m/z = 468$ (M+1).

Step 6: 60-7

[00555] To a mixture of **60-6** (100 mg, 213.76 μmol), acetic acid (0.3 mL) in THF (10 mL) was added H_2O_2 (0.1 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, to the solution was added Na_2SO_3 (0.5g) and then filtered and concentrated with a rotary evaporator to obtain **60-7** (110 mg, crude). MS: $m/z = 358$ (M+1).

Step 7: 60-8

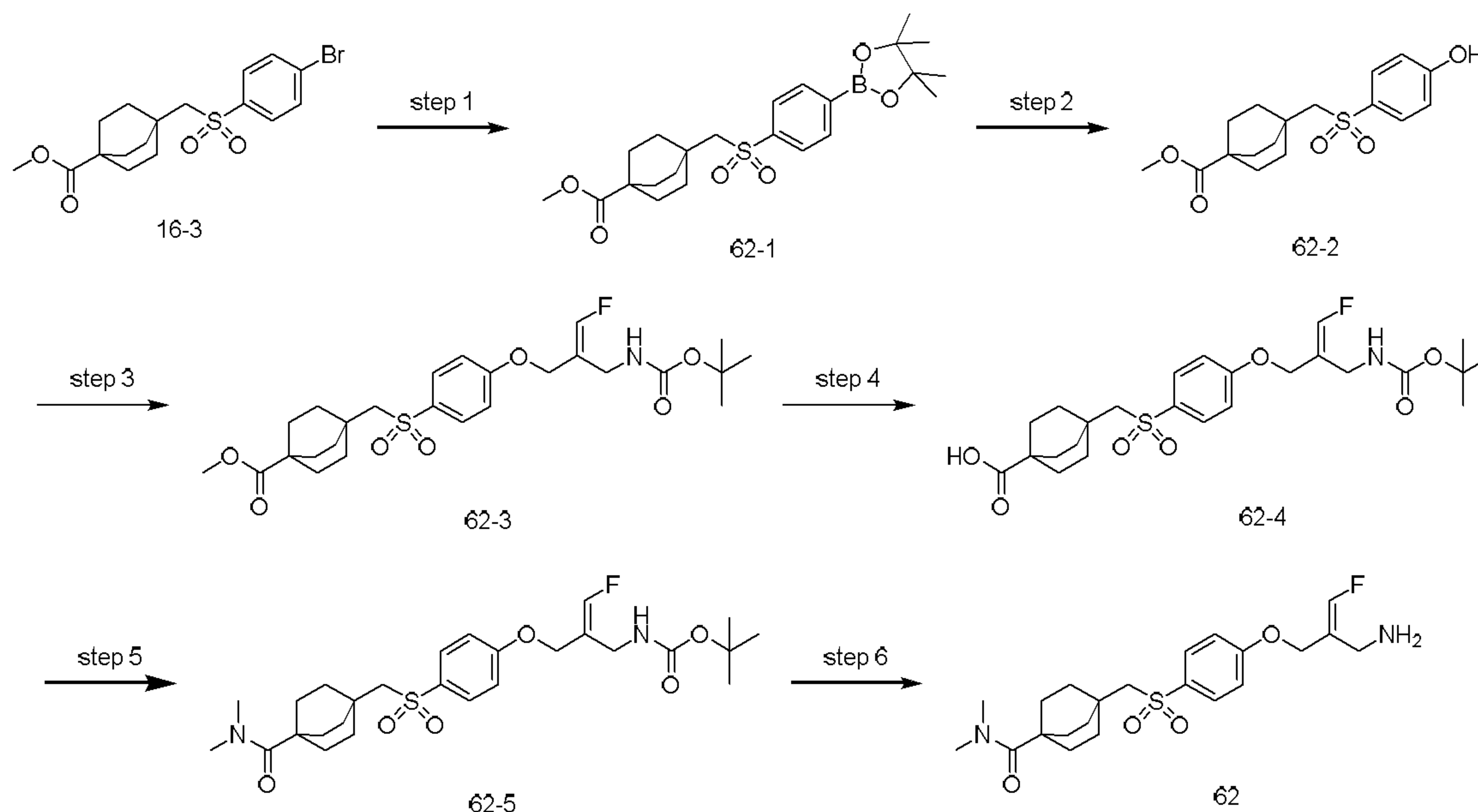
[00556] To a mixture of **60-7** (100 mg, 279.45 μmol), **Intermediate A** (74.93 mg, 279.45 μmol) in MeCN (20 mL) was added Cs_2CO_3 (273.15 mg, 838.34 μmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **60-8** (160 mg, crude). MS: $m/z = 545$ (M+1).

Step 8: Compound 60

[00557] To a mixture of **60-8** (100 mg, 183.47 μmol) in DCM (20 mL) was added HCl/Dioxane (4 M, 2 mL) at 20 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by prep-HPLC (column: XBridge@ Prep C18 5 μm 19×150 mm; A: 0.1% HCO_2H water, GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 60** (25 mg, 50.92 μmol , 27.75% yield, HCO_2H salt). ^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 8.08 (d, $J = 8.9$ Hz, 1H), 7.34 (d, $J = 2.5$ Hz, 1H), 7.26 (d, $J = 80.9$ Hz, 1H), 7.20 (dd, $J = 8.9, 2.5$ Hz, 1H), 4.75 (d, $J = 3.4$ Hz, 2H), 3.83 (d, J

= 2.2 Hz, 2H), 3.27-3.09 (m, 2H), 2.69 (t, $J = 13.0$ Hz, 2H), 2.31-2.15 (m, 2H), 2.06-1.77 (m, 6H), 1.50-1.17 (m, 4H), 0.83-0.75 (m, 4H). MS: $m/z = 445.56$ ($M+1$, ESI+).

Example 53: Synthesis of Compound 62



5 Step 1: 62-1

[00558] A 8 mL microwave reaction tube was charged with **16-3** (140 mg, 348.85 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (106.30 mg, 418.62 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.50 mg, 34.85 μ mol) and potassium acetate (102.71 mg, 1.05 mmol) in Dioxane (3 mL). After oxygen was
 10 purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure to give **62-1** (300 mg, crude).

Step 2: 62-2

[00559] To a mixture of methyl **62-1** (300 mg, 669.08 μ mol), acetate acid (669.08 μ mol, 0.5 mL) in THF (2 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction
 15 solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography on silica gel (20 g, ethyl acetate in petroleum ether, 0 - 65%) to **62-2** (120 mg, 354.59 μ mol, 53.0% yield). ^1H NMR (400 MHz, Chloroform- d) δ 7.79-7.73 (m, 2H), 6.98-6.91 (m, 2H), 3.64 (s, 3H), 2.92 (s, 2H),
 20 1.83-1.71 (m, 12H) ppm.

Step 3: 62-3

[00560] To a mixture of **62-2** (120 mg, 354.59 μmol), **Intermediate A** (114.09 mg, 425.51 μmol) in acetonitrile (10 mL) was added Cesium carbonate (346.60 mg, 1.06 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered and the filtrate
5 was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography on silica gel (20 g, ethyl acetate in petroleum ether, 0 - 40%) to give **62-3** (120 mg, 228.30 μmol , 64.38% yield).

Step 4: 62-4

[00561] To a solution of **62-3** (120 mg, 228.30 μmol) in THF (4 mL) and water (2 mL) was
10 added Lithium hydroxide monohydrate (95.79 mg, 2.28 mmol) at 20 °C. The reaction solution was heated to 55 °C and stirred for 1 hr. Then, the mixture was adjusted to pH ~5 with 1 M HCl solution. The reaction mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (20 mL $\times$ 2), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to give **62-4** (110 mg, 215.01 μmol , 94.18%
15 yield).

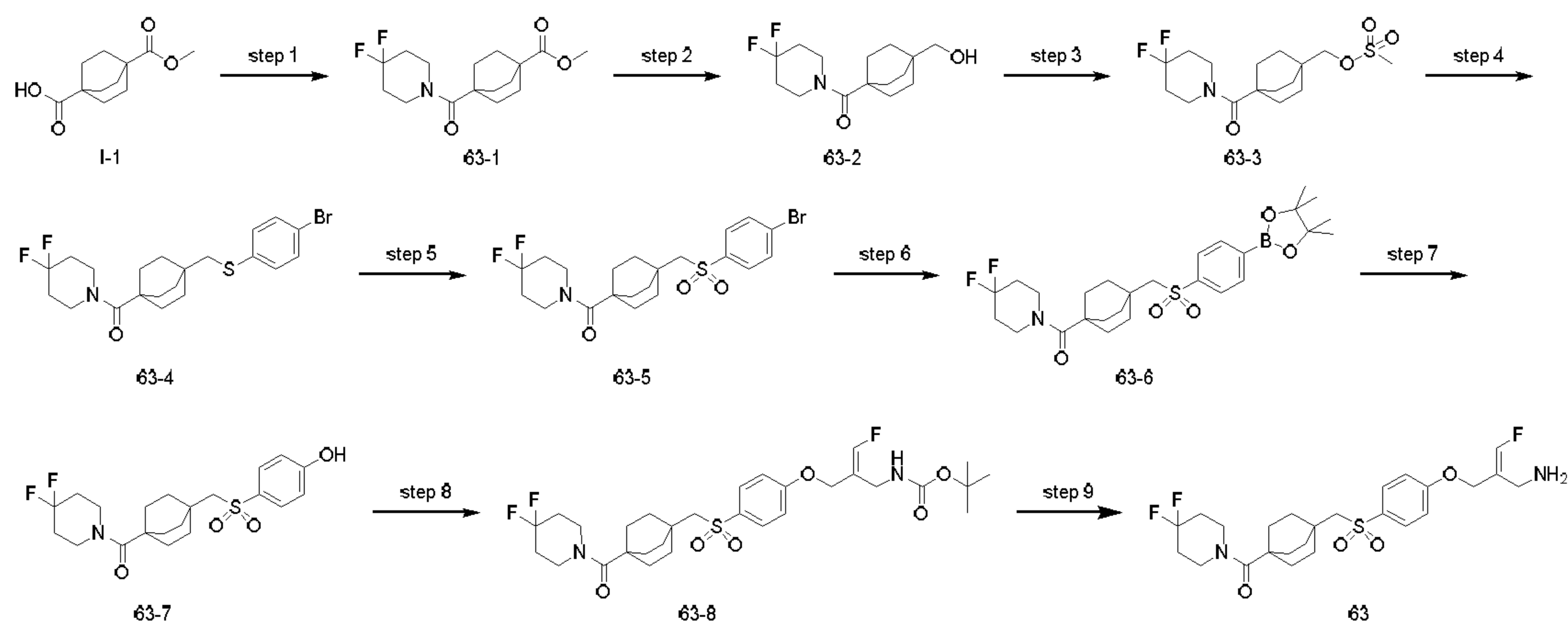
Step 5: 62-5

[00562] To a mixture of N-methylmethanamine (20.72 mg, 254.10 μmol , HCl salt), **62-4** (100 mg, 195.46 μmol) in DCM (10 mL) was added TEA (59.34 mg, 586.39 μmol , 81.73 μL) and HATU (89.19 mg, 234.56 μmol) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C.
20 The crude product was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 100%, v/v) to obtain **62-5** (100 mg, 185.64 μmol , 94.97% yield).

Step 6: Compound 62

[00563] To a solution of **62-5** (100 mg, 185.64 μmol) in DCM (2 mL) was added HCl/Dioxane (2 mL, 4 M) at 20 °C and stirred at 20 °C for 1 hr. The reaction mixture was
25 concentrated to give crude, which was slurried with acetonitrile (6 mL) for 15 minutes and filtered. The filter cake was dried by lyophilization (water: acetonitrile = 4: 1, 20 mL) to give **Compound 62** (67.0 mg, 141.05 μmol , 75.98% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.83 (m, 2H), 7.27 (d, J = 84.0 Hz, 1H), 7.24-7.18 (m, 2H), 4.73 (dd, J = 3.6, 1.1 Hz, 2H), 3.84 (d, J = 2.2 Hz, 2H), 3.09 (s, 2H), 3.03 (s, 6H), 1.94-1.85 (m, 6H), 1.77-1.72 (m, 6H)
30 ppm. MS: m/z = 439.2 (M+1).

Example 54: Synthesis of Compound 63



Step 1: 63-1

[00564] To a mixture of 4,4-difluoropiperidine (684.85 mg, 5.65 mmol), **I-1** (1 g, 4.71 mmol) in DCM (20 mL) was added TEA (1.43 g, 14.13 mmol, 1.97 mL) and HATU (2.15 g, 5.65 mmol) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The mixture was concentrated and crude product was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 35%, v/v) to obtain **63-1** (1.28 g, 4.06 mmol, 86.15% yield). ¹H NMR (400 MHz, Chloroform-d) δ 3.75-3.70 (m, 4H), 3.66 (s, 3H), 2.02-1.80 (m, 16H).

Step 2: 63-2

[00565] To a mixture of **63-1** (473 mg, 1.5 mmol) in THF (10 mL) was added LiAlH₄ (45.79 mg, 1.21 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 0 °C. Water (0.1 mL) was added and stirred for 15 minutes, the mixture was then dried over anhydrous sodium sulfate, filtered and concentrated to obtain **63-2** (370 mg, 1.29 mmol, 85.84% yield).

Step 3: 63-3

[00566] To a mixture of **63-2** (370 mg, 1.29 mmol), TEA (390.89 mg, 3.86 mmol, 538.42 μL) in DCM (5 mL) was added methanesulfonic anhydride (336.46 mg, 1.93 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (4 g, ethyl acetate in petroleum ether, 0 - 40%, v/v) to obtain **63-3** (390 mg, 1.07 mmol, 82.88% yield). ¹H NMR (400 MHz, Chloroform-d) δ 3.88 (s, 2H), 3.73 (t, *J* = 5.8 Hz, 4H), 3.00 (s, 3H), 2.01-1.87 (m, 10H), 1.57-1.53 (m, 6H) ppm.

Step 4: 63-4

[00567] To a solution of 4-bromobenzenethiol (504.46 mg, 2.67 mmol), cesium carbonate (1.04 g, 3.20 mmol) and potassium iodide (88.58 mg, 533.61 μmol) in DMF (3 mL) was added

63-3 (390 mg, 1.07 mmol) under the nitrogen atmosphere. The reaction mixture was heated at 55 °C for 2 hr. Ethyl acetate (60 mL) and water (50 mL) were added, the organic was washed with brine (50 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated to a residue, which was purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 0 - 25%, v/v) to give **63-4** (300 mg, 654.45 μmol, 61.32% yield). MS: m/z = 458.1 (M+1).

Step 5: 63-5

[00568] To a mixture of **63-4** (300 mg, 654.45 μmol) and m-CPBA (398.60 mg, 1.96 mmol, 85% purity) in DCM (10 mL) was stirred at 20 °C for 2 hr. The sodium sulfite (1 g) was added to the mixture and stirred for 20 min. Then, to the solution was added ethyl acetate (20 mL) and water (20 mL). The organic layer was washed with aqueous NaHCO₃ (30 mL × 3), brine (30 mL × 3), dried over anhydrous sodium sulfate, filtered, concentrated to obtain **63-5** (270 mg, crude).

Step 6: 63-6

[00569] A 30 mL microwave reaction tube was charged with **63-5** (270 mg, 550.57 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (167.77 mg, 660.68 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (40.29 mg, 55.06 μmol) and potassium acetate (162.10 mg, 1.65 mmol) in Dioxane (10 mL). After oxygen was purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure to give **63-6** (500 mg, crude).

Step 7: 63-7

[00570] To a mixture of **63-6** (500 mg, 930.29 μmol), acetate acid (930.29 μmol, 1 mL) in tetrahydrofuran (4 mL) was added hydrogen peroxide (1 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **63-7** (400 mg, crude).

Step 8: 63-8

[00571] To a mixture of **63-7** (200 mg, 467.83 μmol), **Intermediate A** (150.52 mg, 561.40 μmol) in MeCN (20 mL) was added Cesium carbonate (457.29 mg, 1.40 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography on silica gel (20 g, ethyl acetate in petroleum ether, 0 - 65%, v/v) to give **63-8** (70 mg, 113.87 μmol, 24.34% yield).

Step 9: Compound 63

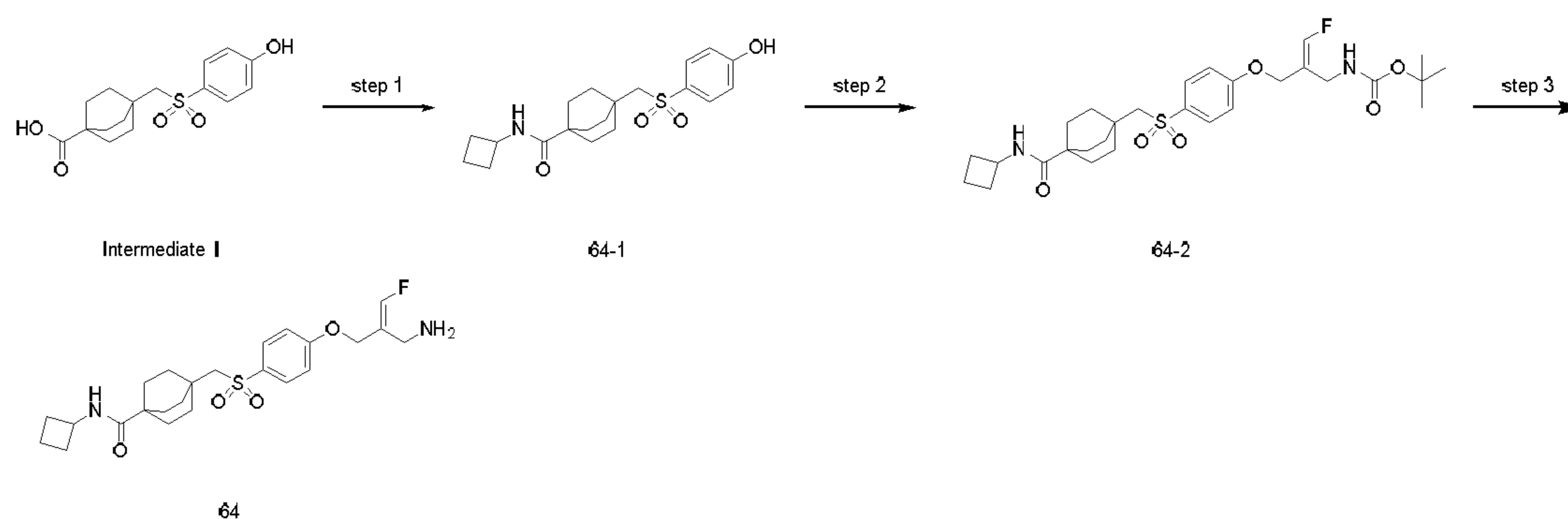
[00572] To a mixture of **63-8** (70 mg, 113.87 μmol) in Dioxane (4 mL) was added HCl/Dioxane (2 mL, 4 M) at 40 °C and stirred at 40 °C for 1 hr. The reaction mixture was concentrated with a rotary evaporator to give a crude, which was purified by *prep*-HPLC

5 (column: XBridge[®] Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; GT: 15 min; flow rate: 15 mL/min) to give **Compound 63** (7.5 mg, 13.38 μmol , 11.75% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.54 (s, 1H), 7.89-7.83 (m, 2H), 7.27 (d, *J* = 84.0 Hz, 1H), 7.22-7.18 (m, 2H), 4.70 (d, *J* = 3.6 Hz, 2H), 3.79-3.70 (m, 6H), 3.09 (s, 2H), 2.00-1.86 (m, 10H), 1.80-1.74 (m, 6H) ppm. MS: *m/z* = 515.2 (M+1).

10 [00573] The compounds of Formula (I') or (I) in Table 9 below were made according to Example 54 of *Compound 63*.

Table 9

Cmpd No.	¹ H NMR and/or LC/MS data
61	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.89-7.82 (m, 2H), 7.26 (d, <i>J</i> = 80.0 Hz, 1H), 7.24-7.17 (m, 2H), 4.72 (dd, <i>J</i> = 3.5, 1.0 Hz, 2H), 3.83 (d, <i>J</i> = 2.2 Hz, 2H), 3.67-3.58 (m, 2H), 3.45-3.35 (m, 2H), 3.08 (s, 2H), 1.96-1.68 (m, 16H) ppm. MS: <i>m/z</i> = 465.2 (M+H).

Example 55: Synthesis of Compound 64

15

Step 1: 64-1

[00574] A mixture of **Intermediate I** (400 mg, 1.23 mmol), diisopropylethylamine (318.73 mg, 2.47 mmol, 429.55 μL), HATU (562.62 mg, 1.48 mmol), cyclobutanamine (105.24 mg, 1.48 mmol) in DMF (4 mL) was stirred at 20 °C for 16 hr. The mixture was poured into aqueous

NaHCO₃ and filtered. The cake was dissolved with DCM/MeOH and concentrated to afford **64-1** (461 mg, 1.22 mmol, 99.04% yield). MS: m/z = 378.1 (M+1).

Step 2: 64-2

[00575] To a mixture of **64-1** (461 mg, 1.22 mmol), **Intermediate A** (360.18 mg, 1.34 mmol) in MeCN (4 mL) was added Cesium carbonate (795.78 mg, 2.44 mmol) at 20 °C. The reaction solution was heated to 94 °C and stirred for 1 hr at 94 °C. The mixture was filtered and the filtrate was concentrated with a rotary evaporator. The residue was purified by column chromatography on silica gel (12 g, ethyl acetate in petroleum ether, 20 - 100%, v/v) to give **64-2** (578 mg, 1.02 mmol, 83.81% yield). MS: m/z = 509.2 (M+1-56).

Step 3: Compound 64

[00576] A mixture of **64-2** (578 mg, 1.02 mmol) and Hydrochloric acid/Dioxane (4 M, 20 mL) was stirred for 1 hr at 20 °C. The mixture was concentrated, slurried in acetonitrile and filtered. The cake was dissolved in water and freeze-dried to give **Compound 64** (494 mg, 985.92 μmol, 96.32% yield, HCl salt). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.27 (s, 3H), 7.87-7.79 (m, 2H), 7.48-7.44 (m, 1H), 7.35 (d, *J* = 72.0 Hz, 1H), 7.24-7.18 (m, 2H), 4.75 (d, *J* = 3.4 Hz, 2H), 4.20-4.11 (m, 1H), 3.62 (d, *J* = 5.8 Hz, 2H), 3.14 (s, 2H), 2.13-2.01 (m, 2H), 1.98-1.83 (m, 2H), 1.65-1.50 (m, 14H). MS: m/z = 465.2 (M+1).

[00577] The compounds of Formula (I') or (I) in Table 10 below were made according to **Example 55** of *Compound 64*.

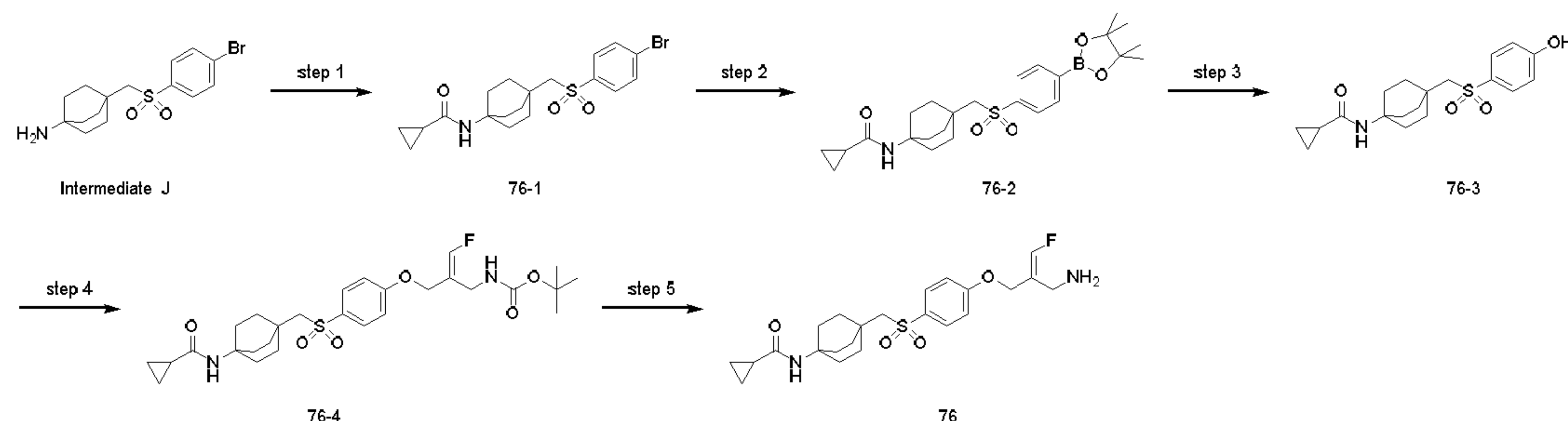
Table 10

Cmpd No.	¹ H NMR and/or LC/MS data
65	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.26 (s, 3H), 7.99 (t, <i>J</i> = 6.4 Hz, 1H), 7.86-7.79 (m, 2H), 7.34 (d, <i>J</i> = 80.0 Hz, 1H), 7.22-7.17 (m, 2H), 4.74 (d, <i>J</i> = 3.4 Hz, 2H), 3.80 (dd, <i>J</i> = 9.8, 6.3 Hz, 2H), 3.60 (s, 2H), 3.14 (s, 2H), 1.62 (s, 12H) ppm. MS: m/z = 493.1 (M+1).
66	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.87 (d, <i>J</i> = 8.9 Hz, 2 H), 7.26 (d, <i>J</i> = 80.9 Hz, 1 H), 7.21 (d, <i>J</i> = 8.9 Hz, 2 H), 4.73 (d, <i>J</i> = 3.5 Hz, 2 H), 3.84 (s, 2 H), 3.09 (s, 2 H), 3.01 (d, <i>J</i> = 6.8 Hz, 2 H), 1.75 (s, 12 H), 1.06-0.83 (m, 1 H), 0.48-0.39 (m, 2 H), 0.20-0.15 (m, 2 H) ppm. MS: m/z = 465.2 (M+1).
67	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.18 (s, 3H), 7.78-7.74 (m, 2H), 7.41 (s, 1H),

Cmpd No.	¹ H NMR and/or LC/MS data
	7.28 (d, $J = 80.0$ Hz, 1H), 7.16-7.11 (m, 2H), 4.67 (d, $J = 3.4$ Hz, 2H), 3.55 (s, 2H), 3.05 (s, 2H), 1.49 (s, 12H), 1.13 (s, 3H), 0.49-0.35 (m, 4H) ppm. MS: $m/z = 465.2$ (M+1).
68	¹ H NMR (400 MHz, DMSO- d_6) δ 8.22 (s, 3H), 7.86-7.79 (m, 2H), 7.34 (d, $J = 80.0$ Hz, 1H), 7.30 (t, $J = 5.7$ Hz, 1H), 7.22-7.17 (m, 2H), 4.73 (d, $J = 3.4$ Hz, 2H), 3.61 (d, $J = 2.1$ Hz, 2H), 3.55-3.43 (m, 1H), 3.33-3.25 (m, 2H), 3.15-3.06 (m, 4H), 1.59 (s, 12H), 1.04 (d, $J = 6.1$ Hz, 6H) ppm. MS: $m/z = 497.2$ (M+1).
69	¹ H NMR (400 MHz, Methanol- d_4) δ 7.86 (d, $J = 8.7$ Hz, 2 H), 7.26 (d, $J = 80.9$ Hz, 1 H), 7.21 (d, $J = 8.6$ Hz, 2 H), 4.72 (d, $J = 3.5$ Hz, 2 H), 4.07 (q, $J = 7.3, 6.8$ Hz, 1 H), 3.83 (d, $J = 2.2$ Hz, 2 H), 3.08 (s, 2 H), 2.90-2.78 (m, 2 H), 2.65-2.47 (m, 2 H), 1.74 (s, 12 H) ppm. MS: $m/z = 501.2$ (M+1).
70	¹ H NMR (400 MHz, Methanol- d_4) δ 8.55 (br, 1 H), 7.90 (d, $J = 8.9$ Hz, 2 H), 7.24 (d, $J = 8.9$ Hz, 2 H), 7.24 (d, $J = 81.8$ Hz, 1 H), 6.40 (s, 1 H), 4.75 (d, $J = 3.5$ Hz, 2 H), 3.74 (s, 2 H), 3.12 (s, 2 H), 1.74 (s, 12 H), 1.32 (s, 9 H) ppm. MS: $m/z = 467.3$ (M+1).
71	¹ H NMR (400 MHz, DMSO- d_6) δ 8.23 (s, 1H), 7.84-7.66 (m, 2H), 7.21-7.04 (m, 2H), 7.01 (d, $J = 84.0$ Hz, 1H), 4.60 (d, $J = 3.4$ Hz, 2H), 4.23 (s, 2H), 3.70 (s, 2H), 3.30 (d, $J = 2.4$ Hz, 2H), 3.05 (s, 2H), 2.15-1.98 (m, 2H), 1.63-1.43 (m, 12H) ppm. ¹⁹ F NMR (376 MHz, DMSO- d_6) δ -129.62 ppm. MS: $m/z = 451.3$ (M+1).
72	¹ H NMR (400 MHz, Methanol- d_4) δ 8.44 (s, 1H), 7.75 (d, $J = 8.9$ Hz, 2H), 7.13-7.01 (m, 2H), 7.00 (d, $J = 84.0$ Hz, 1H), 4.59-4.11 (m, 6H), 3.54 (d, $J = 2.7$ Hz, 2H), 2.97 (s, 2H), 1.66 (t, $J = 9.8$ Hz, 12H) ppm. ¹⁹ F NMR (376 MHz, Methanol- d_4) δ -103.39 ppm. MS: $m/z = 487.2$ (M+1).
73	¹ H NMR (400 MHz, DMSO- d_6) δ 8.28 (s, 1H), 7.84-7.76 (m, 2H), 7.21-7.15 (m, 2H), 7.11 (d, $J = 84.0$ Hz, 1H), 4.67 (d, $J = 3.5$ Hz, 2H), 3.41 (s, 2H), 3.12 (s, 2H), 2.83 (s, 3H), 2.81-2.74 (m, 1H), 1.79 (dd, $J = 10.1, 5.5$ Hz, 6H), 1.61 (dd, $J = 9.9, 5.5$ Hz, 6H), 0.70-0.64 (m, 2H), 0.57 (dt, $J = 7.1, 4.7$ Hz, 2H) ppm. MS: $m/z = 465.2$ (M+1).
74	¹ H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1 H), 7.86 (d, $J = 8.9$ Hz, 2 H), 7.22

Cmpd No.	¹ H NMR and/or LC/MS data
	(d, $J = 81.2$ Hz, 1 H), 7.20 (d, $J = 8.9$ Hz, 2 H), 4.71 (d, $J = 3.5$ Hz, 2 H), 3.80 (d, $J = 2.2$ Hz, 2 H), 3.42 (br, 4 H), 3.08 (s, 2 H), 1.87 (dd, $J = 10.1, 5.2$ Hz, 6 H), 1.75 (dd, $J = 10.0, 5.2$ Hz, 6 H), 1.12 (br, 6 H) ppm. MS: $m/z = 467.2$ (M+1).
75	¹ H NMR (400 MHz, DMSO- d_6) δ 8.19 (s, 3H), 7.86-7.78 (m, 2H), 7.35 (d, $J = 84.0$ Hz, 1H), 7.29 (d, $J = 4.0$ Hz, 1H), 7.23-7.16 (m, 2H), 4.77-4.67 (m, 2H), 3.61 (d, $J = 6.1$ Hz, 3H), 3.13 (s, 2H), 2.60-2.53 (m, 1H), 1.57 (s, 12H), 0.53-0.48 (m, 2H), 0.41-0.32 (m, 2H) ppm. MS: $m/z = 451.3$ (M+1).

Example 56: Synthesis of Compound 76



Step 1: 76-1

- 5 [00578] To a mixture of **Intermediate J** (700 mg, 1.77 mmol, HCl salt) and TEA (538.31 mg, 5.32 mmol, 741.47 μ L) in DCM (30 mL) was added cyclopropanecarbonyl chloride (222.44 mg, 2.13 mmol, 193.43 μ L) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The mixture was concentrated and the crude product was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 35%, v/v) to obtain **76-1** (590 mg, 1.38 mmol, 78.04% yield).

10 Step 2: 76-2

- [00579] A 30 mL microwave reaction tube was charged with **76-1** (590 mg, 1.38 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (421.67 mg, 1.66 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (101.25 mg, 138.38 μ mol) and potassium acetate (407.41 mg, 4.15 mmol) in Dioxane (8 mL). After oxygen was
- 15 purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure to give **76-2** (1 g, crude).

Step 3: 76-3

[00580] To a mixture of **76-2** (1 g, 2.10 mmol), acetate acid (0.5 mL) in THF (4 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 65%, v/v) to obtain **76-3** (450 mg, 1.23 mmol, 58.54% yield).

Step 4: 76-4

[00581] To a mixture of **76-3** (450 mg, 1.24 mmol), **Intermediate A** (398.34 mg, 1.49 mmol) in MeCN (15 mL) was added Cesium carbonate (806.77 mg, 2.48 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 65%, v/v) to obtain **76-4** (620 mg, 1.13 mmol, 90.94% yield).

Step 5: Compound 76

[00582] To a mixture of **76-4** (620 mg, 1.13 mmol) in DCM (10 mL) was added HCl/Dioxane (4 M, 10 mL) at 20 °C and stirred at 20 °C for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (6 mL) for 15 minutes and filtered. The filter cake was dried by lyophilization (water: acetonitrile= 4: 1, 20 mL) to give **Compound 76** (449.5 mg, 922.95 μmol, 81.98% yield, HCl salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.90 – 7.84 (m, 2H), 7.27 (d, *J* = 80.0 Hz, 1H) 7.25-7.19 (m, 2H), 4.75-4.71 (m, 2H), 3.84 (s, 2H), 3.07 (s, 2H), 1.93-1.86 (m, 6H), 1.82-1.74 (m, 6H), 1.55-1.49 (m, 1H), 0.74 (dt, *J* = 4.6, 2.9 Hz, 2H), 0.66-0.61 (m, 2H) ppm. MS: *m/z* = 451.2 (M+1).

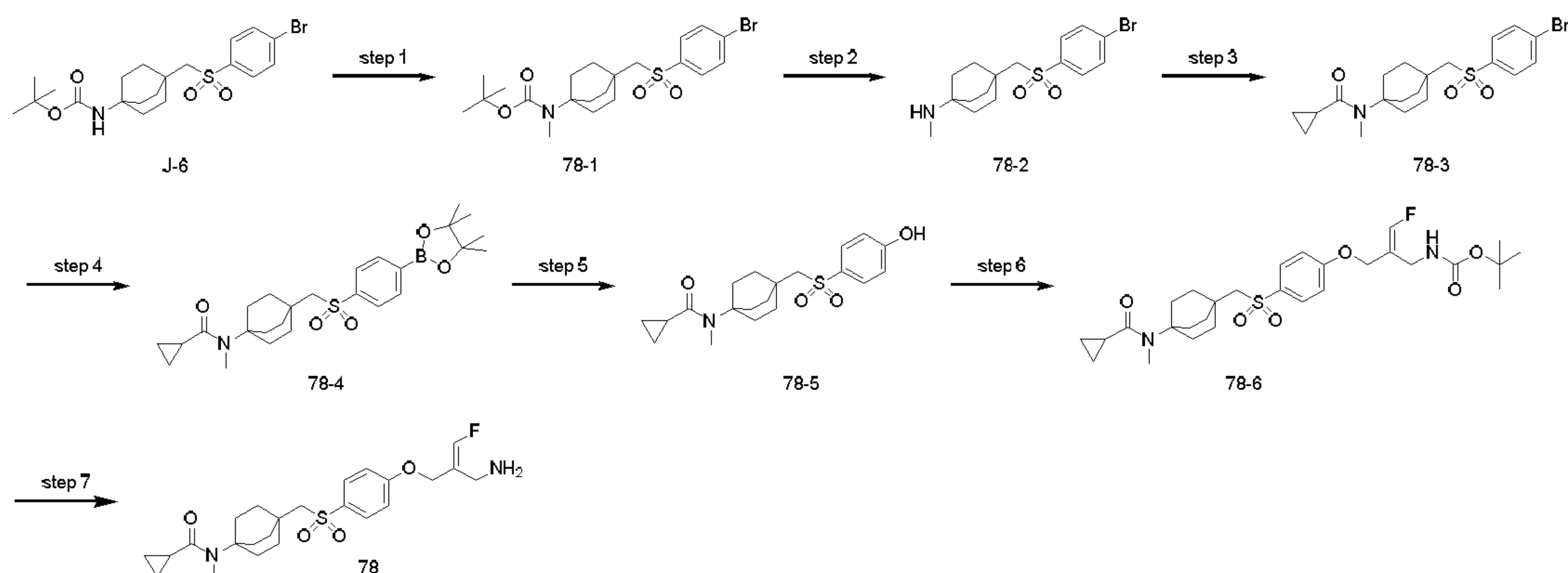
[00583] The compounds of Formula (I') or (I) in Table 11 below were made according to **Example 56 of Compound 76**.

Table 11

Cmpd No.	¹ H NMR and/or LC/MS data
77	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.95 (s, 1H), 7.91-7.86 (m, 2H), 7.27 (d, <i>J</i> = 80.0 Hz, 1H), 7.26-7.20 (m, 2H), 4.73 (d, <i>J</i> = 3.5 Hz, 2H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.54 (s, 2H), 1.99 (s, 6H), 1.11 (s, 9H) ppm. MS: <i>m/z</i> = 425.2 (M+1).
80	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.89-7.84 (m, 2H), 7.27 (d, <i>J</i> = 80.0 Hz, 1H),

Cmpd No.	¹ H NMR and/or LC/MS data
	7.24-7.19 (m, 2H), 4.73 (d, <i>J</i> = 3.6 Hz, 2H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.07 (s, 2H), 2.38-2.32 (m, 1H), 1.93-1.84 (m, 6H), 1.82-1.74 (m, 6H), 1.03 (d, <i>J</i> = 6.8 Hz, 6H) ppm. MS: <i>m/z</i> = 453.2 (M+1).
81	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.52 (s, 1 H), 7.93-7.80 (m, 2 H), 7.28-7.18 (m, 2 H), 7.23 (d, <i>J</i> = 80.0 Hz, 1H), 4.72 (d, <i>J</i> = 3.6 Hz, 2 H), 3.80 (d, <i>J</i> = 2.2 Hz, 2 H), 3.07 (s, 2 H), 2.50-2.45 (m, 1 H), 1.95-1.74 (m, 12 H), 1.07-0.95 (m, 4 H) ppm. MS: <i>m/z</i> = 487.2 (M+H).
90	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.90-7.83 (m, 2H), 7.27 (d, <i>J</i> = 80.0 Hz, 1H), 7.25-7.19 (m, 2H), 4.73 (d, <i>J</i> = 3.5 Hz, 2H), 3.84 (d, <i>J</i> = 2.2 Hz, 2H), 3.08 (s, 2H), 1.94-1.87 (m, 6H), 1.83-1.76 (m, 6H), 1.13 (s, 9H) ppm. MS: <i>m/z</i> = 467.3 (M+1).

Example 57: Synthesis of Compound 78



Step 1: 78-1

- 5 **[00584]** To a mixture of **J-6** (300 mg, 654.44 μmol) in DMF (5 mL) was added NaH (34.03 mg, 850.77 μmol, 60% purity) at 0 °C and stirred at 0 °C for 30 min. Iodomethane (279 mg, 1.97 mmol, 122.37 μL) was added at 0 °C. After addition, the mixture was stirred at 25 °C for 16 hr. Upon completion, the resulting mixture was quenched with water (20 mL) and extracted with ethyl acetate (30 mL). The separated organic layer was washed with water (20 mL × 3) and brine, dried over anhydrous sodium sulfate, filtered and concentrated to give crude **78-1** (300 mg, 635.01 μmol, 97.03% yield). MS: *m/z* = 416.0 (M+1-56).
- 10

Step 2: 78-2

[00585] A mixture of **78-1** (300 mg, 635.01 μmol) and HCl/Dioxane (4 M, 5 mL) in Dioxane (2 mL) was stirred at 25 °C for 1 hr. The resulting mixture was concentrated to give crude **78-2** (230 mg, 617.75 μmol , 97.28% yield, HCl salt). MS: $m/z = 372.1$ (M+1)

Step 3: 78-3

5 [00586] To a mixture of **78-2** (230 mg, 617.75 μmol) and diisopropylethylamine (79.84 mg, 617.75 μmol , 107.60 μL) in DCM (20 mL) was added cyclopropanecarbonyl chloride (64.58 mg, 617.75 μmol , 56.15 μL) at 0 °C. After addition, the solution was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was washed with water (20 mL) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 5 - 10%, v/v) to give **78-3** (200 mg, 454.14 μmol , 73.52% yield). MS: $m/z = 440.1$ (M+1)

Step 4: 78-4

15 [00587] A mixture of **78-3** (200 mg, 454.14 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (173 mg, 681.27 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (33 mg, 45.10 μmol) and potassium acetate (82 mg, 1.37 mmol) in Dioxane (10 mL) was microwaved at 120 °C for 40 min. Upon completion, the resulting mixture was cooled to room temperature, filtered and concentrated to give crude **78-4** (220 mg, 451.32 μmol , 99.38% yield). MS: $m/z = 488.2$ (M+1).

Step 5: 78-5

20 [00588] A mixture of **78-4** (220 mg, 451.32 μmol), hydrogen peroxide (1 mL, 30% purity) and acetate acid (1 mL) in THF (4 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with sodium sulfite, filtered and concentrated to give crude **78-5** (170 mg, 450.34 μmol , 99.78% yield). MS: $m/z = 378.1$ (M+1).

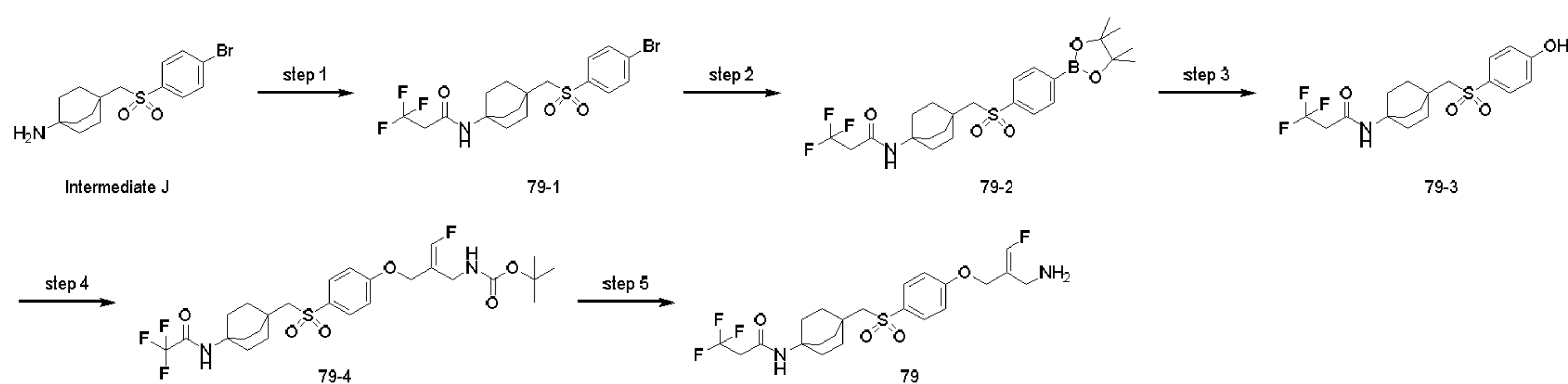
Step 6: 78-6

25 [00589] A mixture of **78-5** (170 mg, 450.34 μmol) and Cs_2CO_3 (733.64 mg, 2.25 mmol) in MeCN (20 mL) was stirred at 95 °C for 2 hr. Upon completion, the resulting mixture was filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 25 - 50%, v/v) to give **78-6** (180 mg, 318.75 μmol , 70.78% yield). MS: $m/z = 509.2$ (M+1-56)

30 *Step 7: Compound 78*

[00590] A mixture of **78-6** (180 mg, 318.75 μ mol) and HCl/Dioxane (4 M, 5 mL) in Dioxane (2 mL) was stirred at 25 °C for 1 hr. The resulting mixture was concentrated and purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile; gradient: 5 - 50% B; GT: 25 min; flow rate: 15 mL/min) to give **Compound 78** (15 mg, 32.29 μ mol, 10.13% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.43 (s, 1H), 7.84-7.70 (m, 2H), 7.17-7.07 (m, 2H), 7.14 (d, *J* = 80.0 Hz, 1H), 4.63 (d, *J* = 3.5 Hz, 2H), 3.72 (d, *J* = 2.1 Hz, 2H), 3.00 (s, 3H), 2.98 (s, 2H), 1.97 (dd, *J* = 9.9, 5.8 Hz, 6H), 1.76-1.63 (m, 7H), 0.67-0.61 (m, 4H) ppm. MS: *m/z* = 465.2 (M+1).

Example 58: Synthesis of Compound 79



Step 1: 79-1

[00591] To a mixture of 3,3,3-trifluoropropanoic acid (71.36 mg, 557.31 μ mol, 49.22 μ L), **Intermediate J** (200 mg, 506.64 μ mol, HCl salt) in DCM (5 mL) was added TEA (153.80 mg, 1.52 mmol, 211.85 μ L) and HATU (231.17 mg, 607.97 μ mol) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The crude product was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 35%, v/v) to obtain **79-1** (160 mg, 341.64 μ mol, 67.43% yield).

Step 2: 79-2

[00592] A 30 mL microwave reaction tube was charged with **79-1** (160 mg, 341.64 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (104.11 mg, 409.97 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.0 mg, 34.16 μ mol) and potassium acetate (100.59 mg, 1.02 mmol) in Dioxane (2 mL). After oxygen was purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure to give **79-2** (300 mg, crude).

Step 3: 79-3

[00593] To a mixture of **79-2** (300 mg, 582.08 μmol), acetate acid (0.2 mL) in THF (1 mL) was added hydrogen peroxide (0.2 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 65%, v/v) to obtain **79-3** (55 mg, 135.66 μmol , 23.31% yield).

Step 4: 79-4

[00594] To a mixture of **79-3** (55 mg, 135.66 μmol), **Intermediate A** (43.65 mg, 162.79 μmol) in MeCN (5 mL) was added Cesium carbonate (132.60 mg, 406.97 μmol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 65%, v/v) to obtain **79-4** (28 mg, 47.25 μmol , 34.83% yield).

Step 5: Compound 79

[00595] To a solution of **79-4** (28 mg, 47.25 μmol) in DCM (1 mL) was added HCl/Dioxane (4 M, 222.34 μL) at 20 °C and stirred at 20 °C for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (3 mL) for 15 minutes and filtered. The filter cake was dried by lyophilization (water: acetonitrile = 4: 1, 20 mL) to give **Compound 79** (7.5 mg, 14.18 μmol , 30.01% yield, HCl salt). ^1H NMR (400 MHz, DMSO- d_6) δ 8.25 (s, 3H), 7.86-7.81 (m, 2H), 7.78 (s, 1H), 7.35 (d, J = 80.0 Hz, 1H), 7.22-7.19 (m, 2H), 4.74 (d, J = 3.5 Hz, 2H), 3.62 (s, 2H), 3.59-3.56 (m, 1H), 3.17-3.14 m, 1H), 3.12 (s, 2H), 1.80-1.62 (m, 12H) ppm. MS: m/z = 493.2 (M+1).

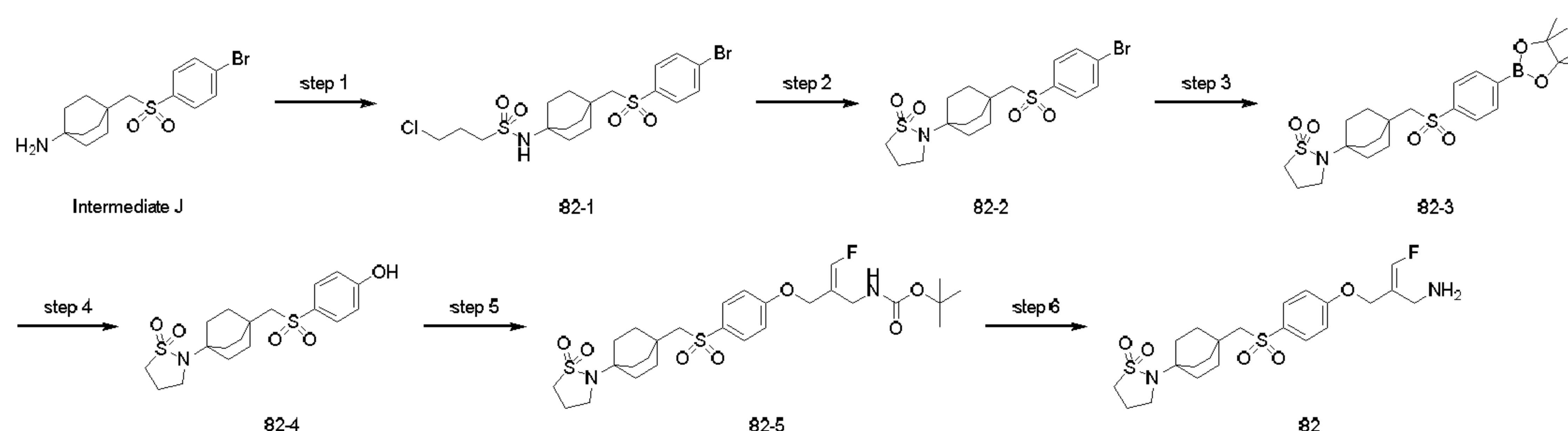
[00596] The compounds of Formula (I') or (I) in Table 12 below were made according to **Example 58** of **Compound 79**.

Table 12

Cmpd No.	^1H NMR and/or LC/MS data
84	^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.81 (m, 2H), 7.27 (d, J = 80.0 Hz, 1H), 7.24-7.18 (m, 2H), 4.73 (d, J = 3.6 Hz, 2H), 3.84 (d, J = 2.2 Hz, 2H), 3.08 (s, 2H), 2.45-2.40 (m, 1H), 1.95-1.73 (m, 13H), 1.69-1.58 (m, 1H) ppm. MS: m/z = 487.2 (M+1).
85	^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.83 (m, 2H), 7.27 (d, J = 80.0 Hz, 1H),

Cmpd No.	¹ H NMR and/or LC/MS data
	7.21 (d, <i>J</i> = 8.9 Hz, 2H), 6.98 (s, 1H), 4.73 (d, <i>J</i> = 3.6 Hz, 2H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.08 (s, 2H), 1.90 (dd, <i>J</i> = 10.4, 5.1 Hz, 6H), 1.80 (dd, <i>J</i> = 10.5, 5.1 Hz, 6H), 1.19 (s, 4H) ppm. MS: <i>m/z</i> = 519.2 (M+1).
86	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.91-7.82 (m, 2H), 7.27 (d, <i>J</i> = 80.0 Hz, 1H), 7.24-7.20 (m, 2H), 4.73 (d, <i>J</i> = 3.5 Hz, 2H), 3.84 (d, <i>J</i> = 2.2 Hz, 2H), 3.09 (s, 2H), 1.98-1.92 (m, 6H), 1.85-1.78 (m, 6H), 1.28-1.17 (m, 4H) ppm. MS: <i>m/z</i> = 469.2 (M+1).
91	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.90-7.83 (m, 2H), 7.27 (d, <i>J</i> = 84.0 Hz, 1H), 7.24-7.17 (m, 2H), 6.38 (s, 0.5H), 4.72 (d, <i>J</i> = 3.5 Hz, 2H), 3.84 (d, <i>J</i> = 2.3 Hz, 2H), 3.07 (s, 2H), 1.94-1.86 (m, 6H), 1.82-1.74 (m, 6H), 1.27 (s, 3H), 0.99 (q, <i>J</i> = 3.8 Hz, 2H), 0.53 (q, <i>J</i> = 3.9 Hz, 2H) ppm. MS: <i>m/z</i> = 465.2 (M+1).
92	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.88-7.84 (m, 2H), 7.27 (d, <i>J</i> = 84.0 Hz, 1H), 7.23-7.18 (m, 2H), 7.07 (s, 0.3H), 4.72 (d, <i>J</i> = 3.5 Hz, 2H), 3.84 (d, <i>J</i> = 2.2 Hz, 2H), 3.07 (s, 2H), 3.03-2.97 (m, 1H), 2.17-2.12 (m, 2H), 2.08-2.00 (m, 2H), 1.97-1.91 (m, 1H), 1.90-1.75 (m, 13H) ppm. MS: <i>m/z</i> = 465.2 (M+1).

Example 59: Synthesis of Compound 82



Step 1: 82-1

- 5 [00597] To a mixture of **Intermediate J** (300 mg, 759.97 μmol, HCl salt) and DIPEA (294.65 mg, 2.28 mmol, 397.11 μL) in DMF (4 mL) was added 3-chloropropylamine (269.10 mg, 1.52 mmol, 185.59 μL) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The mixture was added ethyl acetate (50 mL) and washed with brine (50 mL). The organic layer was concentrated with a rotary evaporator to obtain crude product, which was purified by silica

gel chromatography (4 g, ethyl acetate in petroleum ether, 0 - 35%, v/v) to obtain **82-1** (80 mg, 160.36 μ mol, 21.10% yield).

Step 2: 82-2

5 **[00598]** To a mixture of **82-1** (80 mg, 160.36 μ mol) in DMF (2 mL) was added Cesium carbonate (156.74 mg, 481.08 μ mol) at 30 °C. The reaction solution was stirred for 0.5 hr at 30 °C. The mixture was added ethyl acetate (50 mL) and washed with brine (50 mL). The organic layer was concentrated with a rotary evaporator to obtain **82-2** (75 mg, crude). MS: m/z = 462.0 (M+1).

Step 3: 82-3

10 **[00599]** A 30 mL microwave reaction tube was charged with **82-2** (75 mg, 162.19 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (49.42 mg, 194.63 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (11.87 mg, 16.22 μ mol) and potassium acetate (47.75 mg, 486.57 μ mol) in Dioxane (4 mL). After oxygen was
15 purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure to give **82-3** (120 mg, crude).

Step 4: 82-4

[00600] To a mixture of **82-3** (120 mg, 235.53 μ mol), acetate acid (0.1 mL) in THF (2 mL) was added hydrogen peroxide (0.1 mL, 30% purity) at 20 °C. The reaction solution was stirred
20 for 0.5 hr at 20°C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (4 g, ethyl acetate in petroleum ether, 0 - 80%, v/v) to obtain **82-4** (50 mg, 125.15 μ mol, 53.13% yield).

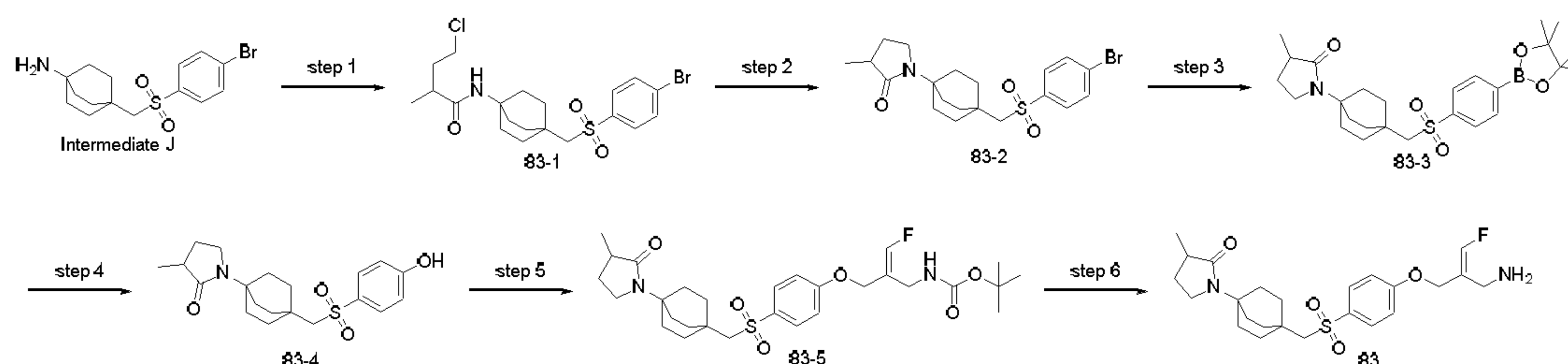
Step 5: 82-5

[00601] To a mixture of **82-4** (50 mg, 125.15 μ mol), **Intermediate A** (40.27 mg, 150.18 μ mol)
25 in MeCN (3 mL) was added Cesium carbonate (81.55 mg, 250.30 μ mol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (12 g, ethyl acetate in petroleum ether, 0 - 65%, v/v) to obtain **82-5** (45 mg, 76.70 μ mol, 61.28% yield).

30 *Step 6: Compound 82*

[00602] To a mixture of **82-5** (45 mg, 76.70 μ mol) in DCM (1 mL) was added HCl/Dioxane (4 M, 1 mL) at 20 °C and stirred at 20 °C for 1 hr. The reaction mixture was concentrated to give crude. The crude was added dichloromethane (20 mL) and washed with saturated NaHCO₃ solution (15 mL $\times$ 3) and water (15 mL). The organic layer was concentrated and dried by lyophilization (water: acetonitrile = 4: 1, 10 mL) to give **Compound 82** (8 mg, 16.44 μ mol, 21.44% yield). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.86-7.80 (m, 2H), 7.20-7.14 (m, 2H), 6.94 (d, *J* = 84.0 Hz, 1H), 4.66 (dd, *J* = 3.6, 1.2 Hz, 2H), 3.46 (d, *J* = 2.5 Hz, 2H), 3.34 (d, *J* = 6.5 Hz, 2H), 3.16 (t, *J* = 7.5 Hz, 2H), 3.06 (s, 2H), 2.26-2.18 (m, 2H), 2.01-1.94 (m, 6H), 1.84-1.77 (m, 6H) ppm. MS: *m/z* = 487.2 (M+1).

10 Example 60: Synthesis of Compound 83



Step 1: 83-1

[00603] To a mixture of **Intermediate J** (700.27 mg, 1.77 mmol, HCl salt), DIPEA (625.28 mg, 4.84 mmol, 842.69 μ L) in DCM (15 mL) was added 4-chloro-2-methyl-butanoyl chloride (250 mg, 1.61 mmol, 103.62 μ L). After addition, the mixture was stirred at 25 °C for 16 hr. Upon completion, the resulting solution was concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 3: 1) to give **83-1** (700 mg, 1.47 mmol, 91.03% yield). MS: *m/z* = 476.1 (M+1).

Step 2: 83-2

[00604] A mixture of **83-1** (400 mg, 838.83 μ mol) and *t*-BuOK (188 mg, 1.68 mmol) in DMSO (10 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was diluted with water and extracted with DCM. The separated organic layer was washed with water for three times and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 1: 1) to give **83-2** (250 mg, 567.67 μ mol, 67.67% yield). MS: *m/z* = 440.1 (M+1).

Step 3: 83-3

[00605] A mixture of **83-2** (250 mg, 567.67 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (216 mg, 850.60 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 57.40 μmol) and potassium acetate (433 mg, 1.70 mmol) in Dioxane (5 mL) was microwaved at 120 °C for 30 min. Upon completion, the resulting mixture was cooled to room temperature, filtered and concentrated to give **83-3** (crude, 250 mg).

Step 4: 83-4

[00606] A mixture of **83-3** (250 mg, 512.86 μmol), hydrogen peroxide (1 mL, 30% purity) and acetate acid (1 mL) in THF (4 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with sodium sulfite, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 1: 1) to give **83-4** (120 mg, 317.88 μmol , 61.98% yield). MS: m/z = 378.2 (M+1).

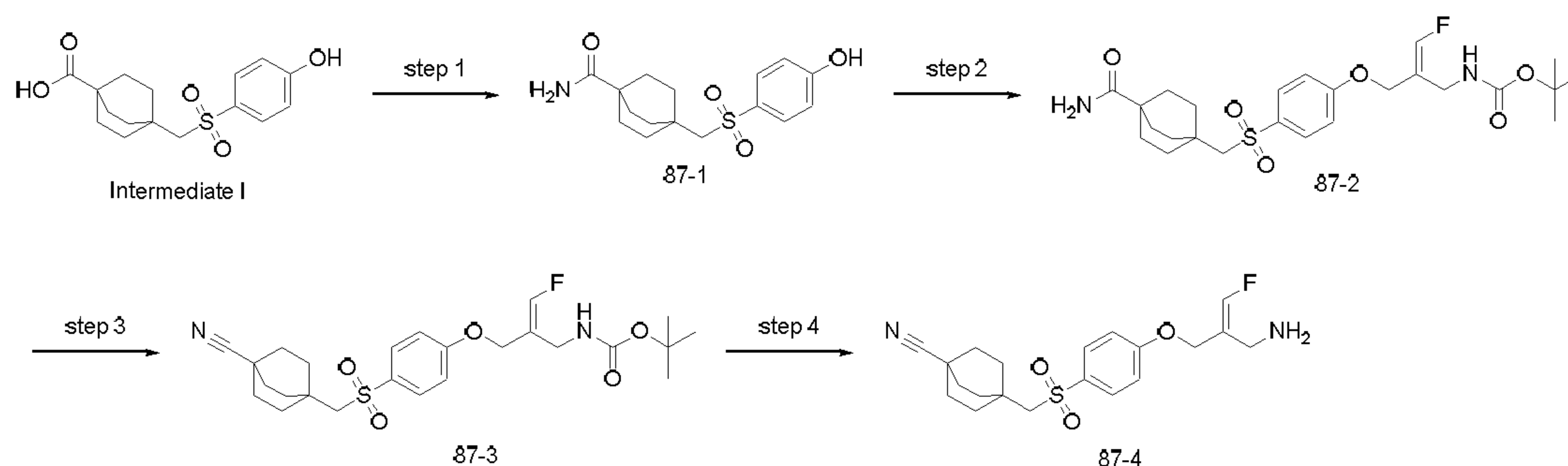
Step 5: 83-5

[00607] A mixture of **83-4** (120 mg, 317.88 μmol), **Intermediate A** (94 mg, 350.59 μmol) and cesium carbonate (517.86 mg, 1.59 mmol) in MeCN (20 mL) was stirred at 95 °C for 1 hr. Upon completion, the resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 20 - 50%, v/v) to give **83-5** (130 mg, 230.21 μmol , 72.42% yield). MS: m/z = 509.2 (M+1-56).

Step 6: Compound 83

[00608] A mixture of **83-5** (130 mg, 230.21 μmol) and HCl/Dioxane (4 M, 5 mL) in Dioxane (4 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was filtered to obtain the filter cake as **Compound 83** (80 mg, 159.66 μmol , 69.36% yield, HCl salt). ^1H NMR (500 MHz, Methanol- d_4) δ 7.79-7.73 (m, 2H), 7.20 (d, J = 64.0 Hz, 1H), 7.14-7.10 (m, 2H), 4.63 (d, J = 3.4 Hz, 2H), 3.74 (d, J = 2.1 Hz, 2H), 3.35-3.30 (m, 1H), 3.29-3.23 (m, 1H), 2.97 (s, 2H), 2.27-2.21 (m, 1H), 2.05-2.02 (m, 1H), 2.01-1.88 (m, 6H), 1.70 (t, J = 7.9 Hz, 6H), 1.41-1.38 (m, 1H), 0.99 (d, J = 7.1 Hz, 3H) ppm. MS: m/z = 465.2 (M+1).

Example 61: Synthesis of Compound 87



Step 1: 87-1

[00609] To a mixture of **Intermediate I** (200 mg, 616.54 μmol), Ammonium chloride (989.39 mg, 18.50 mmol) and HATU (352 mg, 925.76 μmol) in DMF (10 mL) was added DIPEA (239 mg, 1.85 mmol, 322.10 μL). After addition, the mixture was stirred at 25 °C for 16 hr. Upon completion, the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The separated organic layer was washed with water (20 mL $\times$ 3) and brine, dried over anhydrous sodium sulfate, filtered and concentrated to **87-1** (180 mg, 556.58 μmol , 90.27% yield). MS: m/z = 324.1 (M+1).

Step 2: 87-2

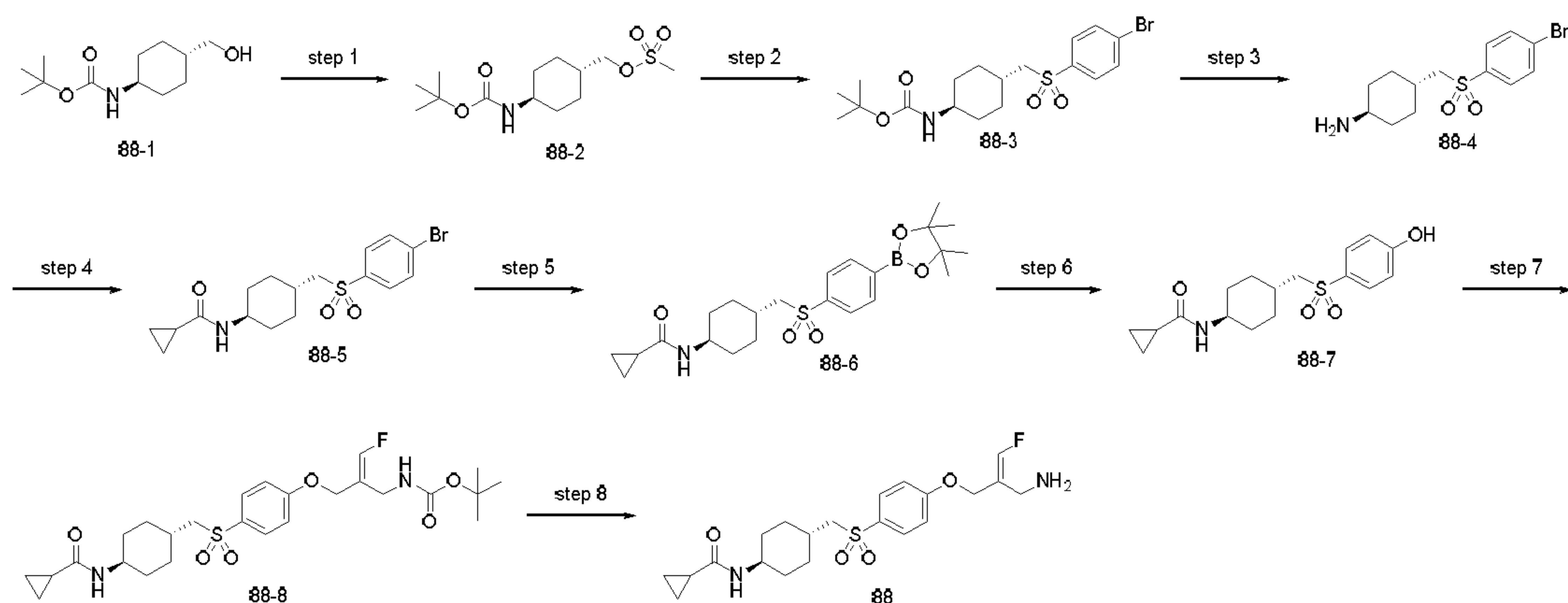
[00610] A mixture of **87-1** (180 mg, 556.58 μmol), **Intermediate A** (179.08 mg, 667.89 μmol) and cesium carbonate (906.72 mg, 2.78 mmol) in MeCN (30 mL) was stirred at 95 °C for 1 hr. The resulting mixture was filtered and concentrated to give **87-2** (280 mg, 548.36 μmol , 98.52% yield). MS: m/z = 455.1 (M+1-56).

Step 3: 87-3

[00611] A mixture of **87-2** (280 mg, 548.36 μmol) and Burgess Reagent (392 mg, 1.64 mmol) in DCM (10 mL) was stirred at 25 °C for 1 hr. The resulting solution was concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 5/1, v/v) to give **87-3** (200 mg, 406.01 μmol , 74.04% yield). MS: m/z = 437.1 (M+1-56).

Step 4: Compound 87

[00612] A mixture of **87-3** (200 mg, 406.01 μmol) and HCl/Dioxane (4 M, 5 mL) in Dioxane (2 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was filtered to give the filter cake as **Compound 87** (120 mg, 279.75 μmol , 68.90% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.83 (m, 2 H), 7.27 (d, J = 80.0 Hz, 1 H), 7.25-7.18 (m, 2 H), 4.73 (d, J = 3.5 Hz, 2 H), 3.84 (d, J = 2.3 Hz, 2 H), 3.09 (s, 2 H), 1.99-1.90 (m, 6 H), 1.80 (dd, J = 10.4, 5.5 Hz, 6 H). MS: m/z = 393.1 (M+1).

Example 62: Synthesis of Compound 88**Step 1: 88-2**

[00613] A mixture of **88-1** (1 g, 4.36 mmol), TEA (1.32 g, 13.08 mmol, 1.82 mL) in DCM (20 mL) was added methanesulfonic acid anhydride (911.56 mg, 5.23 mmol) in one portion at 0 °C. The reaction mixture was stirred at 20 °C for 1 hr. Water (30 mL) was added, and the mixture was extracted with DCM (150 mL), washed with water and brine, dried over anhydrous sodium sulfate. Then, the organic phases were concentrated to obtain **88-2** (1.3 g, 4.23 mmol, 96.98% yield).

Step 2: 88-3

[00614] A mixture of **88-2** (1.3 g, 4.23 mmol), 4-bromobenzenesulfinic acid (1.22 g, 5.50 mmol) and Cesium carbonate (4.13 g, 12.69 mmol) in DMF (10 mL) was heated to 120 °C and stirred at 120 °C for 1 hr. Water (30 mL) was added, and the mixture was extracted with ethyl acetate (150 mL), washed with water and brine, dried over anhydrous sodium sulfate. Then, the solution was concentrated with a rotary evaporator, the crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **88-3** (1.2 g, 2.78 mmol, 65.61% yield).

Step 3: 88-4

[00615] A mixture of **88-3** (0.35 g, 809.49 μmol) in HCl/Dioxane (4 M, 6.07 mL) was stirred at 30 °C for 1 hr. The reaction mixture was concentrated to obtain **88-4** (0.29 g, 786.51 μmol, 97.16% yield, HCl salt). MS: m/z = 332.0 (M+1).

Step 4: 88-5

[00616] To a mixture of **88-4** (0.29 g, 786.51 μmol, HCl salt), TEA (397.94 mg, 3.93 mmol, 548.12 μL) in DCM (10 mL) was added cyclopropanecarbonyl chloride (246.65 mg, 2.36 mmol,

214.48 μ L) dropwise at 0 °C for 0.2 hr and stirred at 30 °C for 0.8 hr. Water (20 mL) was added, and the mixture was extracted with DCM (30 mL), washed with brine, dried over anhydrous sodium sulfate. The organic phases were concentrated to obtain **88-5** (300 mg, 749.38 μ mol, 95.28% yield). MS: m/z = 400.0 (M+1).

5 *Step 5: 88-6*

[00617] A mixture of **88-5** (300 mg, 749.38 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (228.36 mg, 899.26 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27.42 mg, 37.47 μ mol), potassium acetate (227.66 mg, 2.25 mmol) in Dioxane (15 mL) was stirred at 120 °C under microwave
10 for 0.7 hr. The reaction mixture was filtered and concentrated to give **88-6** (335 mg, 748.78 μ mol, 99.92% yield).

Step 6: 88-7

[00618] To a mixture of **88-6** (335 mg, 748.78 μ mol) in acetate acid (1 mL) and THF (4 mL) was added hydrogen peroxide (0.25 mL, 30% purity) dropwise at 20 °C and stirred for 1 hr.
15 Sodium sulfite (1.0 g) was added, and the mixture was filtered and concentrated to give **88-7** (200 mg, 592.71 μ mol, 79.16% yield).

Step 7: 88-8

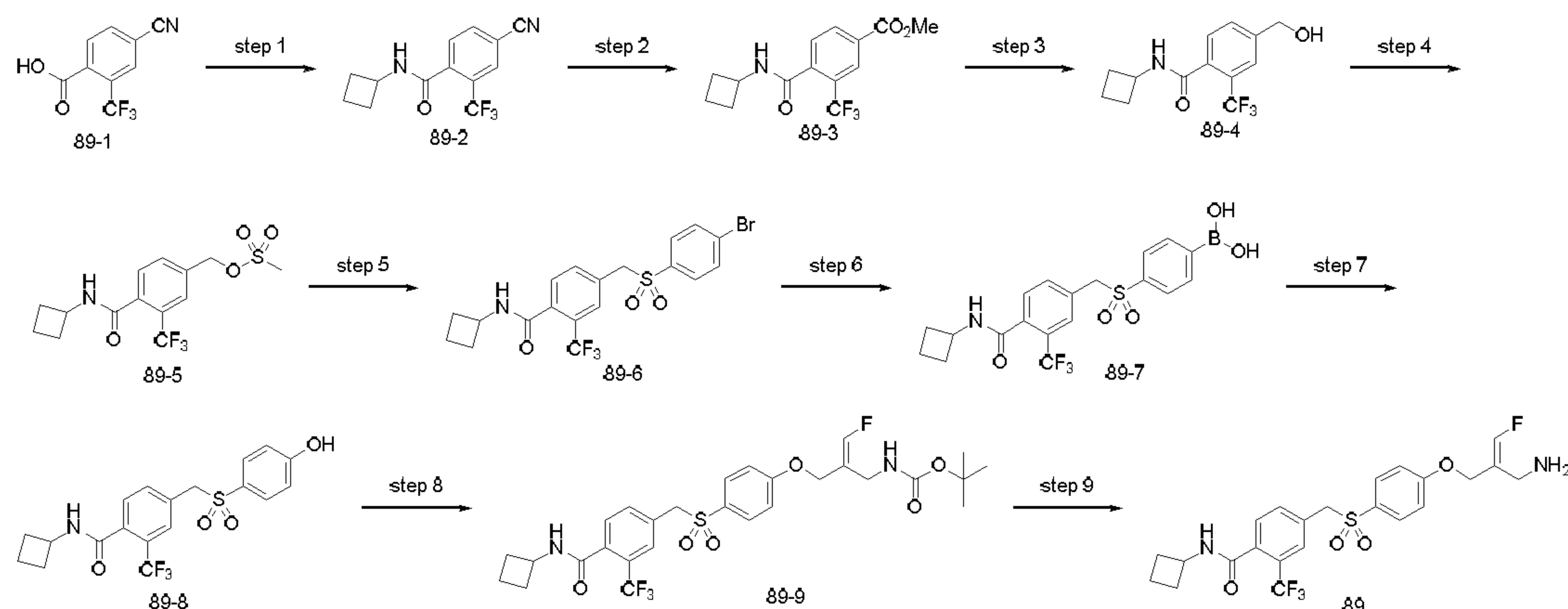
[00619] To a mixture of **88-7** (200 mg, 592.71 μ mol) in MeCN (30 mL) was added Cesium carbonate (579.35 mg, 1.78 mmol), **Intermediate A** (190.70 mg, 711.25 μ mol) and stirred
20 at 95 °C for 0.8 hr. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 30%, v/v) to give **88-8** (145 mg, 276.38 μ mol, 46.63% yield).

Step 8: Compound 88

[00620] A mixture of **88-8** (145 mg, 276.38 μ mol) in HCl/Dioxane (4 M, 2.07 mL) was stirred
25 at 30 °C for 1 hr. Then, the solution was concentrated and the residue was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile; gradient: 5 - 95% B; GT: 25 min; flow rate: 15 mL/min) to obtain **Compound 88** (5.6 mg, 11.90 μ mol, 4.31% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.44 (s, 1H), 7.91-7.69 (m, 2H), 7.12 (d, J = 80.0 Hz, 1H), 7.20-7.08 (m, 2H), 4.63 (d, J = 3.5 Hz, 2H), 3.69 (d, J = 2.3 Hz, 2H), 3.52-3.44 (m, 1H), 3.28 (d, J = 6.4 Hz, 1H), 3.03 (d, J = 6.0 Hz, 2H), 1.80 (d, J = 14.9 Hz,
30 2H).

4H), 1.45-1.39 (m, 1H), 1.12 (q, $J = 10.6$ Hz, 4H), 0.73 (td, $J = 4.7, 2.1$ Hz, 2H), 0.62-0.58 (m, 2H) ppm. MS: $m/z = 425.1$ ($M+1$).

Example 63: Synthesis of Compound 89



5 Step 1: 89-2

[00621] A mixture of **89-1** (1.1 g, 5.11 mmol), cyclobutanamine (400.02 mg, 5.62 mmol, 480.22 μ L), HATU (2.92 g, 7.67 mmol), DIPEA (1.98 g, 15.34 mmol, 2.67 mL) in DMF (10 mL) was stirred at 30 °C for 3 hr. Water (50 mL) was added, and the mixture was extracted with ethyl acetate (150 mL), washed with brine, dried over anhydrous sodium sulfate, the organic phases were concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to **89-2** (1.3 g, 4.85 mmol, 94.78% yield). MS: $m/z = 269.0$ ($M+1$).

Step 2: 89-3

[00622] A mixture of **89-2** (1 g, 3.73 mmol) in HCl in methanol (4 M, 46.60 mL) was heated to 90 °C and stirred at 90 °C for 2 hr. The reaction mixture was concentrated and purified by flash chromatography on silica gel (ethyl acetate in petroleum ether, 5 - 50%, v/v) to give **89-3** (0.5 g, 1.66 mmol, 44.52% yield). MS: $m/z = 302.1$ ($M+1$).

Step 3: 89-4

[00623] A mixture of **89-3** (several batches, 1 g, 3.32 mmol) in THF (30 mL) was added DIBAL-H in hexane (1 M, 13.28 mL) dropwise and stirred at 0 °C for 1 hr. Water (5 mL) was added, the mixture was filtered, the filtrate was concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **89-4** (700 mg, 2.56 mmol, 77.18% yield). MS: $m/z = 274.1$ ($M+1$).

Step 4: 89-5

[00624] To a mixture of **89-4** (0.5 g, 1.83 mmol), TEA (555.48 mg, 5.49 mmol, 765.12 μ L) in DCM (20 mL) was added methanesulfonic acid anhydride (382.50 mg, 2.20 mmol) in portions at 0 °C and stirred for 1 hr. Water (20 mL) was added, and the mixture was extracted with DCM (60 mL), washed with brine, dried over anhydrous sodium sulfate. The organic
5 phases were concentrated to obtain **89-5** (600 mg, 1.71 mmol, 93.33% yield). MS: $m/z = 352.1$ (M+1).

Step 5: 89-6

[00625] A mixture of **89-5** (0.3 g, 853.87 μ mol), Cesium carbonate (556.42 mg, 1.71 mmol), 4-bromobenzenesulfinic acid (245.40 mg, 1.11 mmol) in DMF (10 mL) was stirred
10 at 120 °C under microwave for 1 hr. Water (20 mL) was added, and the mixture was extracted with ethyl acetate (100 mL), washed with brine, dried over anhydrous sodium sulfate. The organic phases were concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 90%, v/v) to obtain **89-6** (260 mg, 545.87 μ mol, 63.93% yield). MS: $m/z = 476.0$ (M+1).

15 *Step 6: 89-7*

[00626] A mixture of **89-6** (260 mg, 545.87 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (207.93 mg, 818.80 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (19.97 mg, 27.29 μ mol), potassium acetate (160.72 mg, 1.64 mmol) in Dioxane (10 mL) was stirred at 120 °C for 1 hr. The
20 reaction mixture was filtered and the filtrate was concentrated to obtain **89-7** (240 mg, 543.94 μ mol, 99.65% yield). MS: $m/z = 442.1$ (M+1).

Step 7: 89-8

[00627] A mixture of **89-7** (240 mg, 543.94 μ mol) in THF (4 mL), acetate acid (1 mL) was added hydrogen peroxide (0.18 mL, 30% purity) dropwise and stirred at 30 °C for 1 hr. Sodium
25 sulfite (1.0 g) was added, filtered and concentrated to get crude product **89-8** (224 mg, 541.83 μ mol, 99.61% yield). MS: $m/z = 414.1$ (M+1).

Step 8: 89-9

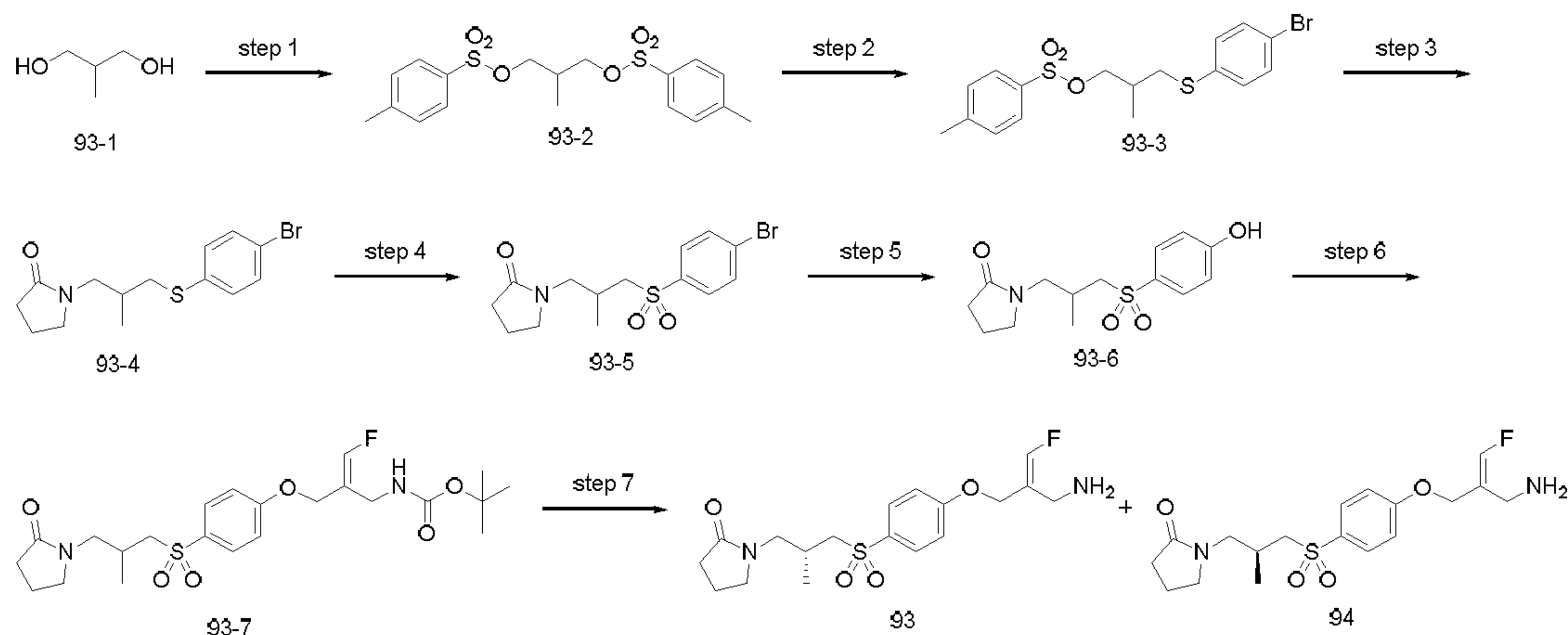
[00628] A mixture of **89-8** (224 mg, 541.83 μ mol), **Intermediate A** (188.86 mg, 704.39 μ mol), Cesium carbonate (529.62 mg, 1.63 mmol) in MeCN (20 mL) was heated to 95 °C and
30 stirred at 95 °C for 1 hr. The reaction mixture was filtered, the filtrate was concentrated and

purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 30%, v/v) to obtain **89-9** (145 mg, 241.42 μ mol, 44.56% yield). MS: m/z = 501.2 ($M+1-100$).

Step 9: Compound 89

[00629] A mixture of **89-9** (145 mg, 241.42 μ mol) in HCl/Dioxane (4 M, 6.04 mL) was stirred at 30 °C for 1 hr. Then, the solution was concentrated and the residue was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile; gradient: 5 - 90% B; GT: 25 min; flow rate: 15 mL/min) to obtain **Compound 89** (25 mg, 46.56 μ mol, 19.29% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.54 (s, 1H), 7.68-7.57 (m, 2H), 7.52 (d, J = 7.5 Hz, 1H), 7.47-7.34 (m, 2H), 7.17 (d, J = 84.0 Hz, 1H), 7.18-7.10 (m, 2H), 4.76-4.67 (m, 2H), 4.63 (s, 2H), 4.44 (p, J = 8.2 Hz, 1H), 3.72 (d, J = 2.3 Hz, 2H), 2.47-2.22 (m, 2H), 2.04-2.00 (m, 2H), 1.80-1.78 (m, 2H) ppm. MS: m/z = 501.2 ($M+1$).

Example 64: Synthesis of Compounds 93 & 94



Step 1: 93-2

[00630] To a mixture of **93-1** (10.0 g, 110.96 mmol) and TEA (33.68 g, 332.89 mmol) in DCM (250 mL) was added tosyl chloride (52.85 g, 277.41 mmol) in portions while the internal temperature was kept below 10 °C. After addition, the resulting mixture was warmed up to 25 °C and stirred for 5 hr. The reaction mixture was poured into water (300 mL) and the organic layer was separated. The aqueous phase was extracted with DCM (200 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether: ethyl acetate = 4: 1 to give **93-2** (43.0 g, 97.25% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.67 (d, J = 8.3 Hz, 4H), 7.28 (d, J = 8.1 Hz, 4H), 3.90-3.74 (m, 4H), 2.39 (s, 6H), 2.15-2.01 (m, 1H), 0.84 (d, J = 7.0 Hz, 3H) ppm.

Step 2: 93-3

[00631] To a mixture of **93-2** (10 g, 25.09 mmol) and potassium acetate (10.39 g, 75.28 mmol) in MeCN (80 mL) was added 4-bromobenzenethiol (4.74 g, 25.09 mmol) in portions while the internal temperature was kept below 25 °C. After stirred at 50 °C for 3 hr, the reaction mixture was poured into water (300 mL) and the organic layer was separated. The aqueous phase was extracted with dichloromethane (200 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column eluted with petroleum ether: ethyl acetate = 4: 1 to give **93-3** (3.5 g, 33.58% yield). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.74 (dd, *J* = 17.1, 10.4 Hz, 2H), 7.35 (dd, *J* = 15.9, 8.3 Hz, 4H), 7.16-7.07 (m, 2H), 4.06-3.95 (m, 2H), 2.93 (dd, *J* = 13.3, 6.6 Hz, 1H), 2.74 (dd, *J* = 13.3, 6.8 Hz, 1H), 2.45 (d, *J* = 3.9 Hz, 3H), 2.06-1.95 (m, 1H), 1.00 (t, *J* = 13.0 Hz, 3H) ppm.

Step 3: 93-4

[00632] To a mixture of pyrrolidin-2-one (245.87 mg, 2.89 mmol) in DMF (50 mL) was added *t*-BuOK (808.93 mg, 7.22 mmol) and **93-3** (1.0 g, 2.41 mmol) at 25 °C. After stirred at 25 °C for 3 hr, the reaction mixture was poured into water (200 mL) and extracted with DCM (150 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column (petroleum ether: ethyl acetate = 3: 1) to give **93-4** (600 mg, 75.92% yield). MS: *m/z* = 328 (*M*+1).

Step 4: 93-5

[00633] To a mixture of **93-4** (550 mg, 1.68 mmol) in water/methanol (25 mL, 1/4) was added Oxone (2.06 g, 3.35 mmol) at 25 °C. After stirred at 25 °C for 3 hr, the reaction mixture was poured into water (60 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give **93-5** (530 mg, 87.80% yield). MS: *m/z* = 360 (*M*+1).

Step 5: 93-6

[00634] To a mixture of **93-5** (300 mg, 832.73 μmol) in Dioxane/water (30 mL, 4/1) was added *t*-BuXPhos (70.62 mg, 166.55 μmol), KOH (140.18 mg, 2.51 mmol) and Pd₂(dba)₃ (76.20 mg, 83.27 μmol). The resulting mixture was stirred at 100 °C for 3 hr under argon atmosphere. After cooling down to room temperature, the reaction mixture was filtered and the filter cake was washed with ethyl acetate (150 mL). The filtrate was washed with brine (50 mL × 3), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by

silica gel column (dichloromethane: ethyl acetate = 2: 1) to give **93-6** (240 mg, 96.92% yield). MS: $m/z = 298$ (M+1).

Step 6: 93-7

[00635] To a mixture of **93-6** (240 mg, 807.08 μmol) and potassium carbonate (348.05 mg, 2.52 mmol) in MeCN (15 mL) was added **Intermediate A** (225.41 mg, 840.71 μmol). The resulting mixture was stirred at 80 °C for 3 hr. After cooling down to room temperature, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (40 mL $\times$ 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography column (dichloromethane: methanol = 10: 1) to give **93-7** (329 mg, 84.12% yield). MS: $m/z = 485$ (M+1).

Step 7: Compound 93 & 94

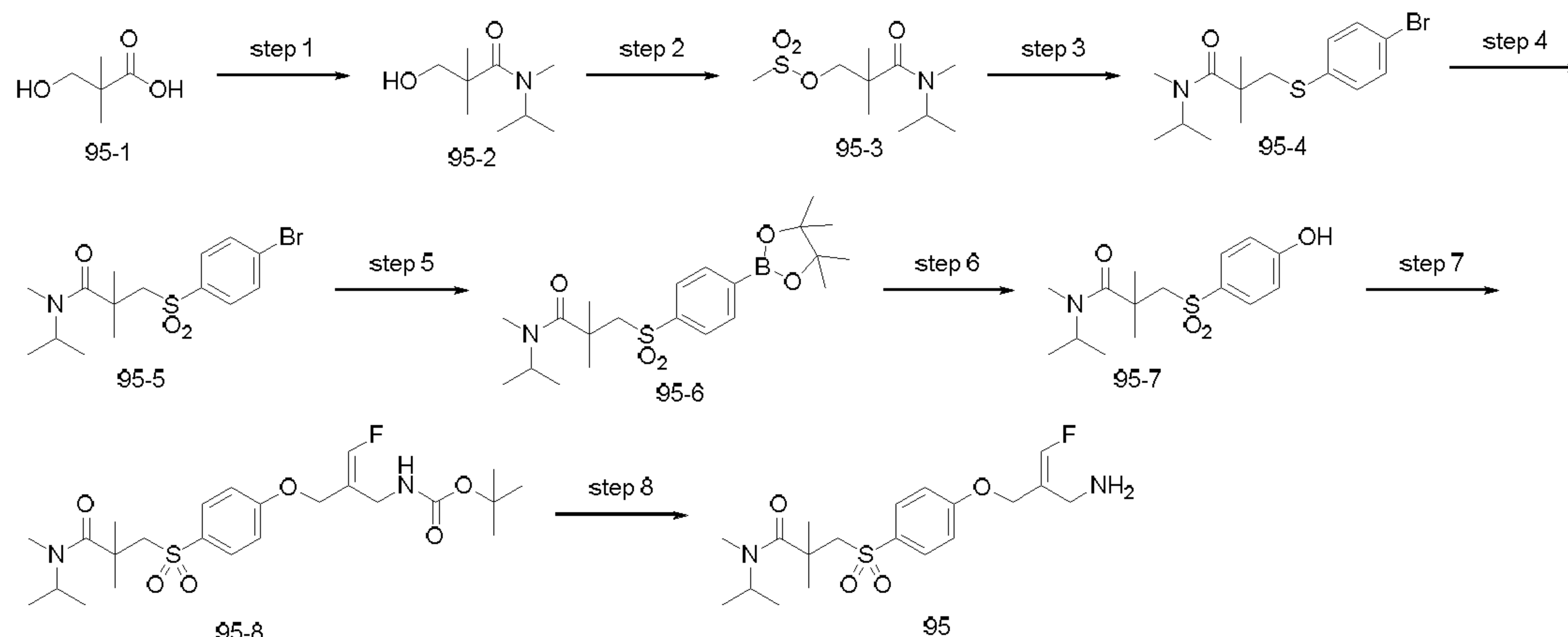
[00636] To a mixture of **93-7** (329 mg, 678.94 μmol) in DCM (5 mL) was added HCl (3 M in ethyl acetate, 5 mL). After stirred at 25 °C for 1 hr, the excess solvent was removed under reduced pressure. The residue was purified by *prep*-HPLC (HCO₂H) and SFC (column: Daicel chiralpak AD Prep C18 10 μm 25 $\times$ 250 mm; A: Supercritical CO₂, B: EtOH; GT: 12 min; flow rate: 70 g/min) and *prep*-HPLC (column: Sunfire Prep C18 10 μm 19 $\times$ 250 mm; A: 0.05% HCl water, B: acetonitrile; gradient: 15 - 35% B; GT: 18 min; flow rate: 20 mL/min) to give Enantiomer 1 (**Compound 93 or 94**) (50 mg, 17.50% yield, HCl salt) and Enantiomer 2 (**Compound 94 or 93**) (50 mg, 17.50% yield, HCl salt). Enantiomer 1: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 3H), 7.89-7.82 (m, 2H), 7.29 (dd, $J = 48.7, 41.7$ Hz, 3H), 4.76 (d, $J = 3.2$ Hz, 2H), 3.61 (d, $J = 4.5$ Hz, 2H), 3.27-3.12 (m, 4H), 3.09-2.91 (m, 2H), 2.20 (dd, $J = 16.8, 9.0$ Hz, 2H), 2.14-2.04 (m, 1H), 1.95-1.73 (m, 2H), 0.92 (d, $J = 6.7$ Hz, 3H). MS: $m/z = 385.2$ (M+1). Enantiomer 2: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.35 (s, 3H), 7.85 (t, $J = 5.9$ Hz, 2H), 7.32 (dd, $J = 59.8, 29.5$ Hz, 3H), 4.77 (d, $J = 3.1$ Hz, 2H), 3.61 (d, $J = 4.8$ Hz, 2H), 3.26-3.11 (m, 4H), 3.09-2.91 (m, 2H), 2.19 (t, $J = 8.3$ Hz, 2H), 2.09 (dt, $J = 14.1, 6.9$ Hz, 1H), 1.91-1.75 (m, 2H), 0.92 (d, $J = 6.7$ Hz, 3H). MS: $m/z = 385.2$ (M+1).

[00637] The compounds of Formula (I') or (I) in Table 13 below were made according to **Example 64 of Compound 93 & 94**.

Table 13

Cmpd No.	¹ H NMR and/or LC/MS data
104 or 105	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 (s, 3H), 7.85 (d, <i>J</i> = 8.9 Hz, 2H), 7.46-7.23 (m, 3H), 4.76 (d, <i>J</i> = 3.1 Hz, 2H), 3.61 (d, <i>J</i> = 5.4 Hz, 2H), 3.40 (dd, <i>J</i> = 13.3, 8.2 Hz, 1H), 3.21-3.06 (m, 3H), 3.03-2.90 (m, 2H), 2.18 (t, <i>J</i> = 5.6 Hz, 3H), 1.75-1.51 (m, 4H), 0.92 (d, <i>J</i> = 6.7 Hz, 3H) ppm. MS: <i>m/z</i> = 399.2 (M+1).
105 or 104	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.30 (s, 3H), 7.85 (d, <i>J</i> = 8.9 Hz, 2H), 7.45-7.22 (m, 3H), 4.76 (d, <i>J</i> = 3.1 Hz, 2H), 3.61 (d, <i>J</i> = 5.4 Hz, 2H), 3.40 (dd, <i>J</i> = 13.3, 8.2 Hz, 1H), 3.21-3.06 (m, 3H), 3.03-2.90 (m, 2H), 2.18 (t, <i>J</i> = 5.6 Hz, 3H), 1.75-1.51 (m, 4H), 0.92 (d, <i>J</i> = 6.7 Hz, 3H) ppm. MS: <i>m/z</i> = 399.2 (M+1).
112 or 113	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 8.38 (s, 3H), 7.94-7.91 (d, <i>J</i> = 8.8 Hz, 2H), 7.45-7.23 (m, 3H), 4.78 (d, <i>J</i> = 2.8 Hz, 2H), 4.03-3.87 (m, 5H), 3.61-3.59 (d, <i>J</i> = 4.8 Hz, 2H), 3.35-3.31 (d, <i>J</i> = 12.4 Hz, 1H), 3.25-3.14 (m, 3H), 3.06-2.97 (m, 3H), 2.45 (s, 1H), 1.13-1.12 (d, <i>J</i> = 6.4 Hz, 3H) ppm. MS: <i>m/z</i> = 387.2 (M+1).
113 or 112	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1H), 8.46 (s, 3H), 7.94-7.91 (d, <i>J</i> = 8.8 Hz, 2H), 7.45-7.23 (m, 3H), 4.80 (s, 2H), 3.96-3.87 (m, 5H), 3.60-3.59 (d, <i>J</i> = 4.8 Hz, 2H), 3.34-3.02 (m, 7H), 2.45 (s, 1H), 1.14-1.12 (d, <i>J</i> = 6.8 Hz, 3H) ppm. MS: <i>m/z</i> = 387.2 (M+1).
109 or 110	Intermediate K was used. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.33 (s, 3H), 7.83 (dd, <i>J</i> = 9.4, 2.4 Hz, 2H), 7.47-7.19 (m, 3H), 4.76 (d, <i>J</i> = 3.1 Hz, 2H), 3.61 (d, <i>J</i> = 4.6 Hz, 2H), 3.20 (dd, <i>J</i> = 8.6, 5.0 Hz, 2H), 3.15-2.93 (m, 4H), 2.24-2.09 (m, 1H), 1.85-1.72 (m, 2H), 1.70-1.55 (m, 6H), 1.50-1.38 (m, 2H), 0.91 (d, <i>J</i> = 6.7 Hz, 3H) ppm. MS: <i>m/z</i> = 439.3 (M+1).
110 or 109	Intermediate K was used. ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (s, 3H), 7.84 (d, <i>J</i> = 8.9 Hz, 2H), 7.47-7.21 (m, 3H), 4.77 (d, <i>J</i> = 3.1 Hz, 2H), 3.61 (d, <i>J</i> = 4.6 Hz, 2H), 3.20 (dd, <i>J</i> = 8.5, 5.1 Hz, 2H), 3.14-2.94 (m, 4H), 2.23-2.10 (m, 1H), 1.85-1.72 (m, 2H), 1.70-1.53 (m, 6H), 1.46 (d, <i>J</i> = 6.7 Hz, 2H), 0.91

Cmpd No.	¹ H NMR and/or LC/MS data
	(d, <i>J</i> = 6.7 Hz, 3H) ppm. MS: <i>m/z</i> = 439.3 (M+1).

Example 65: Synthesis of Compound 95**Step 1: 95-2**

- 5 [00638] To a mixture of **95-1** (500 mg, 4.23 mmol) and N-methylpropan-2-amine (928.67 mg, 12.70 mmol, 1.32 mL) in DCM (20 mL) was added HATU (1.93 g, 5.08 mmol) and TEA (1.28 g, 12.70 mmol, 1.77 mL) at 30 °C. The reaction solution was stirred for 1 hr at 30 °C. Then, ethyl acetate (100 mL) was added and the mixture reaction was washed with water (100 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated to obtain **95-2** (500 mg, crude). MS:
- 10 *m/z* = 173.2 (M+1).

Step 2: 95-3

- [00639] To a mixture of **95-2** (500 mg, 2.89 mmol), TEA (876.09 mg, 8.66 mmol, 1.21 mL) in DCM (10 mL) was added methanesulfonyl chloride (502.72 mg, 2.89 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 0 °C. Water (5 mL) was added, the organic was dried over anhydrous sodium sulfate and concentrated to give **95-3** (400 mg, crude). MS: *m/z* = 251.3 (M+1).
- 15

Step 3: 95-4

- [00640] To a mixture of **95-3** (400 mg, 1.59 mmol) and 4-bromobenzenethiol (361.08 mg, 1.91 mmol) in MeCN (20 mL) was added Cesium carbonate (1.56 g, 4.77 mmol) at 20 °C. The reaction solution was stirred for 24 hr at 80 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether:
- 20

ethylacetate = 4: 1, v/v) to obtain **95-4** (120 mg, 348.52 μmol , 21.90% yield). MS: $m/z = 344.3$ (M+1).

Step 4: 95-5

5 [00641] A mixture of **95-4** (120 mg, 348.52 μmol) and m-CPBA (153.23 mg, 1.05 mmol, 85% purity) in DCM (10 mL) was stirred at 20 °C for 1 hr. The sodium sulfite (6 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 15 - 50%, v/v) to obtain **95-5** (100 mg, 265.74 μmol , 76.25% yield). MS: $m/z = 376.3$ (M+1).

Step 5: 95-6

10 [00642] To a mixture of **95-5** (80 mg, 212.59 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (64.78 mg, 255.11 μmol) in Dioxane (3 mL) was added potassium acetate (63.88 mg, 637.78 μmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (15.56 mg, 21.26 μmol) at 20 °C under nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution
15 was concentrated with a rotary evaporator and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **95-6** (60 mg, 141.72 μmol , 66.66% yield). MS: $m/z = 423.3$ (M+1).

Step 6: 95-7

[00643] To a mixture of **95-6** (60 mg, 141.72 μmol) in THF (4 mL) was added acetate acid (1
20 mL) and hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 25 °C for 30 min. The sodium sulfite (1 g) was added to the mixture. The reaction mixture was filtered and concentrated to give **95-7** (100 mg, crude). MS: $m/z = 313.4$ (M+1).

Step 7: 95-8

[00644] To a mixture of **95-7** (100 mg, 319.07 μmol) and **Intermediate A** (94.79 mg, 353.51
25 μmol) in MeCN (10 mL) was added Cesium carbonate (345.55 mg, 1.06 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 86 °C. Then, the solution was filtered and concentrated to obtain **95-8** (130 mg, crude).

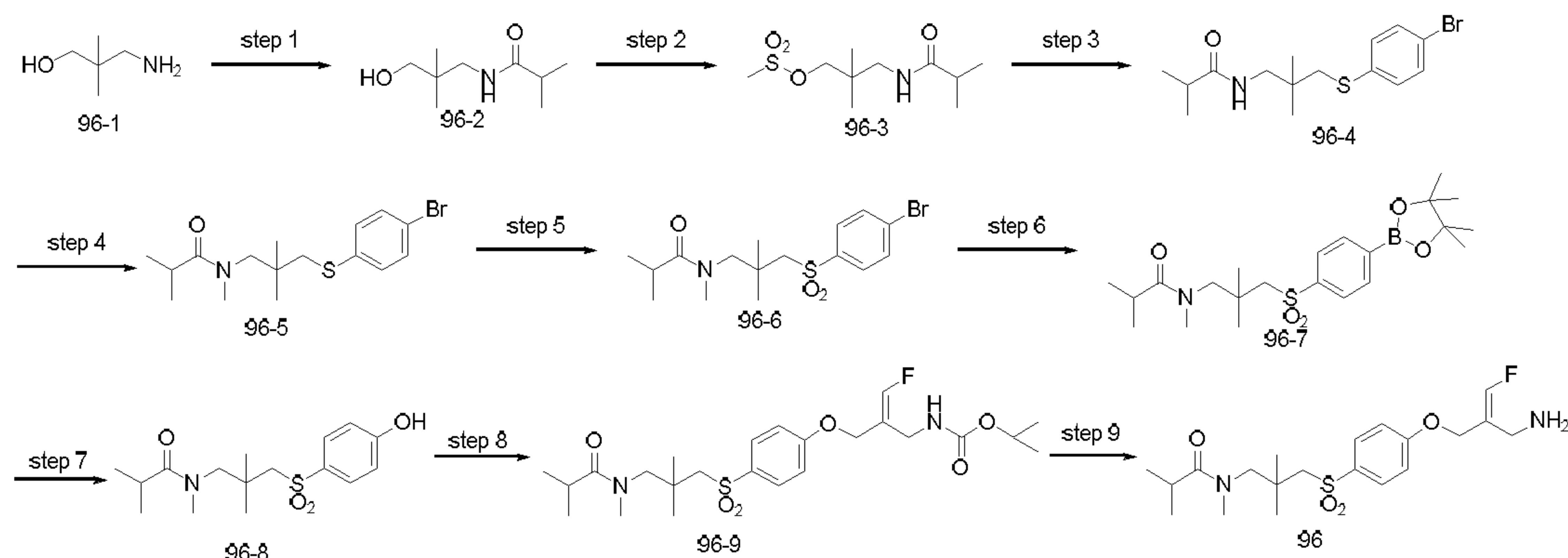
Step 8: Compound 95

[00645] A mixture of **95-8** (120 mg, 239.70 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at
30 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H

water, B: acetonitrile; gradient: 5-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain

Compound 95 (20 mg, 44.79 μ mol, 18.69% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.50 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 80.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 3.6 Hz, 2H), 3.80 (d, *J* = 2.4 Hz, 2H), 3.65 (s, 2H), 2.88 (s, 3H), 2.58-2.52(m, 1H), 1.45 (s, 6H), 1.17 (d, *J* = 6.8 Hz, 6H) ppm. MS: *m/z* = 401.49 (M+1).

Example 66: Synthesis of Compound 96



Step 1: 96-2

[00646] To a mixture of **96-1** (500 mg, 4.85 mmol), TEA (1.47 g, 14.54 mmol, 2.03 mL) in DCM (10 mL) was added 2-methylpropanoyl chloride (309.85 mg, 2.91 mmol, 303.78 μ L) at 0 °C. The reaction solution was stirred for 1 hr at 0 °C. Then, water (20 mL) was added, dried over anhydrous sodium sulfate and concentrated to obtain **96-2** (600 mg, 3.46 mmol, 71.45% yield). MS: *m/z* = 173.2 (M+1).

Step 2: 96-3

[00647] To a mixture of **96-2** (600 mg, 3.46 mmol), TEA (1.05 g, 10.39 mmol, 1.45 mL) in DCM (10 mL) was added methanesulfonic acid anhydride (723.92 mg, 4.16 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 0 °C. Water (5 mL) was added, the organic was dried over anhydrous sodium sulfate and concentrated to give **96-3** (670 mg, crude). MS: *m/z* = 334.4 (M+1).

Step 3: 96-4

[00648] A 30 mL microwave reaction tube was charged with **96-3** (0.6 g, 2.39 mmol), 4-bromobenzenethiol (496.49 mg, 2.63 mmol), Cesium carbonate (2.33 g, 7.16 mmol) in acetonitrile (20 mL). After oxygen was purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 100 °C for 30 min in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The

resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0 - 100%, v/v) to deliver **96-4** (300 mg, 871.31 μ mol, 36.50% yield). MS: $m/z = 344.3$ (M+1).

Step 4: 96-5

5 [00649] To a mixture of **96-4** (300 mg, 871.31 μ mol) and NaH (66.77 mg, 1.67 mmol, 60% purity) in DMF (20 mL) was added iodomethane (247.34 mg, 1.74 mmol, 108.48 μ L) at 0 °C. The reaction solution was stirred for 2 hr at 20 °C. Water (50 mL) was added and the mixture was extracted with ethyl acetate (100 mL), the organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give **96-5** (250 mg, crude). MS: $m/z = 358.3$ (M+1).

Step 5: 96-6

10 [00650] A mixture of **96-5** (200 mg, 558.14 μ mol) and m-CPBA (308.42 mg, 1.67 mmol, 85% purity) in DCM (10 mL) was stirred at 20 °C for 1 hr. The sodium sulfite (4 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 15 - 50%, v/v) to obtain **96-6** (180 mg, 461.14 μ mol, 82.62% yield). MS: $m/z = 390.3$ (M+1).

15 *Step 6: 96-7*

[00651] To a mixture of **96-6** (180 mg, 461.14 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (175.65 mg, 691.71 μ mol) in Dioxane (10 mL) was added bis(diphenylphosphino)ferrocene]dichloropalladium(II) (33.74 mg, 46.11 μ mol) at 30 °C under the nitrogen atmosphere. The reaction solution was stirred for 2 hr at 20 100 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **96-7** (120 mg, 274.35 μ mol, 59.49% yield). MS: $m/z = 437.4$ (M+1).

Step 7: 96-8

25 [00652] To a mixture of **96-7** (120 mg, 274.35 μ mol) in THF (4 mL) and acetate acid (1 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. The sodium sulfite (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **96-8** (0.7 g, crude). MS: $m/z = 327.4$ (M+1).

Step 8: 96-9

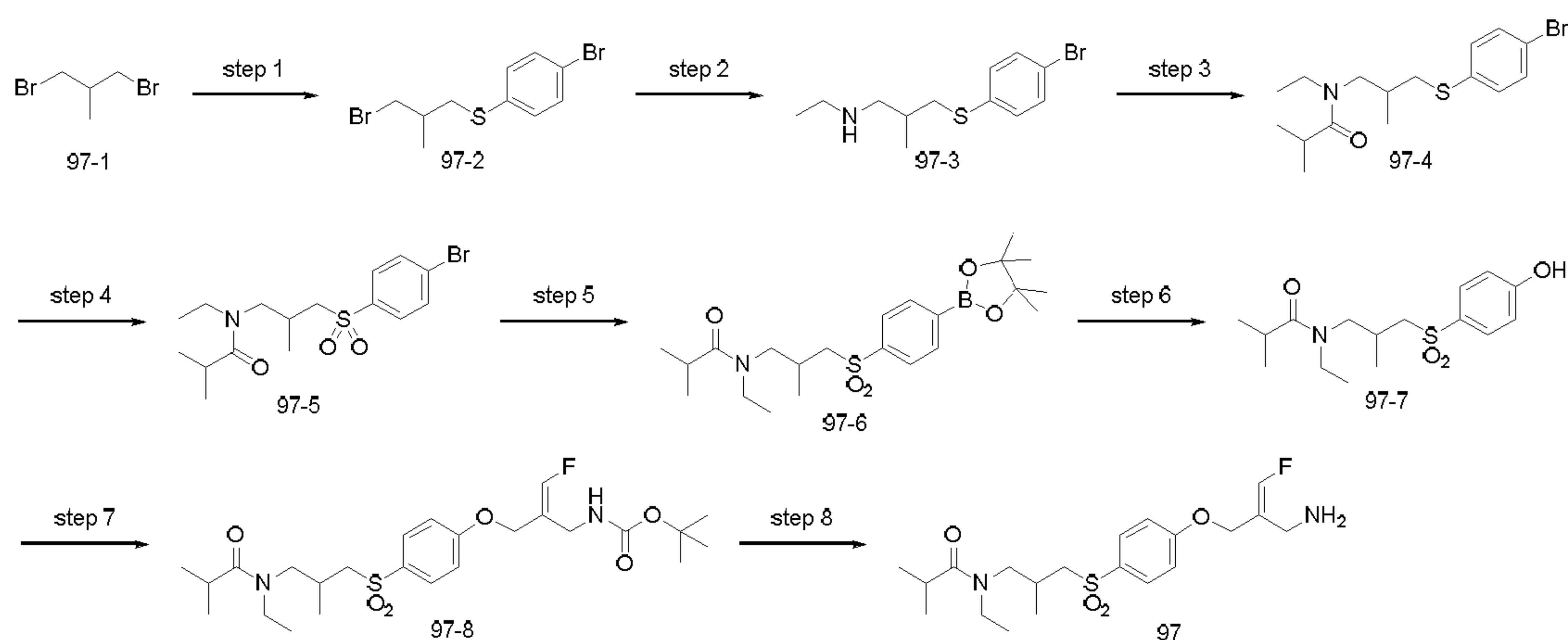
30 [00653] To a mixture of **96-8** (0.7 g, 2.14 mmol) and **Intermediate A** (114.64 mg, 427.56 μ mol) in MeCN (20 mL) was added Cesium carbonate (2.09 g, 6.41 mmol) at 20 °C. The

reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **96-9** (200 mg, crude).

Step 9: Compound 96

[00654] A mixture of **96-9** (190.59 mg, 391.68 μ mol) in HCl/Dioxane (4 M, 4 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 10-40% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Comopund 96** (20 mg, 48.25 μ mol, 12.32% yield, HCO₂H salt). MS: m/z = 415.81 (M+1).

Example 67: Synthesis of Compound 97



Step 1: 97-2

[00655] To a mixture of **97-1** (1.03 g, 4.76 mmol), potassium iodide (66 mg, 397.59 μ mol, 21.15 μ L), Cesium carbonate (2.58 g, 7.93 mmol) in MeCN (15 mL) was added 4-bromobenzenethiol (750 mg, 3.97 mmol) in MeCN (5 mL). After addition, the mixture was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was filtered. The filtrate was concentrated to give **97-2** (1.20 g, 3.70 mmol, 93.35% yield).

Step 2: 97-3

[00656] A mixture of **97-2** (1.20 g, 3.70 mmol), ethanamine (906 mg, 11.11 mmol, HCl salt) and DIPEA (2.39 g, 18.51 mmol, 3.22 mL) in MeCN (10 mL) was microwaved at 120 °C for 1 hr. Upon completion, the resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated and purified by silica gel chromatography (dichloromethane: methanol = 20: 1) to give **97-3** (770 mg, 2.67 mmol, 72.14% yield). MS: m/z = 288.1 (M+1).

Step 3: 97-4

[00657] To a mixture of **97-3** (770 mg, 2.67 mmol) and TEA (810.94 mg, 8.01 mmol, 1.12 mL) in DCM (20 mL) was added 2-methylpropanoyl chloride (1.42 g, 13.36 mmol, 1.40 mL) dropwise. After addition, the solution was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with water (20 mL). The separated organic layer was concentrated. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give **97-4** (160 mg, 446.51 µmol, 16.71% yield). MS: $m/z = 358.1$ (M+1).

Step 4: 97-5

[00658] To a mixture of **97-4** (160 mg, 446.51 µmol) in DCM (10 mL) was added m-CPBA (226.62 mg, 1.12 mmol, 85% purity). After addition, the solution was stirred at 25 °C for 1 hr.

Upon completion, the resulting solution was quenched with aqueous sodium sulfite. The separated organic layer was washed with aqueous NaHCO₃ and brine, dried over anhydrous sodium sulfate, filtered and concentrated to give **97-5** (170 mg, 435.52 µmol, 97.54% yield). MS: $m/z = 390.1$ (M+1).

Step 5: 97-6

[00659] A mixture of **97-5** (170 mg, 435.52 µmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (166 mg, 653.70 µmol), Pd(dppf)Cl₂·dichloromethane (36 mg, 44.08 µmol) and potassium acetate (128 mg, 1.30 mmol) in Dioxane (10 mL) was microwaved at 120 °C for 1 hr. Upon completion, the resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated to give **97-6** (190 mg, 434.39 µmol, 99.74% yield).

Step 6: 97-7

[00660] A mixture of **97-6** (190 mg, 434.39 µmol), hydrogen peroxide (0.5 mL, 30% purity) and acetic acid (0.5 mL) in THF (2 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with sodium sulfite, filtered and concentrated to give **97-7** (140 mg, 427.56 µmol, 98.43% yield).

Step 7: 97-8

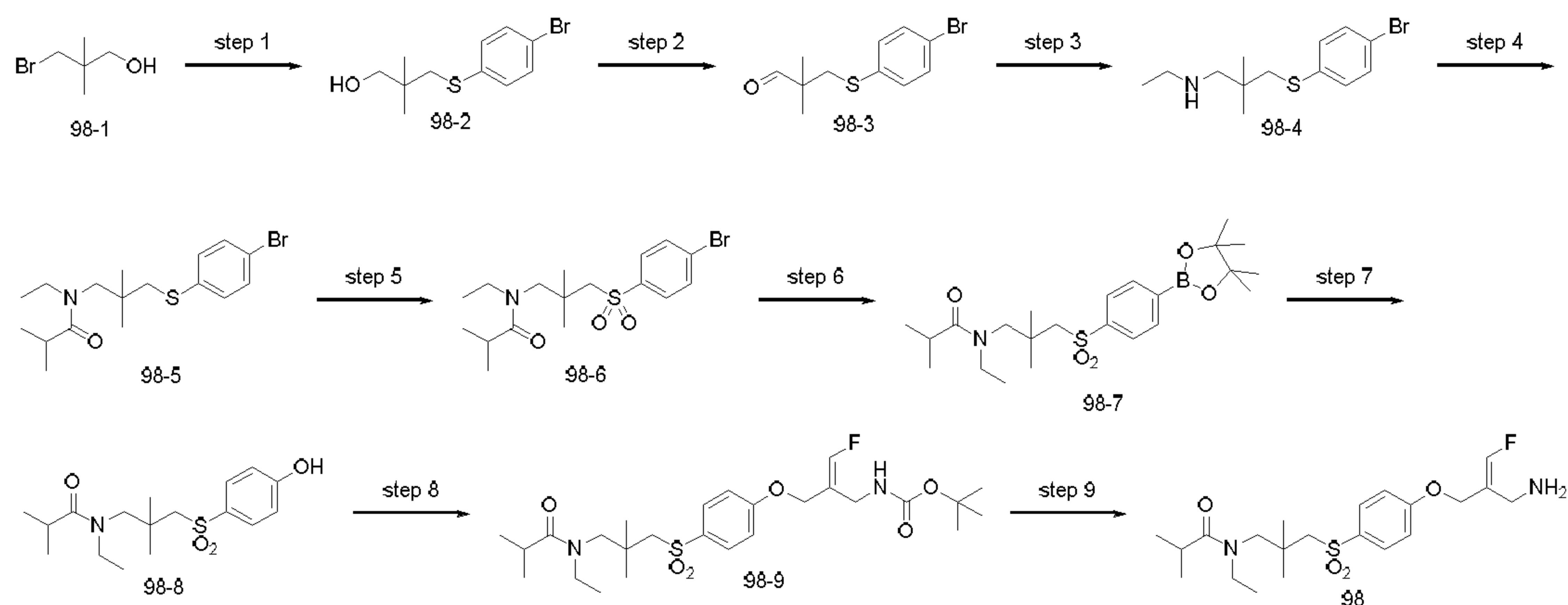
[00661] A mixture of **97-7** (140 mg, 427.56 µmol), **Intermediate A** (140 mg, 522.15 µmol) and Cesium carbonate (700 mg, 2.15 mmol) in MeCN (20 mL) was stirred at 95 °C for 2 hr. Upon completion, the resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography (petroleum

ether: ethyl acetate = 2: 1) to give **97-8** (140 mg, 272.03 μ mol, 63.62% yield). MS: m/z = 515.3 (M+1).

Step 8: Compound 97

[00662] To a mixture of **97-8** (140 mg, 272.03 μ mol) in DCM (4 mL) was added
 5 trifluoroacetic acid (2.96 g, 25.96 mmol, 2 mL). After addition, the solution was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was concentrated. The residue was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to give **Compound 97** (92 mg, 197.76 μ mol, 72.70% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.51 (s, 0.3H), 7.93-7.84 (m, 2H), 7.25 (d, J = 80.0 Hz, 1H), 7.27-7.20 (m, 2H), 4.72 (d, J = 3.3 Hz, 2H),
 10 3.82 (d, J = 2.2 Hz, 2H), 3.58-3.44 (m, 1H), 3.45-3.36 (m, 1H), 3.31-2.96 (m, 4H), 2.96-2.78 (m, 1H), 2.46-2.26 (m, 1H), 1.17 (t, J = 7.1 Hz, 2H), 1.13-0.99 (m, 10H). MS: m/z = 415.7 (M+1).

Example 68: Synthesis of Compound 98



15 Step 1: 98-2

[00663] A mixture of 4-bromobenzenethiol (4 g, 21.16 mmol), **98-1** (4.59 g, 27.50 mmol), Cesium carbonate (13.79 g, 42.31 mmol), potassium iodide (352.00 mg, 2.12 mmol) in MeCN
 (20 mL) was microwaved at 120 °C for 1 hr. Upon completion, the resulting mixture was cooled to room temperature and filtered. The filtrate was concentrated to give **98-2** (5.8 g, 21.08 mmol,
 20 99.62% yield).

Step 2: 98-3

[00664] To a mixture of **98-2** (1 g, 3.63 mmol) DCM (20 mL) was added Dess-Martin Periodinane (2.31 g, 5.45 mmol) at 0 °C. After addition, the mixture was stirred at 25 °C for 1 hr. Upon completion, the resulting mixture was quenched with aqueous Na₂S₂O₃. The separated

organic layer was concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 20%) to give **98-3** (700 mg, 2.56 mmol, 70.52% yield).

Step 3: 98-4

[00665] To a mixture of **98-3** (500 mg, 1.83 mmol) and ethanamine (448 mg, 5.49 mmol, HCl salt) in methanol (15 mL) was added acetate acid (275 mg, 4.58 mmol) and NaBH₃CN (230 mg, 3.66 mmol). After addition, the mixture was stirred at 25 °C for 2 hr. Upon completion, the resulting mixture was washed with saturated aqueous NaHCO₃ and extracted with ethyl acetate (30 mL). The separated organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (dichloromethane: methanol = 20: 1) to give **98-4** (240 mg, 793.98 μmol, 43.38% yield). MS: m/z = 302.1 (M+1).

Step 4: 98-5

[00666] To a mixture of **98-4** (240 mg, 793.98 μmol) and DIPEA (513 mg, 3.97 mmol, 691.37 μL) in DCM (20 mL) was added 2-methylpropanoyl chloride (423.00 mg, 3.97 mmol, 414.71 μL) at 0 °C. After addition, the solution was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was washed with water (20 mL) and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 5 - 10%, v/v) to give **98-5** (200 mg, 537.11 μmol, 67.65% yield). MS: m/z = 372.1 (M+1).

Step 5: 98-6

[00667] To a mixture of **98-5** (200 mg, 537.11 μmol) in DCM (15 mL) was added m-CPBA (327 mg, 1.61 mmol, 85% purity). After addition, the solution was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was washed with saturated aqueous NaHCO₃ and saturated aqueous sodium sulfite. The separated organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give **98-6** (210 mg, 519.34 μmol, 96.69% yield). MS: m/z = 404.1 (M+1).

Step 6: 98-7

[00668] A mixture of **98-6** (210 mg, 519.34 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (198 mg, 779.72 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (38.00 mg, 51.93 μmol) and potassium acetate (153 mg, 1.56 mmol) in Dioxane (10 mL) was microwaved at 120 °C for 40 min. Upon

completion, the resulting mixture was cooled down to room temperature, filtered and concentrated to give **98-7** (230 mg, 509.50 μmol , 98.11% yield). MS: $m/z = 452.3$ (M+1).

Step 7: 98-8

[00669] A mixture of **98-7** (230 mg, 509.50 μmol), hydrogen peroxide (1 mL, 30% purity) and acetate acid (1 mL) in THF (4 mL) was stirred at 25 °C for 1 hr. Upon completion, the resulting solution was quenched with sodium sulfite, filtered and concentrated to give **98-8** (170 mg, 497.86 μmol , 97.72% yield). MS: $m/z = 342.2$ (M+1).

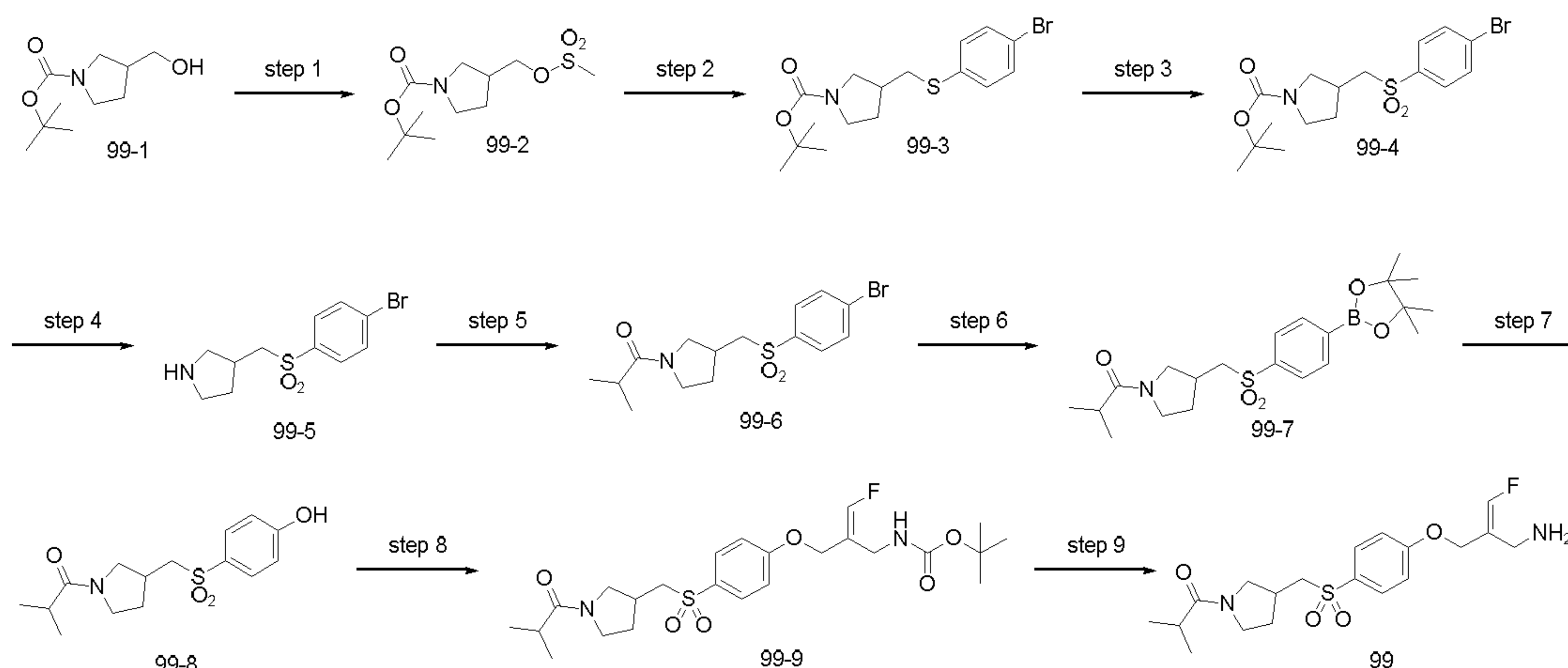
Step 8: 98-9

[00670] A mixture of **98-8** (170 mg, 497.86 μmol), **Intermediate A** (160 mg, 596.74 μmol) and Cesium carbonate (811 mg, 2.49 mmol) in MeCN (20 mL) was stirred at 95 °C for 2 hr. Upon completion, the resulting mixture was cooled down to room temperature and filtered. The filtrate was concentrated. The residue was purified by silica gel chromatography (ethyl acetate in petroleum ether, 20 - 50%) to give **98-9** (160 mg, 302.64 μmol , 60.79% yield). MS: $m/z = 529.3$ (M+1).

Step 9: Compound 98

[00671] To a mixture of **98-9** (160 mg, 302.64 μmol) in Dioxane (3 mL) was added Dioxane/HCl (4 M, 2.5 mL). After addition, the mixture was stirred at 25 °C for 2 hr. Upon completion, the resulting mixture was concentrated and purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; GT: 15 min; flow rate: 15 mL/min) to give **Compound 98** (74 mg, 155.93 μmol , 51.52% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.41 (s, 1H), 7.85-7.73 (m, 2H), 7.16 (d, $J = 80.0$ Hz, 1H), 7.17-7.08 (m, 2H), 4.63 (d, $J = 3.7$ Hz, 2H), 3.73 (d, $J = 2.2$ Hz, 2H), 3.43 (q, $J = 7.1$ Hz, 2H), 3.32 (s, 2H), 3.10 (s, 2H), 2.86 (p, $J = 6.7$ Hz, 1H), 1.15-1.04 (m, 9H), 1.03-0.95 (m, 6H) ppm. MS: $m/z = 429.2$ (M+1).

Example 69: Synthesis of Compound 99



Step 1: 99-2

[00672] To a mixture of **99-1** (1 g, 4.97 mmol) and TEA (1.51 g, 14.91 mmol, 2.08 mL) in DCM (20 mL) was added methyl sulfonyl chloride (683.00 mg, 5.96 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 0 °C. Water (5 mL) was added, the organic was dried over anhydrous sodium sulfate and concentrated to give **99-2** (1.1 g, 3.94 mmol, 79.25% yield). MS: $m/z = 348.4$ (M+1).

Step 2: 99-3

[00673] A mixture of 4-bromobenzenethiol (744.51 mg, 3.94 mmol) and **99-2** (1 g, 3.58 mmol) in MeCN (20 mL) was added Cesium carbonate (3.50 g, 10.74 mmol) at 30 °C. The reaction solution was stirred for 4 hr at 80 °C. Then, the solution was filtered, concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **99-3** (1 g, 2.69 mmol, 75.03% yield). MS: $m/z = 372.3$ (M+1).

Step 3: 99-4

[00674] A mixture of **99-3** (0.5 g, 1.34 mmol) and m-CPBA (681.60 mg, 3.36 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. The sodium sulfite (1 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 25%, v/v) to obtain **99-4** (400 mg, 989.32 μ mol, 73.67% yield). MS: $m/z = 404.3$ (M+1).

Step 4: 99-5

[00675] A mixture of **99-4** (400 mg, 989.32 μ mol) in HCl/Dioxane (4 M, 5 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **99-5** (337 mg, 989.25 μ mol, 99.99% yield, HCl salt). MS: $m/z = 340.6$ (M+1).

Step 5: 99-6

[00676] To a mixture of **99-5** (300 mg, 986.18 μ mol) and TEA (299.38 mg, 2.96 mmol, 412.36 μ L) in DCM (20 mL) was added 2-methylpropanoyl chloride (157.62 mg, 1.48 mmol, 154.53 μ L) at 0 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was
5 concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80 mL), washed with water (100 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated to obtain **99-6** (300 mg, 801.51 μ mol, 81.27% yield). MS: m/z = 374.2 (M+1).

Step 6: 99-7

[00677] A 30 mL microwave reaction tube was charged with **99-6** (300 mg, 801.51 μ mol),
10 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (305.30 mg, 1.20 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (58.65 mg, 80.15 μ mol) and potassium acetate (235.99 mg, 2.40 mmol) in Dioxane (8 mL). After oxygen was purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and
15 concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0 - 100%, v/v) to deliver **99-7** (270 mg, 640.79 μ mol, 79.95% yield). MS: m/z = 421.3 (M+1).

Step 7: 99-8

[00678] To a mixture of **99-7** (270 mg, 640.79 μ mol) in THF (25 mL) and acetate acid (0.5
20 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. The sodium sulfite (0.5 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and concentrated to give **99-8** (0.7 g, crude). MS: m/z = 311.4 (M+1).

Step 8: 99-9

[00679] To a mixture of **99-8** (0.7 g, 2.25 mmol) and **Intermediate A** (241.09 mg, 899.18
25 μ mol) in MeCN (50 mL) was added Cesium carbonate (2.20 g, 6.74 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **99-9** (340 mg, 681.90 μ mol, 30.33% yield). MS: m/z = 499.6 (M+1).

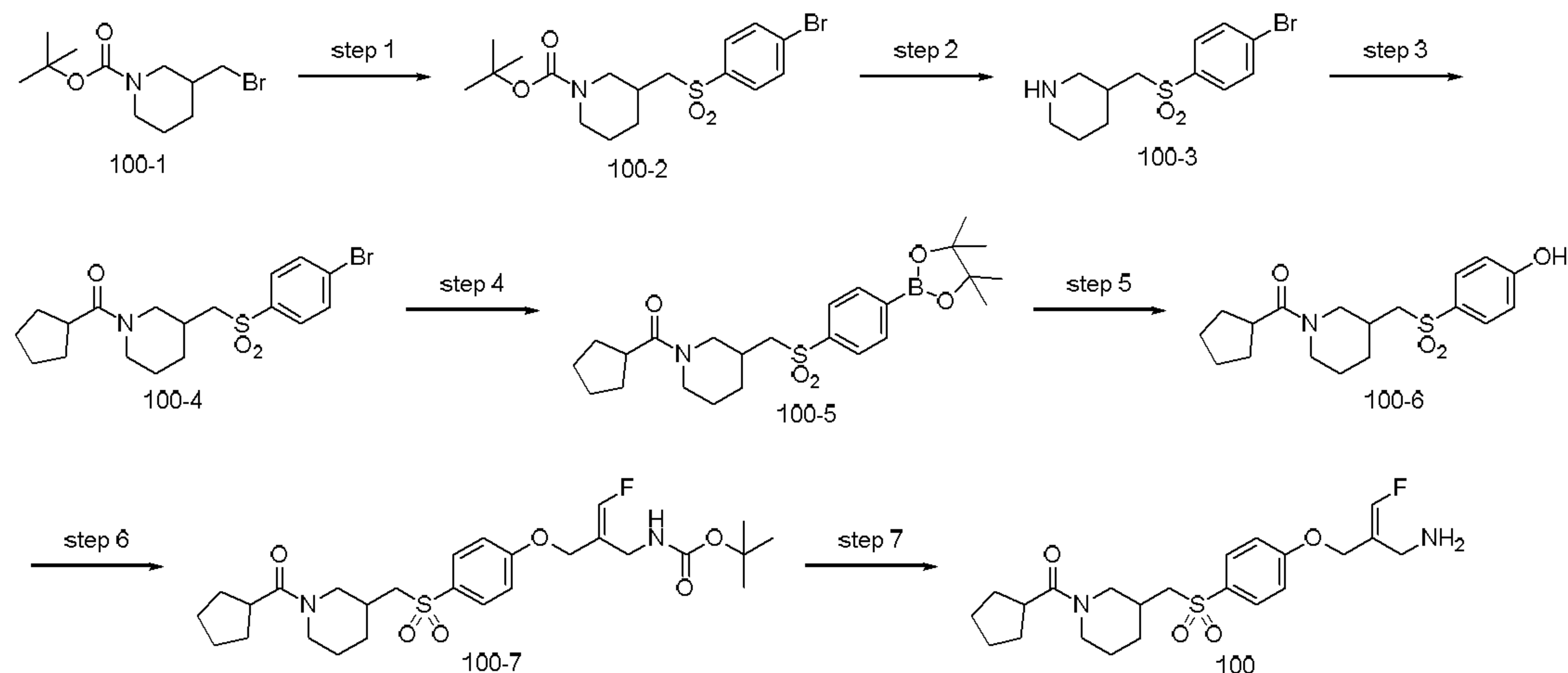
Step 9: Compound 99

[00680] A mixture of **99-9** (300 mg, 601.68 μ mol) in HCl/Dioxane (4 M, 4 mL) was stirred at
30 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H

water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain

Compound 99 (16.3 mg, 40.90 μ mol, 6.80% yield). ^1H NMR (400 MHz, Methanol- d_4) δ 7.86-7.73 (m, 2H), 7.16-7.11 (m, 2H), 7.01 (d, $J = 80.0$ Hz, 1H), 4.60 (dd, $J = 3.6, 1.1$ Hz, 2H), 3.58-3.53 (m, 2H), 3.48-3.22 (m, 4H), 2.98-2.86 (m, 1H), 2.66-2.38 (m, 2H), 2.15-1.96 (m, 1H), 1.77-1.50 (m, 1H), 1.19 (t, $J = 7.2$ Hz, 1H), 1.02-0.90 (m, 6H) ppm. MS: $m/z = 399.64$ (M+1).

Example 70: Synthesis of Compound 100



Step 1: 100-2

[00681] To a mixture of 4-bromobenzenesulfinic acid (400 mg, 1.81 mmol) and **100-1** (503.34 mg, 1.81 mmol) in DMF (10 mL) was added sodium carbonate (383.55 mg, 3.62 mmol) at 25°C. The reaction solution was stirred 100 °C for 16 hr. Then, the solution was quenched with water (30 mL), and extracted by ethyl acetate (30 mL $\times$ 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to obtain **100-2** (900 mg).

Step 2: 100-3

[00682] To a mixture of **100-2** (900 mg, 2.15 mmol) in DCM (10 mL) was added HCl/Dioxane (4 M, 1.08 mL) at 25°C and the reaction mixture was stirred at 25 °C for 4 hr. Then, the solution was concentrated with a rotary evaporator to obtain **100-3** (720 mg). MS: $m/z = 319$ (M+1).

Step 3: 100-4

[00683] To a mixture of cyclopentanecarboxylic acid (138.09 mg, 1.21 mmol, 131.52 μ L), HATU (627.29 mg, 1.65 mmol) and TEA (333.88 mg, 3.30 mmol, 459.89 μ L) in DCM (10 mL) was added **100-3** (350 mg, 1.10 mmol) at 25 °C. The reaction solution was stirred for 4 hr at

25 °C. Then, the solution was quenched with water (20 mL), and extracted by DCM (20 mL × 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain the crude product. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0
5 - 50%, v/v) to obtain **100-4** (140 mg, 337.87 μmol, 30.72% yield). MS: m/z = 415 (M+1).

Step 4: 100-5

[00684] To a mixture of **100-4** (100 mg, 241.34 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (73.54 mg, 289.61 μmol) and potassium acetate (71.06 mg, 724.01 μmol) in Dioxane (5 ml) was added 1,1'-

10 Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (19.71 mg, 24.13 μmol) at 30 °C under the nitrogen atmosphere. The reaction solution was stirred at 120 °C for 0.5 hr in a Biotage microwave reactor. The solution was concentrated with a rotary evaporator. The residue was quenched with water (20 mL), and extracted by ethyl acetate (20 mL × 2). The combined organic layers were washed with water (15 mL) and brine (15 mL),
15 dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain **100-5** (150 mg).

Step 5: 100-6

[00685] To a mixture of **100-5** (150 mg, 327.89 μmol) in THF (5 mL) was added acetic acid (0.5 mL) and hydrogen peroxide (0.5 mL, 30% purity) at 25 °C. The reaction solution was stirred
20 for 1 hr at 25 °C. Then sodium sulfite (0.5 g) and water (15 mL) was added to the mixture and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain **100-6** (120 mg).

Step 6: 100-7

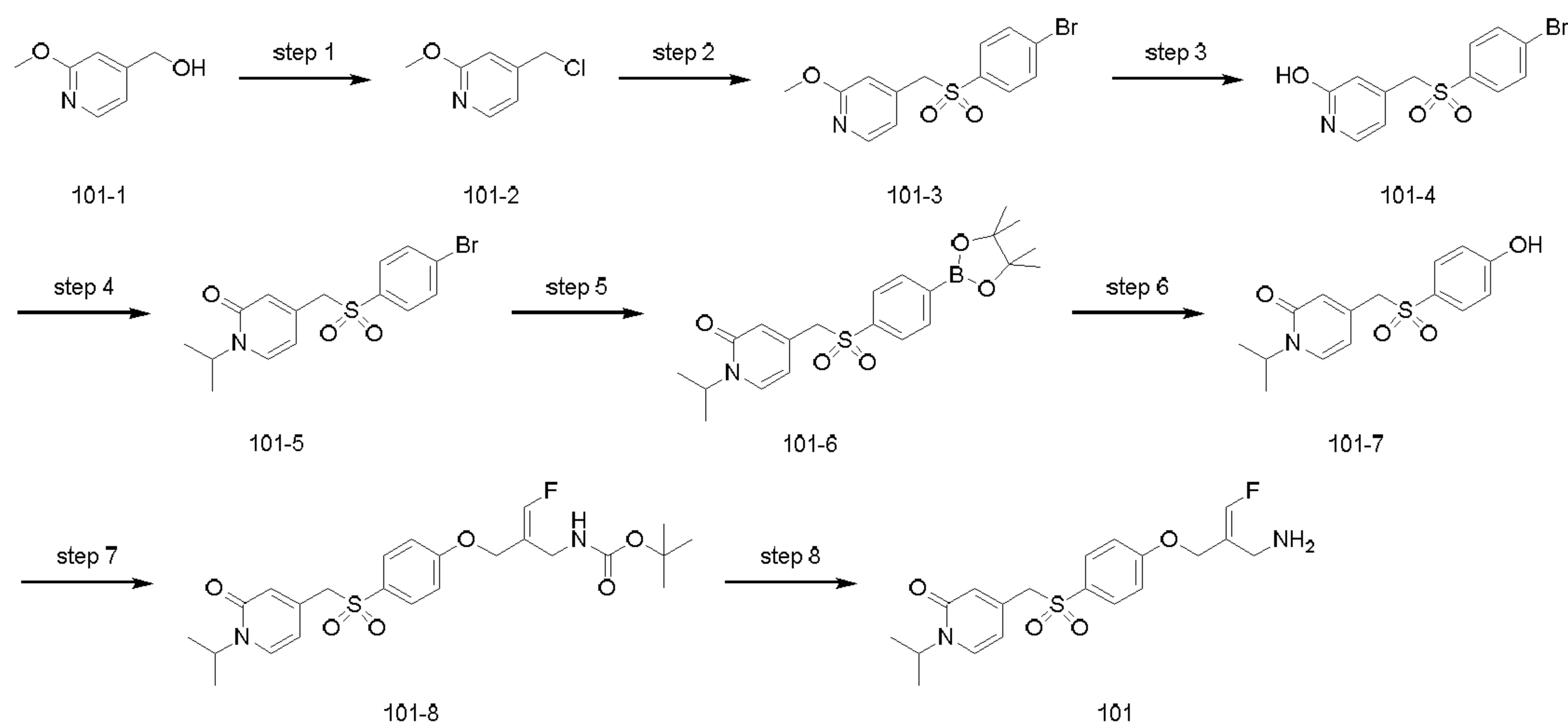
25 [00686] To a mixture of **100-7** (120 mg, 341.43 μmol) and **Intermediate A** (91.55 mg, 341.43 μmol) in MeCN (5 mL) was added Cesium carbonate (333.74 mg, 1.02 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the solution was concentrated with a rotary evaporator. The residue was quenched with water (20 mL) and extracted by ethyl acetate (20 mL × 2). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried
30 over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain the crude

product. The crude product was purified by Silica gel chromatography (petroleum ether: ethyl acetate = 1: 2) to obtain **100-7** (50 mg, 92.82 μ mol, 27.19% yield). MS: m/z = 539 (M+1).

Step 7: Compound 100

[00687] To a mixture of **100-7** (50 mg, 92.82 μ mol) in DCM (5 mL) was added
 5 trifluoroacetate acid (740.0 mg, 6.49 mmol, 0.5 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 2 hr. Then, the solution was concentrated with a rotary evaporator to obtain the crude product. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-35% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 100** (19 mg, 43.32 μ mol, 46.67% yield, HCO₂H salt). ¹H
 10 NMR (400 MHz, Methanol-*d*₄): δ 8.53 (s, 1H), 7.95-7.88 (m, 2H), 7.23 (d, J = 84.0 Hz, 1H), 7.28-7.19 (m, 2H), 4.73 (dd, J = 3.5, 1.1 Hz, 2H), 4.26 (t, J = 14.8 Hz, 1H), 3.79 (dd, J = 4.2, 2.2 Hz, 2H), 3.27-3.09 (m, 3H), 3.07-2.92 (m, 1H), 2.76-2.63 (m, 1H), 2.02-1.80 (m, 4H), 1.78-1.55 (m, 8H), 1.43-1.39 (m, 2H) ppm. MS: m/z = 439.66 (M+1).

Example 71: Synthesis of Compound 101



Step 1: 101-2

[00688] To a mixture of **101-1** (500 mg, 3.59 mmol) in DCM (10 mL) was added SOCl₂ (2.14 g, 17.97 mmol) at 0 °C. The reaction solution was stirred for 1 hr at 60 °C. The mixture was concentrated to give **102-2** (600 mg, crude, HCl salt). MS: m/z = 194.06 (M+1).

Step 2: 101-3

[00689] To a mixture of (4-bromophenyl)sulfonyloxysodium (1 g, 4.11 mmol) and **101-2** (600.0 mg, 3.81 mmol) in DMF (20 mL) was stirred at 20 °C. The reaction solution was stirred for 1 hr at 70 °C. Then ethyl acetate (100 mL) were added, the organic phase was washed with

H₂O (100 mL × 3) and brine (50 mL), dried over Na₂SO₄ and concentrated to obtain **101-3** (800 mg, 2.34 mmol, 56.82% yield).

Step 3: 101-4

[00690] A mixture of **101-3** (780 mg, 2.28 mmol) and TMSI (2.28 mmol, 2 mL) in MeCN (10 mL) was stirred at 80 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **101-4** (800 mg, crude). MS: m/z = 328.18 (M+1).

Step 4: 101-5

[00691] To a mixture of **101-4** (800 mg, 2.44 mmol) and 2-iodopropane (1.24 g, 7.31 mmol, 731.27 µL) in MeCN (20 mL) was added Cesium carbonate (2.38 g, 7.31 mmol) at 20 °C. The reaction solution was stirred for 4 hr at 80 °C. Then, the solution was filtered and concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 20%, v/v) to obtain **101-5** (120 mg, 324.10 µmol, 13.30% yield). MS: m/z = 370.26 (M+1).

Step 5: 101-6

[00692] To a mixture of **101-5** (110 mg, 297.09 µmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (75.44 mg, 297.09 µmol) in Dioxane (5 mL) was added potassium acetate (87.47 mg, 891.26 µmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (260.86 mg, 356.51 µmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **101-6** (80 mg, 191.70 µmol, 64.53% yield). MS: m/z = 417.33 (M+1).

Step 6: 101-7

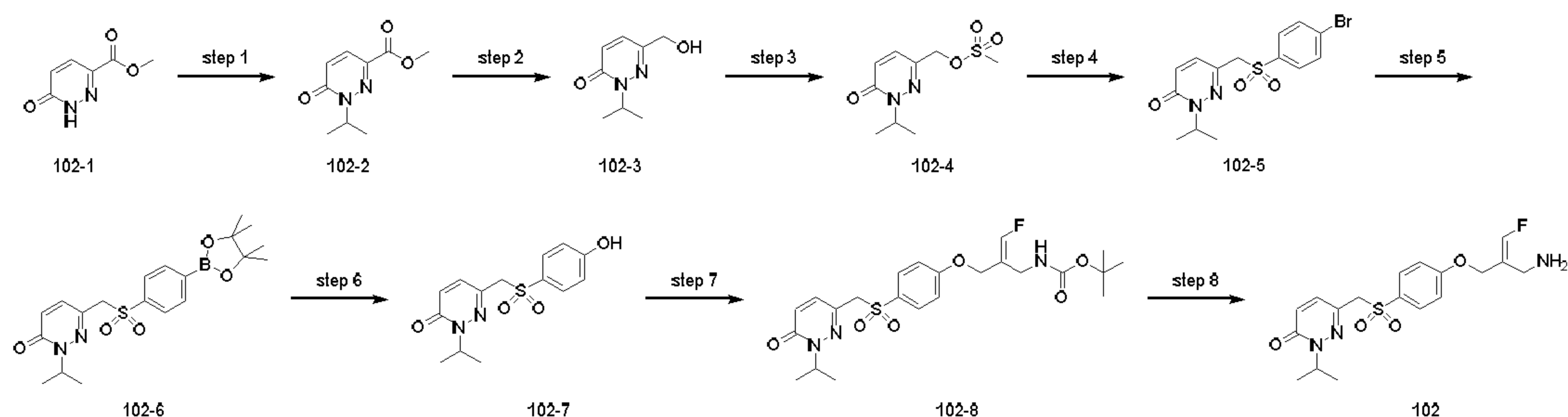
[00693] To a mixture of **101-6** (80 mg, 191.70 µmol) in acetate acid (0.5 mL) and THF (2 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. The sodium sulfite (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **101-7** (60 mg, crude).

Step 7: 101-8

[00694] To a mixture of **101-7** (60 mg, 195.21 µmol) and **Intermediate A** (52.34 mg, 195.21 µmol) in MeCN (10 mL) was added Cesium carbonate (190.81 mg, 585.62 µmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **101-8** (100 mg, crude).

Step 8: Compound 101

[00695] A mixture of **101-8** (90 mg, 181.97 μ mol) in HCl/Dioxane (4 M, 4.0 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 101** (20 mg, 45.40 μ mol, 24.95% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.51 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 80.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.42 (dd, *J* = 7.2, 2.4 Hz, 1H), 6.11 (d, *J* = 2.4 Hz, 1H), 5.13-5.06 (m, 1H), 4.93-4.88 (m, 2H), 4.69 (d, *J* = 3.6 Hz, 2H), 3.79 (d, *J* = 2.4 Hz, 2H), 1.35 (d, *J* = 6.8 Hz, 6H) ppm. MS: *m/z* = 395.13 (M+1).

Example 72: Synthesis of Compound 102**Step 1: 102-2**

[00696] To a mixture of **102-1** (1.5 g, 9.73 mmol) in DMF (20 mL) was added NaH (409.35 mg, 10.23 mmol, 60% purity) at 0 °C. The reaction solution was stirred for 0.5 hr at 60 °C. Then, 2-iodopropane (1.87 g, 11.00 mmol, 1.10 mL) was added. The reaction solution was stirred for further 4 hr at 60 °C. Then, the solution was poured into water (50 mL), extracted with ethyl acetate (20 mL $\times$ 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 30%) to obtain **102-2** (1.7 g, 8.66 mmol, 89.03% yield). MS: *m/z* = 197 (M+1).

Step 2: 102-3

[00697] To a mixture of **102-2** (500 mg, 2.55 mmol) in THF (10 mL) was added LiBH₄ (2 M in THF, 3.82 mL) at 0 °C. The reaction mixture was stirred for 2 hr at 25 °C. Then, the solution was quenched with MeOH (20 mL) at 0 °C and stirred for 0.25 hr at 20 °C. The solution was concentrated with a rotary evaporator. The crude product was purified by silica gel

chromatography (ethyl acetate in petroleum ether, 0 - 100%) to obtain **102-3** (400 mg, 2.38 mmol, 93.32% yield). MS: $m/z = 169$ (M+1).

Step 3: 102-4

5 [00698] To a mixture of **102-3** (400 mg, 2.38 mmol), TEA (721.95 mg, 7.13 mmol) in DCM (20 mL) was added methane sulfonyl chloride (299.67 mg, 2.62 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was filtered and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 50%) to obtain **102-4** (600 mg, crude). MS: $m/z = 247$ (M+1).

Step 4: 102-5

10 [00699] To a mixture of **102-4** (600 mg, 2.44 mmol), 4-bromobenzenesulfinic acid (807.87 mg, 3.65 mmol) in DMF (20 mL) was added potassium carbonate (1.01 g, 7.31 mmol) at 25 °C. The reaction solution was stirred for 18 hr at 90 °C. Then, the solution was quenched with water (20 mL), and extracted by ethyl acetate (15 mL $\times$ 2). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated
15 with a rotary evaporator to obtain **102-5** (860 mg, crude). MS: $m/z = 372$ (M+1).

Step 5: 102-6

[00700] To a mixture of **102-5** (220 mg, 592.59 μ mol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (180.58 mg, 711.11 μ mol) and potassium acetate (174.48 mg, 1.78 mmol) in Dioxane (10 mL) was
20 added bis(diphenylphosphino)ferrocene]dichloropalladium(II) (43.36 mg, 59.26 μ mol) at 25 °C. The reaction solution was heated at 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was evaporated to obtain **102-6** (310 mg, crude). MS: $m/z = 419$ (M+1).

Step 6: 102-7

[00701] To a mixture of **102-6** (310 mg, 741.07 μ mol), acetate acid (0.5 mL) in THF (20 mL)
25 was added hydrogen peroxide (0.3 mL, 30% purity) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, to the solution was added sodium sulfite (0.3 g), filtered and concentrated with a rotary evaporator to obtain **102-7** (250 mg, crude). MS: $m/z = 309$ (M+1).

Step 7: 102-8

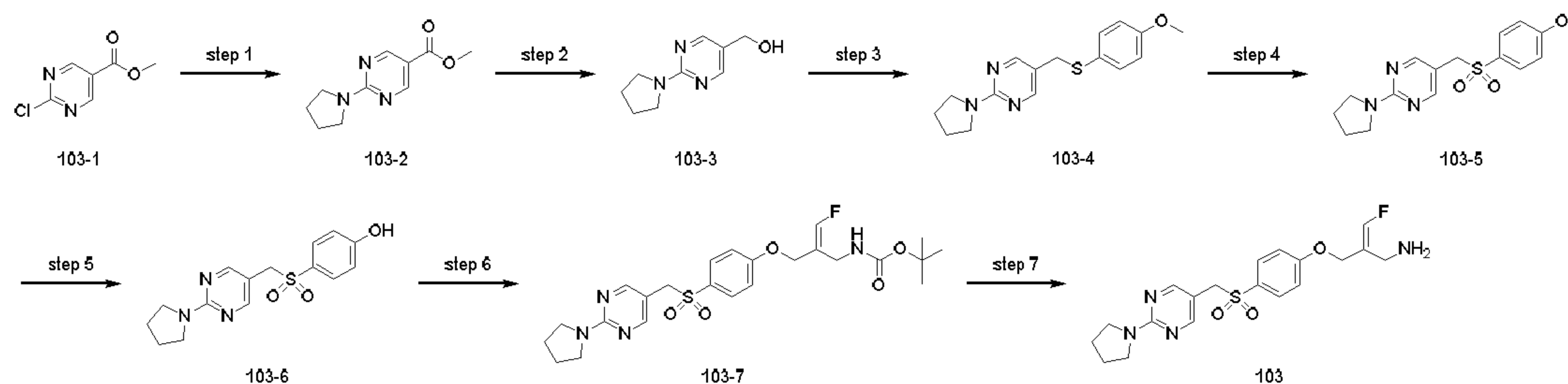
[00702] To a mixture of **102-7** (250 mg, 810.76 μ mol), **Intermediate A** (200 mg, 745.93
30 μ mol) in MeCN (30 mL) was added Cesium carbonate (792.48 mg, 2.43 mmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate

was concentrated with a rotary evaporator to obtain **102-8** (310 mg, crude). MS: $m/z = 496$ (M+1).

Step 8: Compound 102

To a mixture of **102-8** (310 mg, 625.55 μmol) in DCM (15 mL) was added HCl/Dioxane (4 M, 3 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 102** (110 mg, 249.17 μmol , 39.83% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.51 (s, 1H), 7.74-7.64 (m, 2H), 7.50 (d, $J = 9.5$ Hz, 1H), 7.23 (d, $J = 81.0$ Hz, 1H), 7.22-7.13 (m, 2H), 6.93 (d, $J = 9.5$ Hz, 1H), 5.10 (p, $J = 6.6$ Hz, 1H), 4.70 (dd, $J = 3.7, 1.0$ Hz, 2H), 4.56 (s, 2H), 3.79 (d, $J = 2.3$ Hz, 2H), 1.08 (d, $J = 6.7$ Hz, 6H) ppm. MS: $m/z = 396.1$ (M+1).

Example 73: Synthesis of Compound 103



Step 1: 103-2

[00703] To a mixture of **103-1** (1.0 g, 5.79 mmol), TEA (1.76 g, 17.38 mmol) in THF (20 mL) was added pyrrolidine (824.26 mg, 11.59 mmol, 962.92 μL) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 50%, v/v) to obtain **103-2** (1.1 g, 5.31 mmol, 91.60% yield). MS: $m/z = 208.1$ (M+1).

Step 2: 103-3

[00704] To a mixture of **103-2** (700 mg, 3.38 mmol) in THF (15 mL) was added LiBH₄ (2 M in THF, 6.76 mL) at 0 °C. The reaction mixture was stirred for 2 hr at 25 °C. Then, the solution was quenched with methanol (20 mL) at 0 °C and stirred for 0.25 hr at 20 °C. The solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (methanol in dichloromethane, 0 - 10%) to obtain **103-3** (410 mg, 2.29 mmol, 67.73% yield). MS: $m/z = 180.1$ (M+1).

Step 3: 103-4

[00705] To a mixture of **103-3** (410 mg, 2.29 mmol) and 1-methoxy-4-[(4-methoxyphenyl)disulfanyl]benzene (764.25 mg, 2.75 mmol) in MeCN (20 mL) was added tributylphosphane (647.99 mg, 3.20 mmol, 790.23 μ L) at 25 °C. The reaction mixture was stirred for 16 hr at 80 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 50%) to obtain **103-4** (510 mg, 1.69 mmol, 73.96% yield). MS: $m/z = 302.1$ (M+1).

Step 4: 103-5

[00706] To a mixture of **103-4** (510 mg, 1.69 mmol) in DCM (20 mL) was added m-CPBA (1.03 g, 5.08 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous sodium sulfite (10 mL), saturated aqueous NaHCO₃ (20 mL $\times$ 2) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain **103-5** (500 mg, crude). MS: $m/z = 334.1$ (M+1).

Step 5: 103-6

[00707] To a solution of **103-5** (500 mg, 1.50 mmol) in DCM (25 mL) was added boron tribromide (1.13 g, 4.50 mmol) at 0 °C. The reaction mixture was stirred for 1 hr at 25 °C. Then, the solution was quenched with methanol (20 mL) at 0 °C and stirred for 0.25 hr at 20 °C. The solution was filtered and concentrated with a rotary evaporator to obtain **103-6** (310 mg, crude). MS: $m/z = 320.1$ (M+1).

Step 6: 103-7

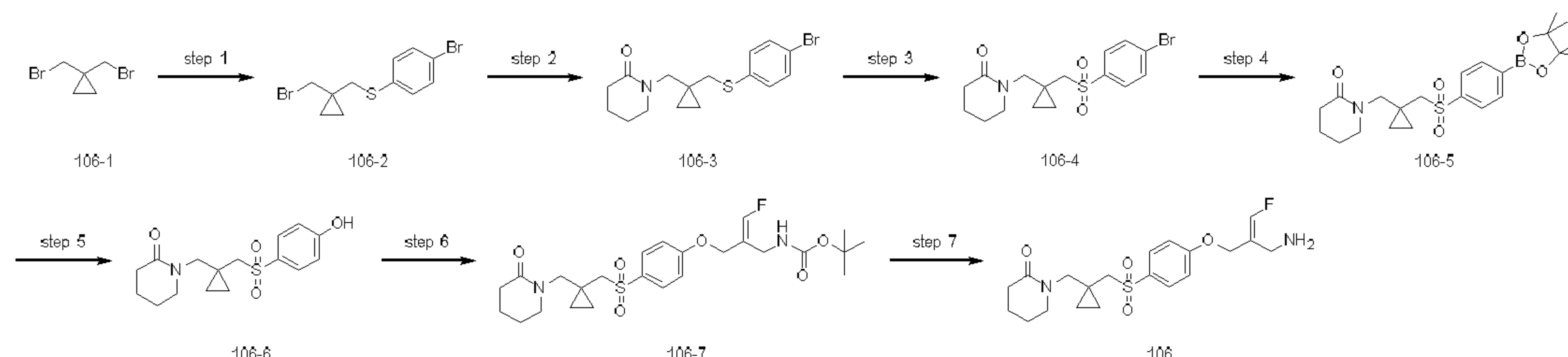
[00708] To a mixture of **103-6** (310 mg, 774.44 μ mol), **Intermediate A** (160 mg, 596.74 μ mol) in MeCN (30 mL) was added cesium carbonate (756.98 mg, 2.32 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 100%) to obtain **103-7** (110 mg, 217.14 μ mol, 28.04% yield). MS: $m/z = 507.2$ (M+1).

Step 7: Compound 103

[00709] To a solution of **103-7** (110 mg, 217.14 μ mol) in DCM (20 mL) was added HCl/Dioxane (4 M, 2 mL) at 25 °C and the reaction mixture was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile;

gradient: 5 - 50% B; GT: 25 min; flow rate: 15 mL/min) to obtain **Compound 103** (25 mg, 55.25 μ mol, 25.44% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.52 (s, 1H), 7.64-7.60 (m, 2H), 7.44-7.42 (m, 1H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.23 (d, *J* = 81.0 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 2H), 4.69 (d, *J* = 3.5 Hz, 2H), 4.54 (s, 2H), 3.81 (d, *J* = 2.2 Hz, 2H), 3.58 (t, *J* = 6.9 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.02-1.87 (m, 4H) ppm. MS: *m/z* = 407.1 (M+1).

Example 74: Synthesis of Compound 106



Step 1: 106-2

[00710] To a mixture of **106-1** (2.41 g, 10.58 mmol), 4-bromothiophenol (1 g, 5.29 mmol) in MeCN (60 mL) was added Cesium carbonate (3.45 g, 10.58 mmol) at 0 °C. The reaction solution was stirred for 1 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 1 - 10%, v/v) to obtain **106-2** (1 g, 2.98 mmol, 56.26% yield). MS: *m/z* = 336.0 (M+1).

Step 2: 106-3

[00711] A mixture of Piperidin-2-one (294.96 mg, 2.98 mmol) and potassium;2-methylpropan-2-olate (667.76 mg, 5.95 mmol) in DMSO (10 mL) was stirred at 50 °C for 1 hr. **106-2** (500 mg, 1.49 mmol) was added at 50 °C and stirred at 50 °C for 3 hr. Water (100 mL) was added and the mixture was extracted with ethyl acetate (100 mL), the organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated to give **106-3** (200 mg, 564.49 μ mol, 37.94% yield). MS: *m/z* = 354.3 (M+1).

Step 3: 106-4

[00712] A mixture of **106-3** (200 mg, 564.49 μ mol) and *m*-CPBA (343.80 mg, 1.69 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. The sodium sulfite (0.3 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **106-4** (150 mg, 388.30 μ mol, 68.79% yield). MS: *m/z* = 386.3 (M+1).

Step 4: 106-5

[00713] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (118.32 mg, 465.96 μmol), **106-4** (120 mg, 310.64 μmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (22.73 mg, 31.06 μmol) in Dioxane (20 mL) was added potassium acetate (91.46 mg, 931.91 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%) to obtain **106-5** (90 mg, 207.68 μmol , 66.85% yield). MS: $m/z = 433.3$ (M+1).

Step 5: 106-6

[00714] To a mixture of **106-5** (90 mg, 207.68 μmol) in THF (2 mL) and acetate acid (0.5 mL) was added hydrogen peroxide (0.5 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. The sodium sulfite (0.3 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **106-6** (0.5 g, crude). MS: $m/z = 323.4$ (M+1).

Step 6: 106-7

[00715] To a mixture of **106-6** (0.5 g, 1.55 mmol) and **Intermediate A** (124.36 mg, 463.81 μmol) in MeCN (50 mL) was added Cesium carbonate (1.51 g, 4.64 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 20%) to obtain **106-7** (160 mg, 313.35 μmol , 20.27% yield).

Step 7: Compound 106

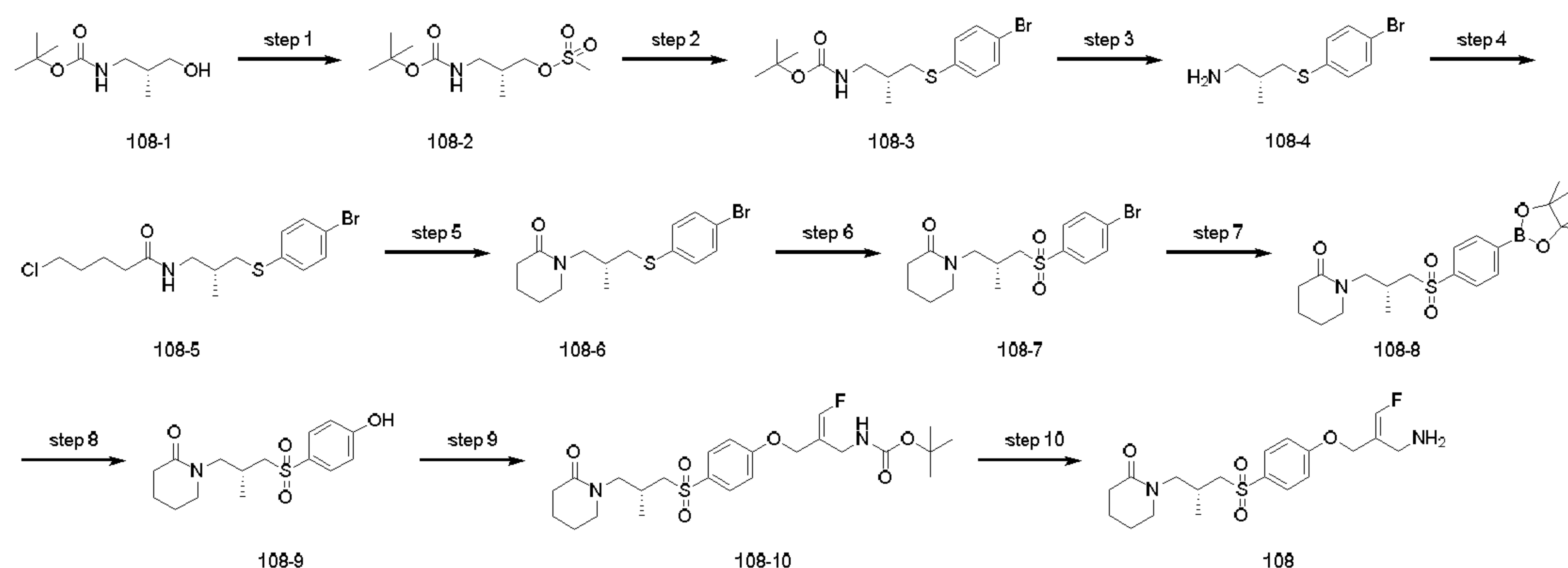
[00716] A mixture of **106-7** (160 mg, 313.35 μmol) in HCl/Dioxane (4 M, 3.0 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 106** (5 mg, 12.18 μmol , 1.55% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.49 (s, 1H), 7.88 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 80.0$ Hz, 1H), 7.20 (d, $J = 8.4$ Hz, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.80 (s, 2H), 3.48 (s, 2H), 3.43 (d, $J = 6.0$ Hz, 2H), 3.35-3.30 (m, 2H), 2.35 (s, 2H), 1.82 (s, 4H), 0.73-0.57 (m, 4H) ppm. MS: $m/z = 411.68$ (M+1).

[00717] The compounds of Formula (I') or (I) in Table 14 below were made according to **Example 74 of Compound 106**.

Table 14

Cmpd No.	¹ H NMR and/or LC/MS data
107	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.48 (s, 1H), 7.89 (d, <i>J</i> = 8.4 Hz, 2H), 7.24 (d, <i>J</i> = 80.0 Hz, 1H), 7.22 (d, <i>J</i> = 8.4 Hz, 2H), 4.72 (d, <i>J</i> = 3.6 Hz, 2H), 3.81 (d, <i>J</i> = 2.4 Hz, 2H), 3.65 (t, <i>J</i> = 7.2 Hz, 2H), 3.48-3.85 (m, 2H), 3.36 (t, <i>J</i> = 5.6 Hz, 2H), 2.24 (t, <i>J</i> = 6.4 Hz, 2H), 1.73 (d, <i>J</i> = 13.6 Hz, 4H) ppm. MS: <i>m/z</i> = 371.61 (M+1).
111	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.51 (s, 1H), 7.92-7.84 (m, 2H), 7.25 (d, <i>J</i> = 80.0 Hz, 1H), 7.28-7.20 (m, 2H), 4.75-4.71 (m, 2H), 3.81 (d, <i>J</i> = 2.4 Hz, 2H), 3.31-3.22 (m, 2H), 3.09-2.95 (m, 2H), 2.40-2.28 (m, 3H), 1.91-1.78 (m, 2H), 1.23 (s, 3H), 1.19 (s, 3H), 1.06 (d, <i>J</i> = 7.0 Hz, 3H) ppm. MS: <i>m/z</i> = 413.68 (M+1).
114	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.43 (s, 1H), 7.90-7.83 (m, 1H), 7.27 (d, <i>J</i> = 80.0 Hz, 1H), 7.11-7.03 (m, 2H), 4.73 (d, <i>J</i> = 3.6 Hz, 2H), 3.90-3.79 (m, 3H), 3.64-3.60 (m, 4H), 3.04-3.01 (m, 1H), 2.37-2.24 (m, 4H), 2.22-2.13 (m, 3H), 1.06 (d, <i>J</i> = 6.0 Hz, 3H) ppm. MS: <i>m/z</i> = 405.66 (M+1).
116	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.86 (d, <i>J</i> = 8.4 Hz, 2H), 7.19 (d, <i>J</i> = 8.4 Hz, 2H), 6.76 (d, <i>J</i> = 80.0 Hz, 1H), 4.67 (d, <i>J</i> = 3.6 Hz, 2H), 3.64 (t, <i>J</i> = 4.4 Hz, 4H), 3.49 (s, 2H), 3.38 (s, 2H), 2.31 (s, 4H), 2.11 (s, 2H), 0.55 (s, 2H), 0.35 (s, 2H) ppm. MS: <i>m/z</i> = 399.64 (M+1).

Example 75: Synthesis of Compound 108



5 Step 1: 108-2

[00718] To a mixture of **108-1** (1 g, 5.71 mmol) and methylsulfonyl chloride (784.49 mg, 6.85 mmol) in DCM (30 mL) was added TEA (577.49 mg, 5.71 mmol, 795.44 μ L) at 0 °C. The reaction was stirred for 1 hr at 0 °C. DCM (50 mL) and water (100 mL) were added, the organic phase was separated and dried over anhydrous sodium sulfate, filtered and concentrated to
5 give **108-2** (1.4 g, 5.53 mmol, 96.84% yield).

Step 2: 108-3

[00719] To a mixture of 4-bromobenzenethiol (500 mg, 2.64 mmol), NaH (101.33 mg, 2.64 mmol, 60% purity) in DMF (20 mL) was added **108-2** (401.93 mg, 1.59 mmol) at 0 °C. The reaction solution was stirred for 4 hr at 30 °C. To the mixture was added saturated aqueous
10 ammonium chloride solution (100 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (50 mL $\times$ 3). The combined organic extracts were dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (ethyl acetate in petroleum ether, 10 - 80%) to give **108-3** (300 mg, 866.35
15 μ mol, 65.52% yield). MS: m/z = 346.2 (M+1).

Step 3: 108-4

[00720] A mixture of **108-3** (300 mg, 866.35 μ mol) in HCl/Dioxane (4 M, 5.0 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator to obtain **108-4** (251 mg, crude, HCl salt). MS: m/z = 282.6(M+1).

20 *Step 4: 108-5*

[00721] To a mixture of 5-chloropentanoyl chloride (157.97 mg, 1.02 mmol, 131.64 μ L) and TEA (257.78 mg, 2.55 mmol, 355.07 μ L) in DCM (20 mL) was added **108-4** (240 mg, 849.17 μ mol, HCl salt) at 0 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (80
25 mL), washed with water (100 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated to obtain **108-5** (300 mg, crude). MS: m/z = 364.7(M+1).

Step 5: 108-6

[00722] A mixture of **108-5** (300 mg, 822.53 μ mol) and potassium;2-methylpropan-2-olate (369.19 mg, 3.29 mmol) in DMSO (10 mL) was stirred at 50 °C for 2 hr. Water (100 mL) was
30 added and extracted with ethyl acetate (100 mL), the organic layer was separated, dried over

anhydrous sodium sulfate, filtered and concentrated to give **108-6** (150 mg, 456.94 μmol , 55.55% yield). MS: $m/z = 328.2(M+1)$.

Step 6: 108-7

5 [00723] A mixture of **108-6** (150 mg, 456.94 μmol) and m-CPBA (278.30 mg, 1.37 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 1 hr. The sodium sulfite (0.3 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **108-7** (120 mg, 333.09 μmol , 72.89% yield). MS: $m/z = 360.2(M+1)$.

Step 7: 108-8

10 [00724] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (126.88 mg, 499.63 μmol), **108-7** (120 mg, 333.09 μmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (24.37 mg, 33.31 μmol) in Dioxane (20 mL) was added potassium acetate (98.07 mg, 999.26 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was
15 concentrated with a rotary evaporator and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%) to obtain **108-8** (110 mg, 270.05 μmol , 81.08% yield). MS: $m/z = 407.3(M+1)$.

Step 8: 108-9

20 [00725] To a mixture of **108-8** (110 mg, 270.05 μmol) in THF (2 mL) and acetate acid (0.5 mL) was added hydrogen peroxide (0.5 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. The sodium sulfite (0.3 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **108-9** (400 mg, crude). MS: $m/z = 297.3(M+1)$.

Step 9: 108-10

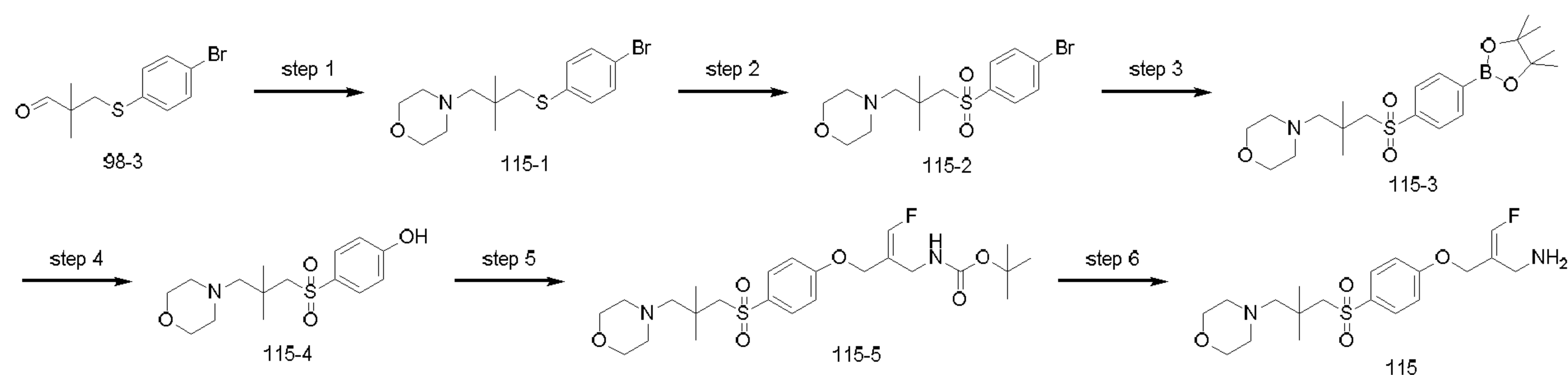
25 [00726] To a mixture of **108-9** (0.4 g, 1.35 mmol) and **Intermediate A** (108.20 mg, 403.54 μmol) in MeCN (50 mL) was added Cesium carbonate (1.31 g, 4.04 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 20%) to obtain **108-10** (90 mg, 185.73 μmol , 13.81% yield).

Step 10: Compound 108

30 [00727] A mixture of **108-10** (90 mg, 185.73 μmol) in HCl/Dioxane (4 M, 4 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude

product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 108** (5 mg, 13.01 μ mol, 7.0% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 80.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.73-4.69 (m, 2H), 3.79-3.75 (m, 2H), 3.25-3.22 (m, 2H), 2.22-2.18 (m, 1H), 1.69 (s, 4H), 1.23 (d, *J* = 6.6 Hz, 4H), 1.19 (s, 3H) ppm. MS: *m/z* = 385.65 (M+1).

Example 76: Synthesis of Compound 115



Step 1: 115-1

[00728] To a mixture of **98-3** (600 mg, 2.20 mmol), morpholine (382.68 mg, 4.39 mmol, 384.22 μ L) in DCM (20 mL) was added NaBH(OAc)₃ (1.40 g, 6.59 mmol) at 0 °C. The reaction solution was stirred for 4 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **115-1** (600 mg, 1.74 mmol, 79.34% yield). MS: *m/z* = 344.3 (M+1).

Step 2: 115-2

[00729] A mixture of **115-1** (600 mg, 1.74 mmol) and *m*-CPBA (1.06 g, 5.23 mmol, 85% purity) in DCM (50 mL) was stirred at 25 °C for 0.5 hr. The sodium sulfite (14 g) was added to the mixture and stirred for 20 min. Then, the solution was filtered, concentrated and purified by silica gel chromatography (ethyl acetate in petroleum ether, 3 - 25%, v/v) to obtain **115-2** (540 mg, 1.43 mmol, 82.35% yield). MS: *m/z* = 376.3 (M+1).

Step 3: 115-3

[00730] A 30 mL microwave reaction tube was charged with **115-2** (540 mg, 1.43 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (506.11 mg, 1.99 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (97.22 mg, 132.87 μ mol) and potassium acetate (391.20 mg, 3.99 mmol) in Dioxane (15 mL). After oxygen was

purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0 - 100%) to deliver **115-3** (580 mg, crude).

5 MS: $m/z = 423.3$ (M+1).

Step 4: 115-4

[00731] A mixture of **115-3** (500 mg, 1.18 mmol) in THF (25 mL) and acetate acid (0.5 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 25 °C for 1 hr. The sodium sulfite (0.6 g) was added to the mixture and stirred for 30 min. The reaction mixture
10 was filtered and concentrated to give **115-4** (1.1 g, crude). MS: $m/z = 313.4$ (M+1).

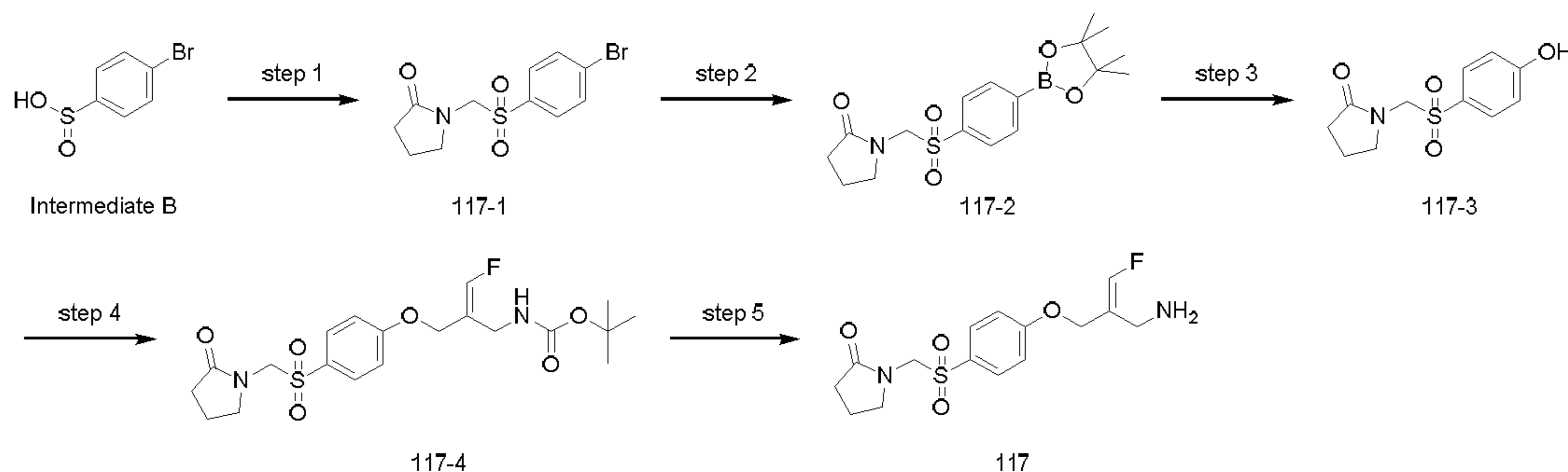
Step 5: 115-5

To a mixture of **115-4** (1 g, 3.19 mmol) and **Intermediate A** (342.20 mg, 1.28 mmol) in MeCN (50 mL) was added Cesium carbonate (3.12 g, 9.57 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **115-5** (400
15 mg, crude).

Step 6: Compound 115

[00732] A mixture of **115-5** (400 mg, 799.01 μ mol) in HCl/Dioxane (4 M, 4 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain
20 **Compound 115** (26.3 mg, 58.90 μ mol, 7.37% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.27 (s, 1H), 7.86 (d, $J = 8.6$ Hz, 2H), 7.25 (d, $J = 80.0$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 3.83 (d, $J = 2.4$ Hz, 2H), 3.64 (t, $J = 4.4$ Hz, 4H), 3.26 (d, $J = 4.4$ Hz, 2H), 2.58 (t, $J = 4.4$ Hz, 4H), 2.38 (s, 2H), 1.10 (s, 6H) ppm. MS: $m/z = 401.63$ (M+1).

25 **Example 77: Synthesis of Compound 117**



Step 1: 117-1

[00733] A mixture of **Intermediate B** (300 mg, 1.36 mmol), pyrrolidin-2-one (577.44 mg, 6.79 mmol) and polyformaldehyde (407.46 mg, 13.57 mmol) in HCO₂H (4 mL) and water (1 mL) was heated to 100 °C and stirred for 1 hr. After cooling to room temperature, the white solid was collected by filtration and washed with water (40 mL) to give **117-1** (200 mg, 628.56 μmol, 46.32% yield). MS: m/z = 318.1 (M+1).

Step 2: 117-2

[00734] To a mixture of **117-1** (200 mg, 628.56 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (191.54 mg, 754.27 μmol) and bis(diphenylphosphino)ferrocene]dichloropalladium(II) (45.99 mg, 62.86 μmol) in Dioxane (10 mL) was added potassium acetate (185.07 mg, 1.89 mmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was dissolved in ethyl acetate (60 mL), washed with water (100 mL × 3), dried over anhydrous sodium sulfate, filtered and concentrated to obtain **117-2** (200 mg, crude). MS: m/z = 365.2 (M+1).

Step 3: 117-3

[00735] To a mixture of **117-2** (200 mg, 547.57 μmol) in THF (4 mL) and acetate acid (1 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 20 °C for 1 hr. Sodium sulfite (0.5 g) was added to the mixture and stirred for 20 min. The mixture was filtered and concentrated to give **117-3** (180 mg, crude). MS: m/z = 255.2 (M+1).

Step 4: 117-4

[00736] To a mixture of **117-3** (180 mg, 705.08 μmol) and **Intermediate A** (150 mg, 559.45 μmol) in MeCN (10 mL) was added Cesium carbonate (689.19 mg, 2.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **117-4** (80 mg, 180.79 μmol, 25.64% yield). MS: m/z = 442.5 (M+1).

Step 5: Compound 117

[00737] A mixture of **117-4** (80 mg, 180.79 μmol) in HCl/Dioxane (4 M, 4.00 mL) was stirred at 25 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 2-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 117** (15 mg, 38.62 μmol, 21.36% yield, HCO₂H salt). ¹H NMR (400 MHz,

Methanol- d_4) δ 8.52 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 80 Hz, 1H), 4.70 (d, J = 4.0 Hz, 2H), 3.79 (s, 2H), 3.71-3.68 (m, 2H), 3.32-3.29 (m, 2H), 3.23-3.19 (m, 2H), 2.08-2.02 (m, 2H) ppm. MS: m/z = 343.0 (M+1, ESI+).

[00738] The compounds of Formula (I') or (I) in Table 15 below were made according to

5 **Example 77 of Compound 117.**

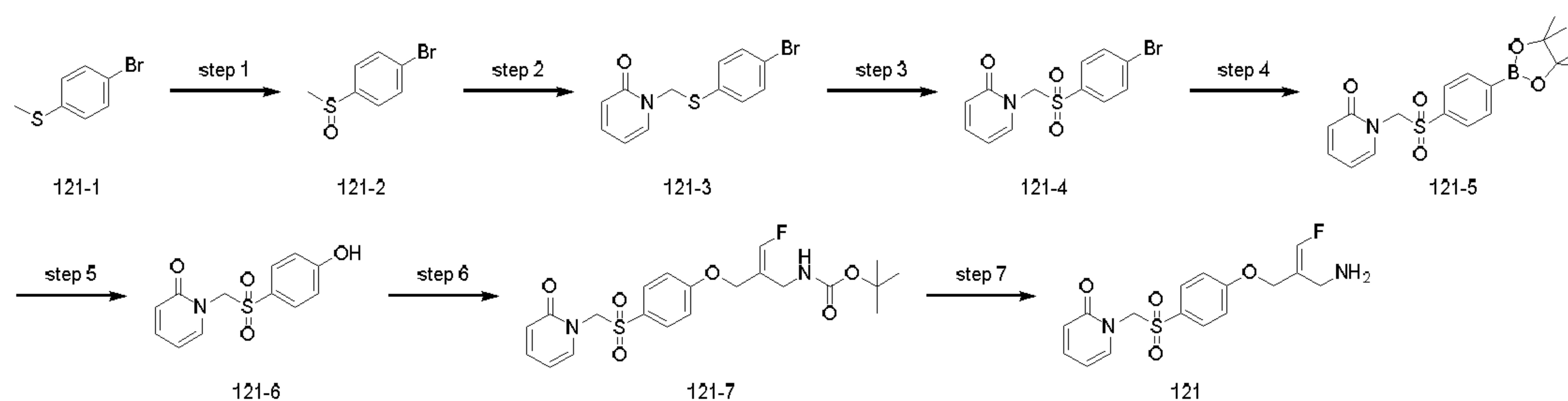
Table 15

Cmpd No.	^1H NMR and/or LC/MS data
118	^1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.68-7.59 (m, 3H), 7.48 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 80.0 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 4.83 (s, 2H), 4.66 (d, J = 3.6 Hz, 2H), 3.76 (d, J = 2.4 Hz, 2H) ppm. MS: m/z = 390.71 (M+1).
119	^1H NMR (400 MHz, Methanol- d_4) δ 8.53 (s, 1H), 7.66-7.59 (m, 2H), 7.21 (d, J = 80.0 Hz, 1H), 7.16-7.12 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.95-6.83 (m, 2H), 6.75 (d, J = 8.1 Hz, 1H), 4.74-4.67 (m, 2H), 4.41 (s, 2H), 3.77 (d, J = 2.4 Hz, 2H), 2.90-2.84 (m, 2H), 2.55 (dd, J = 8.6, 6.4 Hz, 2H) ppm. MS: m/z = 405.3 (M+1).
120	^1H NMR (400 MHz, Methanol- d_4) δ 7.64-7.58 (m, 2H), 7.19-7.10 (m, 2H), 7.05-7.02 (m, 2H), 7.14 (d, J = 80.0 Hz, 1H), 7.01-6.98 (m, 1H), 6.89-6.84 (m, 1H), 5.21 (s, 2H), 4.60 (d, J = 3.6 Hz, 2H), 3.69 (d, J = 2.4 Hz, 2H), 1.49 (q, J = 4.0, 3.6 Hz, 2H), 1.42-1.31 (m, 2H) ppm. MS: m/z = 417.2 (M+1).
122	^1H NMR (400 MHz, Methanol- d_4) δ 7.82 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 80.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 4.89 (s, 2H), 4.70 (d, J = 3.6 Hz, 2H), 3.81 (d, J = 2.4 Hz, 2H), 3.29 (s, 3H), 2.87-2.81 (m, 1H), 0.91 (d, J = 6.8 Hz, 6H) ppm. MS: m/z = 358.8 (M+1).
123	^1H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 80.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 4.71 (d, J = 3.2 Hz, 4H), 3.80 (d, J = 2.4 Hz, 2H), 2.35 (t, J = 8.0 Hz, 2H), 1.96 (t, J = 8.0 Hz, 2H), 1.35 (s, 6H) ppm. MS: m/z = 371.6 (M+1).
124	^1H NMR (400 MHz, Methanol- d_4) δ 8.17 (s, 1H), 7.98-7.91 (m, 1H), 7.28 (dd, J = 15.1, 2.4 Hz, 1H), 7.28 (d, J = 80.9 Hz, 1H), 7.15-7.05 (m, 1H), 4.79 (d, J = 1.6

Cmpd No.	¹ H NMR and/or LC/MS data
	Hz, 2H), 4.73 (d, $J = 3.5$ Hz, 1H), 4.65-4.61 (m, 1H), 4.15-4.07 (m, 1H), 3.84 (dd, $J = 8.2, 2.4$ Hz, 1H), 2.48-2.39 (m, 2H), 1.92 (t, $J = 7.9$ Hz, 2H), 1.35 (s, 6H) ppm. MS: $m/z = 405.57$ (M+1).
125	¹ H NMR (400 MHz, Methanol- d_4) δ 8.50 (s, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 80.0$ Hz, 1H), 7.19 (d, $J = 8.5$ Hz, 2H), 4.78-4.67 (m, 4H), 3.80 (d, $J = 2.4$ Hz, 2H), 3.62 (t, $J = 7.0$ Hz, 2H), 1.90 (t, $J = 7.0$ Hz, 2H), 0.98 (s, 6H) ppm. MS: $m/z = 371.6$ (M+1).
126	¹ H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.92-7.82 (m, 2H), 7.25 (d, $J = 80.0$ Hz, 1H), 7.27-7.19 (m, 2H), 4.75 (s, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 3.82 (d, $J = 2.4$ Hz, 2H), 3.44 (s, 2H), 2.08 (s, 2H), 1.15 (s, 6H) ppm. MS: $m/z = 371.6$ (M+1).
127	¹ H NMR (400 MHz, Methanol- d_4) δ 7.83 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 80.0$ Hz, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 4.74 (s, 2H), 4.71 (d, $J = 3.6$ Hz, 2H), 3.82 (d, $J = 2.4$ Hz, 2H), 3.63 (t, $J = 7.0$ Hz, 2H), 1.94 (t, $J = 7.0$ Hz, 2H), 1.68-1.49 (m, 8H) ppm. MS: $m/z = 397.6$ (M+1).
128	MS: $m/z = 415.5$ (M+1).
129	¹ H NMR (400 MHz, Methanol- d_4) δ 8.51 (s, 1H), 7.83 (d, $J = 8.9$ Hz, 2H), 7.23 (d, $J = 81.1$ Hz, 1H), 7.21-7.15 (m, 2H), 4.74-4.67 (m, 2H), 3.80 (d, $J = 2.3$ Hz, 2H), 3.65 (t, $J = 5.9$ Hz, 2H), 3.31 (s, 2H), 2.17 (t, $J = 6.6$ Hz, 2H), 1.91-1.72 (m, 4H). MS: $m/z = 357.00$ (M+1).
130	¹ H NMR (400 MHz, Methanol- d_4) δ 8.28 (s, 3H), 7.82 (d, $J = 8.0$ Hz, 2H), 7.36 (d, $J = 80.0$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 4.97 (s, 2H), 4.75 (d, $J = 3.6$ Hz, 2H), 3.94 (s, 2H), 3.84 (dd, $J = 6.4, 4.0$ Hz, 2H), 3.62 (dd, $J = 6.4, 4.0$ Hz, 4H) ppm. MS: $m/z = 359.2$ (M+1).
131	¹ H NMR (400 MHz, Methanol- d_4) δ 7.80 (t, $J = 8.4$ Hz, 1H), 7.25 (d, $J = 80.0$ Hz, 1H), 6.99 (d, $J = 9.6$ Hz, 2H), 5.01 (s, 2H), 4.70 (d, $J = 3.6$ Hz, 2H), 3.95 (s, 2H), 3.92-3.85 (m, 2H), 3.84-3.79 (m, 2H), 3.76 (t, $J = 5.0$ Hz, 2H) ppm. MS: $m/z = 377.5$ (M+1).
132	¹ H NMR (400 MHz, Methanol- d_4) δ 8.52 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.21

Cmpd No.	¹ H NMR and/or LC/MS data
	(d, <i>J</i> = 80.0 Hz, 1H), 7.17 (d, <i>J</i> = 8.4 Hz, 2H), 4.70 (d, <i>J</i> = 3.6 Hz, 2H), 4.03 (s, 2H), 3.96 (t, <i>J</i> = 5.2 Hz, 2H), 3.77 (d, <i>J</i> = 6.4 Hz, 4H), 1.29 (s, 6H) ppm. MS: <i>m/z</i> = 387.5 (M+1).

Example 78: Synthesis of Compound 121



Step 1: 121-2

[00739] To a mixture of **121-1** (2 g, 9.85 mmol) in DCM (50 mL) was added m-CPBA (2.10 g, 10.34 mmol, 85% purity) at 20 °C. The mixture was stirred for 1 hr at 20 °C. Then, the solution was washed with saturated aqueous sodium sulfite (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL), dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 60%) to obtain **121-2** (2.0 g, 9.13 mmol, 92.70% yield). MS: m/z = 220 (M+1).

Step 2: 121-3

[00740] To a mixture of **121-2** (1.0 g, 4.56 mmol), 2-fluoropyridine (1.06 g, 10.95 mmol) in DCM (20 mL) was added trifluoromethanesulfonic anhydride (1.55 g, 5.48 mmol, 919.80 μ L) dropwise at -50 °C. The reaction solution was stirred for 18 hr at 20 °C. Then, the solution was quenched with saturated aqueous NaHCO₃ (5 mL), stirred vigorously for about 10 minutes, diluted with water (10 mL), extracted with DCM (15 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 0 - 40%) to obtain **121-3** (980 mg, 3.31 mmol, 72.49% yield). MS: m/z = 297 (M+1).

20 *Step 3: 121-4*

[00741] To a mixture of **121-3** (350 mg, 1.18 mmol) in DCM (25 mL) was added m-CPBA (839.70 mg, 4.14 mmol, 85% purity) at 20 °C. The mixture was stirred for 4 hr at 20 °C. Then, the solution was washed with saturated aqueous sodium sulfate (10 mL), saturated aqueous NaHCO₃ (20 mL × 2) and brine (15 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated with a rotary evaporator to obtain **121-4** (370 mg, crude). MS: m/z = 328 (M+1).

Step 4: 121-5

[00742] To a mixture of **121-4** (370 mg, 1.13 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (343.55 mg, 1.35 mmol) and potassium acetate (331.94 mg, 3.38 mmol) in Dioxane (10 mL) was added bis(diphenylphosphino)ferrocene]dichloropalladium(II) (82.49 mg, 112.74 μ mol) at 20 °C. The reaction solution was heated to 120 °C for 0.667 hr under microwave. The mixture was filtered and the filtrate was concentrated. The residual material was dissolved in DCM (15 mL), washed with water (15 mL) and brine (15 mL), the organic phase was then concentrated with a rotary evaporator to obtain **121-5** (440 mg, crude). MS: $m/z = 376$ (M+1).

Step 5: 121-6

[00743] To a mixture of **121-5** (440 mg, 1.17 mmol), acetate acid (0.3 mL) in THF (10 mL) was added hydrogen peroxide (0.5 mL, 30% purity) at 20 °C. The reaction solution was stirred for 1 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain **121-6** (350 mg, crude). MS: $m/z = 264$ (M-1).

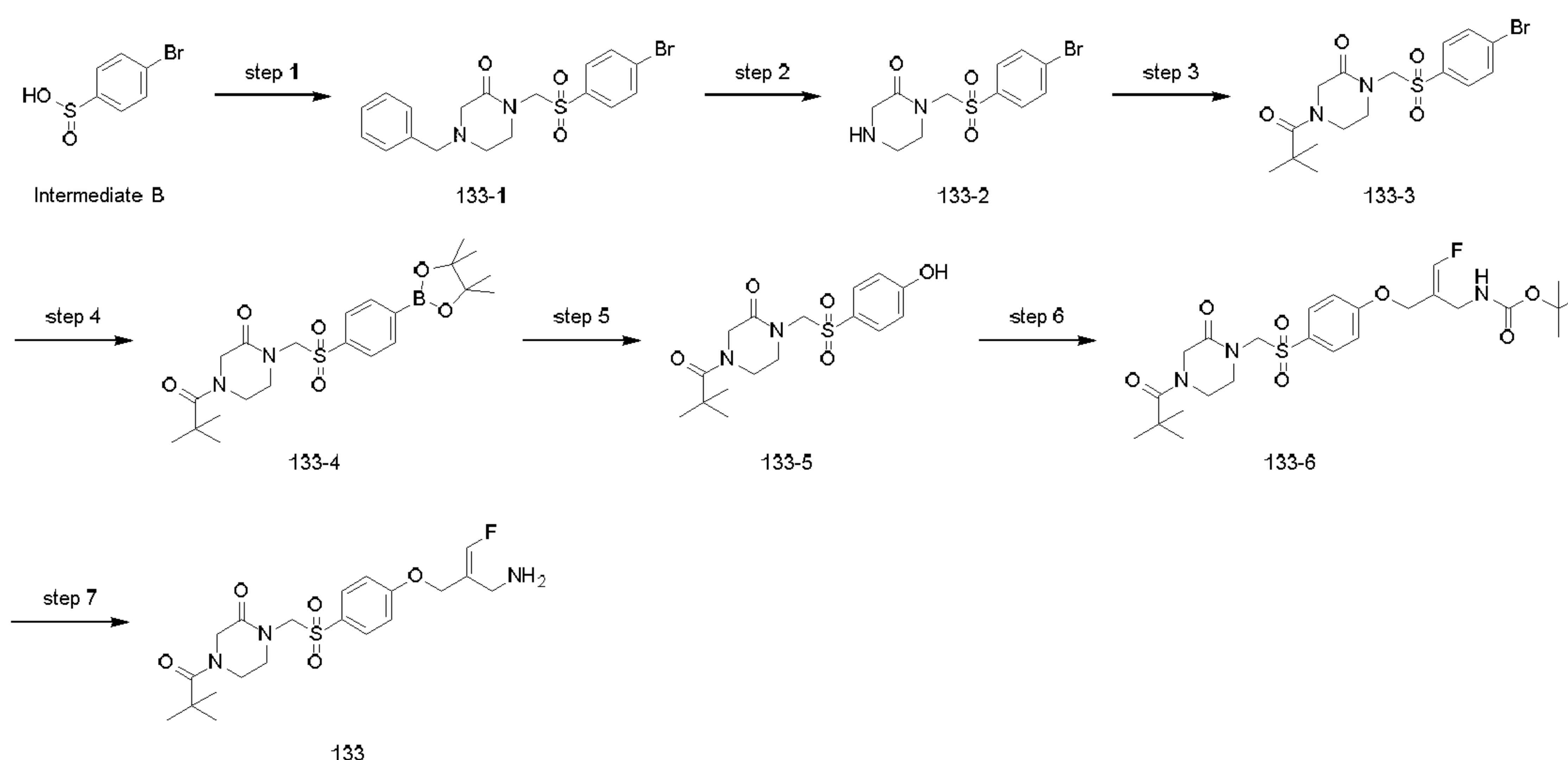
Step 6: 121-7

[00744] To a mixture of **121-6** (350 mg, 1.32 mmol), **Intermediate A** (100 mg, 372.96 μ mol) in MeCN (30 mL) was added Cesium carbonate (364.56 mg, 1.12 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered, and the filtrate was concentrated with a rotary evaporator to obtain **121-7** (180 mg, crude). MS: $m/z = 453$ (M+1).

Step 7: Compound 121

[00745] To a mixture of **121-7** (180 mg, 397.79 μ mol) in DCM (20 mL) was added HCl/Dioxane (4 M, 3 mL) at 20 °C and the reaction mixture was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 121** (38 mg, 95.38 μ mol, 23.98% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.51 (s, 1H), 7.70-7.62 (m, 3H), 7.47 (td, $J = 6.8, 3.3$ Hz, 1H), 7.23 (d, $J = 81.1$ Hz, 1H), 7.12 (d, $J = 8.9$ Hz, 2H), 6.39 (td, $J = 6.8, 1.4$ Hz, 1H), 6.30 (d, $J = 9.2$ Hz, 1H), 5.48 (s, 2H), 4.69 (d, $J = 3.6$ Hz, 2H), 3.79 (d, $J = 2.4$ Hz, 2H) ppm. MS: $m/z = 352.78$ (M+1).

Example 79: Synthesis of Compound 133



Step 1: 133-1

[00746] A mixture of 4-benzylpiperazin-2-one (6.45 g, 33.93 mmol), **Intermediate A** (5 g, 22.62 mmol) and polyformaldehyde (2.04 g, 67.85 mmol) in HCO₂H (20 mL) was heated to 100 °C and stirred at 100 °C for 1 hr. After cooling to room temperature, the reaction was concentrated and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%) to give **133-1** (5 g, 11.81 mmol, 52.22% yield). MS: m/z = 423.3 (M+1).

Step 2: 133-2

[00747] To a mixture of **133-1** (5 g, 11.81 mmol) in DCM (20 mL) was added 1-chloroethyl carbonochloridate (3.38 g, 23.62 mmol, 2.58 mL) at 0 °C. The reaction solution was stirred for 8 hr at 90 °C. Then, MeOH (50 mL) was added and the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 4: 1, v/v) to obtain **133-2** (1 g, 3.0 mmol, 25.41% yield). MS: m/z = 333.2 (M+1).

Step 3: 133-3

[00748] To a mixture of **133-2** (100 mg, 300.12 μmol), 2,2-dimethylpropanoyl chloride (72.37 mg, 600.24 μmol) in DCM (10 mL) was added TEA (91.11 mg, 900.36 μmol, 125.49 μL) at 0 °C. The reaction solution was stirred for 2 hr at 25°C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 4:1, v/v) to obtain **133-3** (100 mg, 239.63 μmol, 79.84% yield). MS: m/z = 317.3 (M+1).

Step 4: 133-4

[00749] A 30 mL microwave reaction tube was charged with 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (91.28 mg, 359.44 μ mol), **133-3** (100 mg, 239.63 μ mol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (17.53 mg, 23.96 μ mol) and potassium acetate (70.55 mg, 718.88 μ mol) in Dioxane (5 mL). After oxygen was
5 purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0 - 100%) to deliver **133-4** (80 mg, 172.27 μ mol, 71.89% yield). MS: $m/z = 464.3$ (M+1).

10 *Step 5: 133-5*

[00750] To a mixture of **133-4** (80 mg, 172.27 μ mol) in THF (1 mL) and acetate acid (0.25 mL) was added hydrogen peroxide (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Sodium sulfite (0.6 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and concentrated to give **133-5** (0.5 g, crude). MS: $m/z = 354.4$ (M+1).

15 *Step 6: 133-6*

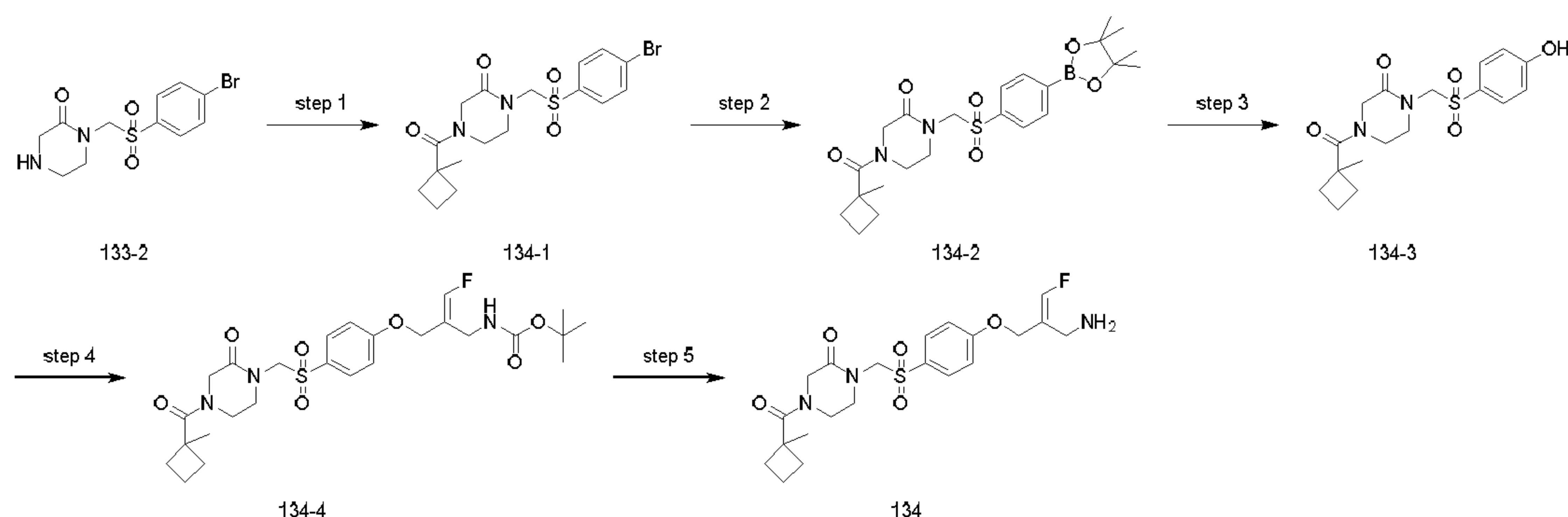
[00751] To a mixture of **133-6** (0.5 g, 1.41 mmol) and **Intermediate A** (151.30 mg, 564.30 μ mol) in MeCN (50 mL) was added Cesium carbonate (1.38 g, 4.23 mmol) at 20 °C. The reaction was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **133-6** (75 mg, crude). MS: $m/z = 541.6$ (M+1).

20 *Step 7: Compound 133*

[00752] A mixture of **133-6** (75 mg, 138.47 μ mol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μ m 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain

25 **Compound 133** (6 mg, 12.31 μ mol, 8.89% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.52 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 80.0$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 2H), 4.91 (s, 2H), 4.70 (d, $J = 3.6$ Hz, 2H), 4.03 (s, 2H), 3.96 (t, $J = 5.2$ Hz, 2H), 3.77 (d, $J = 6.4$ Hz, 4H), 1.29 (s, 9H) ppm. MS: $m/z = 541.6$ (M+1).

Example 80: Synthesis of Compound 134



Step 1: 134-1

[00753] To a mixture of **133-2** (120 mg, 360.14 μmol), 1-methylcyclobutanecarboxylic acid (49.33 mg, 432.17 μmol) and TEA (109.33 mg, 1.08 mmol, 150.59 μL) in DCM (10 mL) was added HATU (205.41 mg, 540.21 μmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 12 - 50%, v/v) to obtain **134-1** (100 mg, 232.92 μmol , 64.67% yield). MS: $m/z = 429.3$ (M+1).

Step 2: 134-2

[00754] A 30 mL microwave reaction tube was charged with 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (88.72 mg, 349.38 μmol), **134-1** (100 mg, 232.92 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (17.04 mg, 23.29 μmol) and potassium acetate (68.58 mg, 698.77 μmol) in Dioxane (10 mL). After oxygen was purged by bubbling nitrogen into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure. The resultant crude product was purified by flash chromatography (ethyl acetate in petroleum ether, 0 - 100%) to deliver **134-2** (60 mg, 125.95 μmol , 54.07% yield). MS: $m/z = 476.3$ (M+1).

Step 3: 134-3

[00755] To a mixture of **134-2** (60 mg, 125.95 μmol) in THF (1 mL) and acetate acid (0.25 mL) was added hydrogen peroxide (0.5 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. The sodium sulfite (0.6 g) was added to the mixture and stirred for 30 min. The reaction mixture was filtered and concentrated to give **134-3** (0.5 g, crude). MS: $m/z = 366.4$ (M+1).

Step 4: 134-4

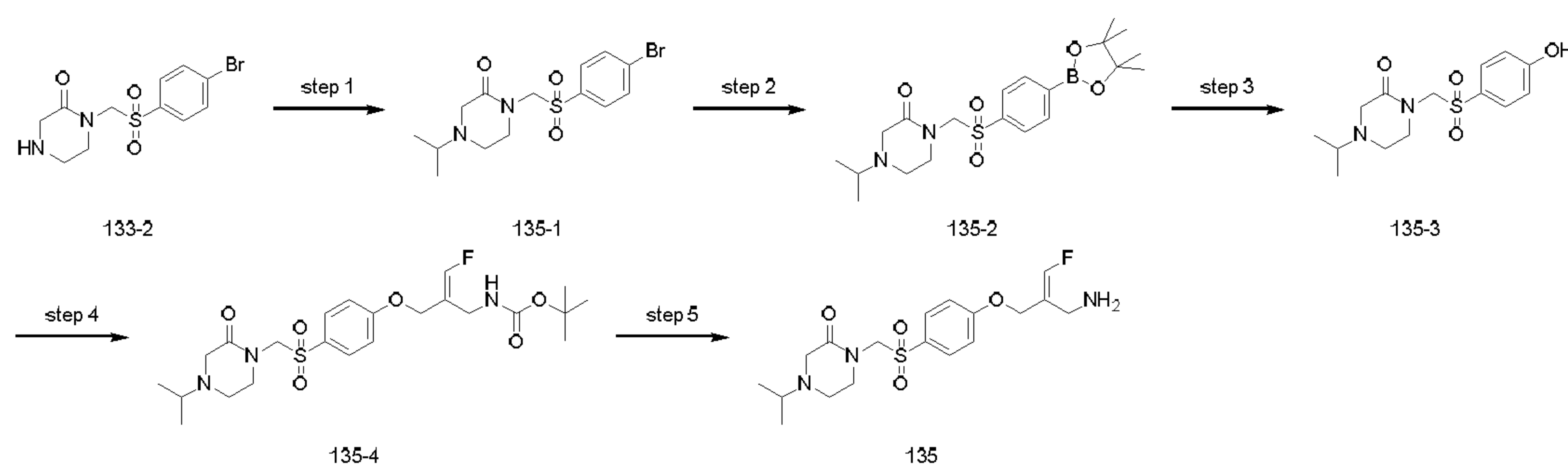
[00756] To a mixture of **134-3** (0.5 g, 1.36 mmol) and **Intermediate A** (146.34 mg, 545.81 μmol) in MeCN (50 mL) was added Cesium carbonate (1.33 g, 4.09 mmol) at 20 °C. The reaction was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **134-4** (90 mg, crude).

5 Step 5: Compound 134

[00757] A mixture of **134-4** (90 mg, 162.56 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19 $\times$ 150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-35% B; GT: 15 min; flow rate: 15 mL/min) to obtain

10 **Compound 134** (9 mg, 18.02 μmol , 11.08% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.50 (s, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 80.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.73-4.69 (m, 2H), 4.60-4.57 (m, 2H), 3.94-3.89 (m, 2H), 3.84-3.80 (m, 2H), 3.73 (d, *J* = 3.2 Hz, 4H), 2.53-2.49 (m, 2H), 2.06-2.03 (m, 1H), 1.95-1.90 (m, 2H), 1.79-1.76 (m, 1H), 1.43 (s, 3H) ppm. MS: *m/z* = 454.6 (M+1).

15 Example 81: Synthesis of Compound 135



Step 1: 135-1

[00758] To a mixture of 2-iodopropane (459.16 mg, 2.70 mmol, 270.09 μL), **133-2** (300 mg, 900.36 μmol) in MeCN (10 mL) was added TEA (273.32 mg, 2.70 mmol, 376.48 μL) at 20 °C.

20 The reaction solution was stirred for 6 hr at 80 °C. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by silica gel chromatography (ethyl acetate in petroleum ether, 20 - 50%, v/v) to obtain **135-1** (100 mg, 266.47 μmol , 29.60% yield). MS: *m/z* = 375.2 (M+1).

Step 2: 135-2

25 [00759] To a mixture of 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (101.50 mg, 399.70 μmol), **135-1** (100 mg, 266.47 μmol) and

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (19.50 mg, 26.65 μmol) in Dioxane (5 mL) was added potassium acetate (80.07 mg, 799.40 μmol) at 20 °C under the nitrogen atmosphere. The reaction solution was stirred for 4 hr at 100 °C. Then, the solution was concentrated with a rotary evaporator and purified by column chromatography on silica gel (ethyl acetate in petroleum ether, 10 - 50%, v/v) to obtain **135-2** (80 mg, 189.42 μmol , 71.09% yield). MS: $m/z = 422.3$ (M+1).

Step 3: 135-3

[00760] To a mixture of **135-2** (80 mg, 189.42 μmol) in THF (2 mL) and acetate acid (0.5 mL) was added hydrogen peroxide (1 mL, 30% purity). The mixture was stirred at 25 °C for 0.5 hr. Sodium sulfite (0.3 g) was added to the mixture and stirred for 0.5 hr. The reaction mixture was filtered and concentrated to give **135-3** (400 mg, crude). MS: $m/z = 312.3$ (M+1).

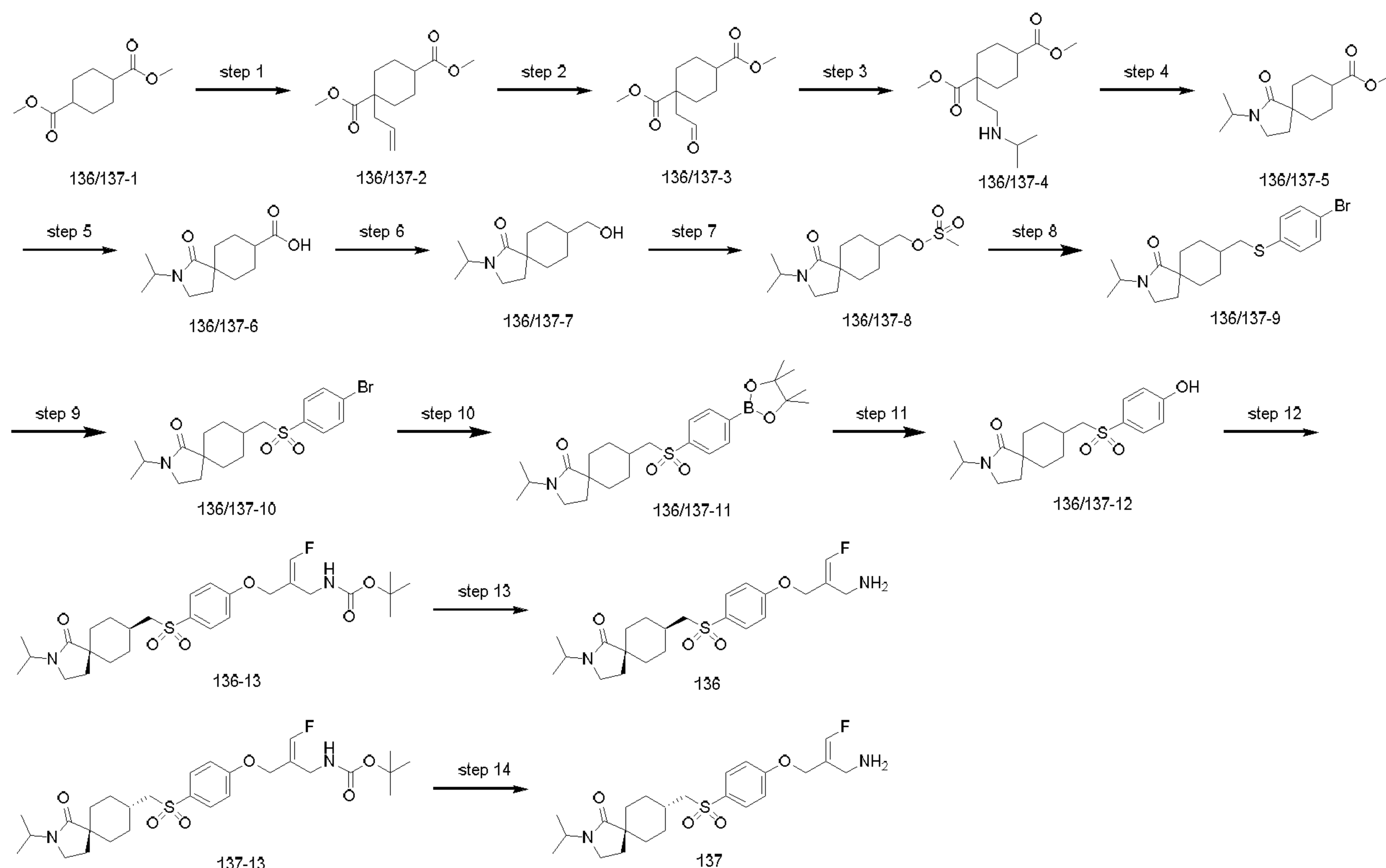
Step 4: 135-4

[00761] To a mixture of **135-3** (400 mg, 1.28 mmol) and **Intermediate A** (137.33 mg, 512.19 μmol) in MeCN (20 mL) was added Cesium carbonate (834.41 mg, 2.56 mmol) at 20 °C. The reaction was stirred for 1 hr at 80 °C. Then, the solution was filtered and concentrated to obtain **135-4** (60 mg, 120.10 μmol , 9.38% yield). MS: $m/z = 499.5$ (M+1).

Step 5: Compound 135

[00762] A mixture of **135-4** (60 mg, 120.10 μmol) in HCl/Dioxane (4 M, 3 mL) was stirred at 20 °C for 1 hr. Then, the solution was concentrated with a rotary evaporator. The crude product was purified by *prep*-HPLC (column: XBridge[®] Prep C18 5 μm 19×150 mm; A: 0.1% HCO₂H water, B: acetonitrile; gradient: 5-30% B; GT: 15 min; flow rate: 15 mL/min) to obtain **Compound 135** (3 mg, 7.51 μmol , 6.25% yield, HCO₂H salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.54 (s, 1H), 7.91-7.85 (m, 2H), 7.21 (d, $J = 80.0$ Hz, 1H), 7.19 (d, $J = 9.0$ Hz, 2H), 4.72 (d, $J = 3.6$ Hz, 2H), 4.61 (d, $J = 6.7$ Hz, 2H), 3.91-3.85 (m, 2H), 3.77 (d, $J = 2.4$ Hz, 2H), 3.61-3.55 (m, 2H), 3.49 (s, 1H), 3.14 (s, 1H), 2.23-2.16 (m, 1H), 1.22-1.18 (d, $J = 8.0$ Hz, 6H) ppm. MS: $m/z = 400.1$ (M+1).

Example 82: Synthesis of Compound 136 & 137



Step 1: 136/137-2

[00763] To a mixture of N-isopropylpropan-2-amine (606.44 mg, 5.99 mmol, 844.62 μ L) in THF (30 mL) was added butyl lithium (2.5 M, 2.40 mL) under the N_2 atmosphere at $-78^\circ C$.

- 5 The solution was stirred for 15 minutes, warmed up to $0^\circ C$ and stirred for an additional 1 hr, then re-cooled to $-78^\circ C$. Then, **136/137-1** (1 g, 4.99 mmol, 900.90 μ L) in THF (2 mL) was added and the reaction mixture was stirred at $-78^\circ C$ for 1 hr followed by the additional of a mixture of HMPA (671.22 mg, 3.75 mmol, 651.67 μ L) and 3-iodoprop-1-ene (1.01 g, 5.99 mmol, 547.12 μ L). The reaction solution was stirred for 1 hr at $-78^\circ C$. Then, the dry ice bath was
- 10 removed and the stirring was continued to allow the reaction mixture to warm to room temperature ($\sim 25^\circ C$) over 1 hr. The reaction mixture was poured into ice-water (20 mL) and ethyl acetate (30 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to obtain
- 15 crude **136/137-2** (1.2 g, 4.99 mmol, 99.99% yield). The crude was used in the next step directly without further purification. ^1H NMR (400 MHz, Chloroform-*d*) δ 5.71-5.62 (m, 1H), 5.07-4.97 (m, 2H), 3.68 (s, 3H), 3.64 (s, 3H), 2.36-2.22 (m, 3H), 2.21-2.19 (m, 2H), 1.94-1.84 (m, 2H),

1.58-1.42 (m, 2H), 1.22-1.14 (m, 2H) ppm.

Step 2: 136/137-3

[00764] To a mixture of **136/137-2** (1.2 g, 4.99 mmol) in water (15 mL) and 2-propanol (30 mL) was added an aqueous solution of sodium periodate (2.67 g, 12.48 mmol) in water (15 mL), followed by addition of potassium osmate(VI) dihydrate (184.0 mg, 499.39 μ mol). The reaction mixture was stirred at 25 °C for 2 hr. The reaction mixture was poured into ice-water (20 mL) and ethyl acetate (30 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to obtain crude **136/137-3** (0.9 g, 3.71 mmol, 74.39% yield). MS: m/z = 243.1 (M+1).

Step 3: 136/137-4

[00765] To a mixture of **136/137-3** (0.9 g, 3.71 mmol) in MeOH (30 mL) was added propan-2-amine (263.50 mg, 4.46 mmol, 381.34 μ L). The reaction mixture was stirred at 25 °C for 0.5 hr, followed by addition of Sodium Cyanoborohydride (350.17 mg, 5.57 mmol). The reaction mixture was stirred at 25 °C for 2 hr. The reaction mixture was poured into ice-water (20 mL) and ethyl acetate (30 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (50 mL $\times$ 3). The combined organic layers were washed with brine (50 mL $\times$ 3), dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (ethyl acetate in petroleum ether: 0 ~ 20%, v/v) to give **136/137-4** (1.2 g, crude). MS: m/z = 286.2 (M+1).

Step 4: 136/137-5

[00766] To a mixture of **136/137-4** (1.2 g, 4.20 mmol) in methanol (20 mL) was added potassium carbonate (1.16 g, 8.41 mmol). The reaction mixture was heated to 80 °C and stirred for 16 hr. The reaction mixture was filtered and concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (ethyl acetate in petroleum ether: 0 ~ 30%, v/v) to give **136/137-5** (200 mg, 789.46 μ mol, 18.77% yield). MS: m/z = 254.2 (M+1).

Step 5: 136/137-6

[00767] To a mixture of **136/137-5** (200 mg, 789.46 μ mol) in water (5 mL) and THF (5 mL) was added Lithium hydroxide, monohydrate (165.63 mg, 3.95 mmol). The reaction mixture was stirred at 25 °C for 3 hr. Then pH of the reaction mixture was adjusted to ~5 with 1 M HCl and the mixture was extracted with ethyl acetate (20 mL $\times$ 3). The combined organic layers were

washed with brine (20 mL $\times$ 3), dried over sodium sulfate, filtered and concentrated with a rotary evaporator to obtain **136/137-6** (180 mg, 752.16 μ mol, 95.28% yield). MS: m/z = 240.2 (M+1).

Step 6: 136/137-7

[00768] To a mixture of **136/137-6** (180 mg, 752.16 μ mol) in THF (5 mL) was added
5 Borane-tetrahydrofuran complex (1 M, 1.13 mL) at 0 °C under the nitrogen atmosphere dropwise. The reaction mixture was stirred for 2 hr at 25 °C. Then, to the reaction mixture was added MeOH (20 mL) at 0~25 °C dropwise. The reaction mixture was stirred at room temperature for 0.5 hr, and concentrated with a rotary evaporator to obtain **136/137-7** (180 mg, crude). MS: m/z = 226.2 (M+1).

10 *Step 7: 136/137-8*

[00769] To a mixture of crude **136/137-7** (180 mg, 798.84 μ mol), Triethylamine (242.50 mg, 2.40 mmol, 334.03 μ L) in DCM (15 mL) was added Methanesulfonic anhydride (208.74 mg, 1.20 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator to obtain **136/137-8** (250 mg, crude). MS: m/z = 304.2
15 (M+1).

Step 8: 136/137-9

[00770] To a mixture of crude **136/137-8** (250 mg, 823.95 μ mol), Cesium carbonate (671.15 mg, 2.06 mmol) and Potassium iodide (68.39 mg, 411.97 μ mol) in DMF (10 mL) was added 4-bromobenzenethiol (311.57 mg, 1.65 mmol) under the nitrogen atmosphere. The
20 reaction mixture was heated at 65 °C for 4 hr. Ethyl acetate (50 mL) and water (50 mL) were added, the organic layer was washed with brine (50 mL $\times$ 4), dried over Na₂SO₄, filtered and concentrated to give a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0~25%, v/v) to give **136/137-9** (200 mg, 504.56 μ mol, 61.24% yield). MS: m/z = 396.1 (M+1).

25 *Step 9: 136/137-10*

[00771] To a mixture of **136/137-9** (200 mg, 504.56 μ mol) and m-CPBA (307.31 mg, 1.51 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 2 hr. Na₂SO₃ (5 g) was added to the mixture and stirred for 20 minutes. Then, to the solution was added DCM (50 mL) and water (50 mL). The organic layer was washed with aqueous NaHCO₃ (50 mL $\times$ 3), brine (50 mL $\times$ 3),
30 dried over Na₂SO₄, filtered, and concentrated to give a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0~35%, v/v) to give **136/137-10** (190 mg,

443.53 μmol , 87.90% yield). MS: $m/z = 428.1$ ($M+1$).

Step 10: 136/137-11

[00772] A mixture of 4,4,5,5-tetramethyl-2-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (127.69 mg, 532.23 μmol), **136/137-10** (190 mg, 443.53 μmol),

5 bis(diphenylphosphino)ferrocene]dichloropalladium(II) (32.45 mg, 44.35 μmol) and Potassium acetate (130.58 mg, 1.33 mmol) in Dioxane (5 mL) was heated at 80 °C for 2 hr under the nitrogen atmosphere. The reaction was cooled to room temperature, filtered and concentrated under reduced pressure to give **136/137-11** (250 mg, crude).

Step 11: 136/137-12

10 [00773] To a mixture of crude **136/137-11** (250 mg, 525.82 μmol), Acetate acid (630.98 μmol , 0.3 mL) in THF (5 mL) was added Hydrogen peroxide (330.0 mg, 2.91 mmol, 0.3 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography (MeOH in DCM: 0 ~ 15%, v/v) to obtain **136/137-12** (144 mg, 394.0 μmol ,
15 74.93% yield).

Step 12: 136/137-13

[00774] To a mixture of **136/137-12** (144 mg, 394.0 μmol), **Intermediate A** (114.09 mg, 425.52 μmol) in Acetonitrile (8 mL) was added potassium carbonate (108.91 mg, 787.99 μmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered and
20 concentrated with a rotary evaporator to obtain a crude, which was purified by *prep*-TLC (petroleum ether: ethyl acetate = 1: 1) to give **136-13** (or 137-13, 100 mg, 180.93 μmol , 45.92% yield) and **137-13** (or 136-13, 50 mg, 90.47 μmol , 22.96% yield). MS: $m/z = 497.2$ ($M+1-56$).

Step 13: Compound 136 or 137

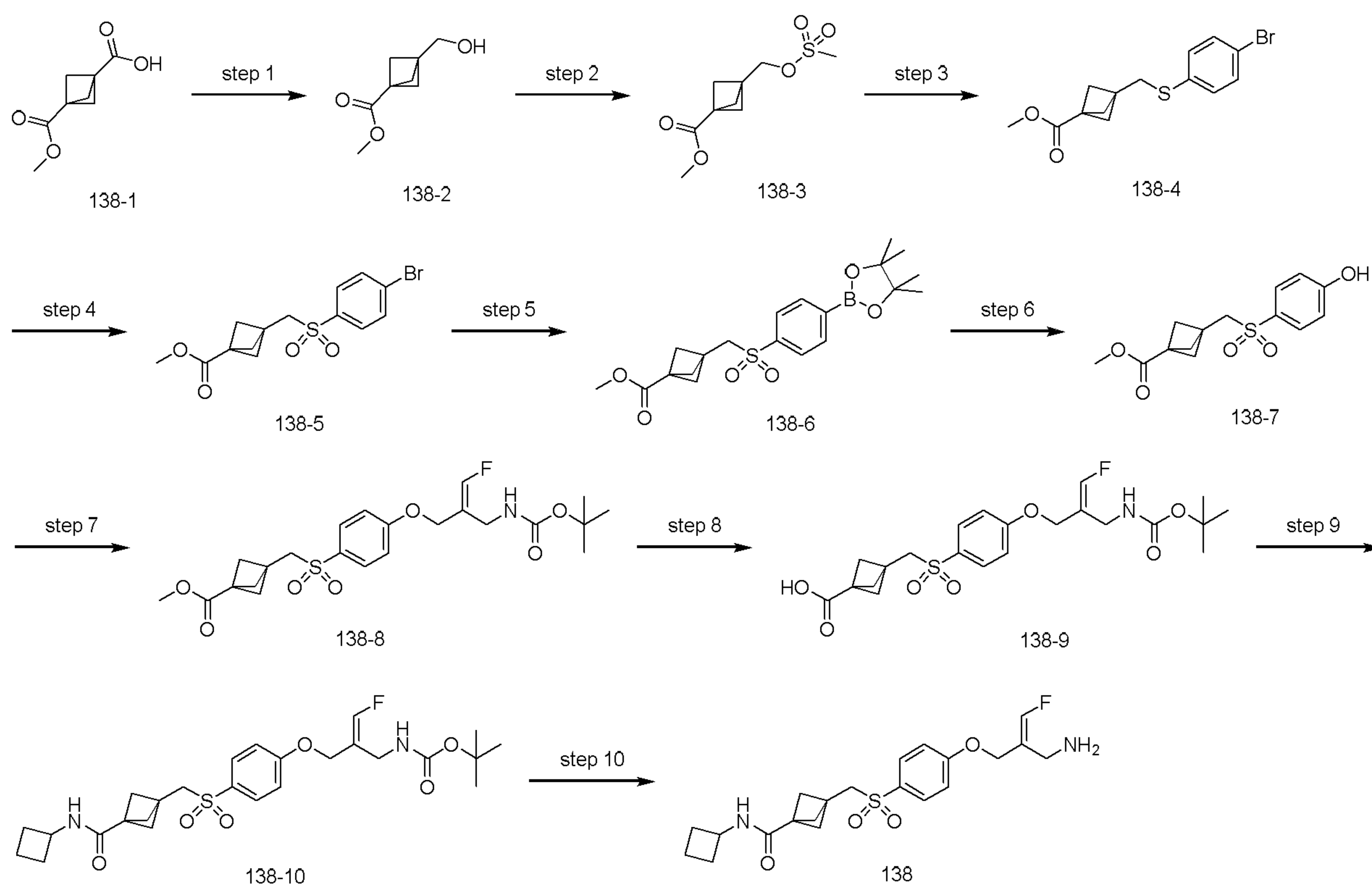
[00775] To a mixture of **136-13** (or 137-13, 100 mg, 180.93 μmol) in DCM (5 mL) was
25 added HCl/dioxane (4 M, 2 mL) at 20 °C and stirred for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (3 mL) for 15 minutes and filtered. The solid was dried by lyophilization (water: acetonitrile = 4: 1, 20 mL) to give **Compound 136 or Compound 137** (68.1 mg, 139.04 μmol , 76.85% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.88 (d, $J = 8.6$ Hz, 2H), 7.27 (d, $J = 80.0$ Hz, 1H), 7.23 (d, $J = 8.6$ Hz, 2H), 4.73
30 (d, $J = 3.5$ Hz, 2H), 4.24-4.15 (m, 1H), 3.86-3.81 (m, 2H), 3.30-3.21 (m, 4H), 2.12 (dd, $J = 8.8$, 4.2 Hz, 1H), 1.86 (t, $J = 6.9$ Hz, 2H), 1.79-1.62 (m, 6H), 1.31-1.25 (m, 2H), 1.12 (d, $J = 6.8$ Hz,

6H) ppm. MS: $m/z = 453.3$ (M+1).

Step 14: Compound 137 or 136

[00776] To a mixture of **137-13** (or 136-13, 50 mg, 90.47 μmol) in DCM (5 mL) was added HCl/Dioxane (4 M, 2.0 mL) at 20 °C and stirred for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (3 mL) for 15 minutes and filtered. The solid was dried by lyophilization (water: acetonitrile = 4: 1, 20 mL) to give **Compound 137 or Compound 136** (32 mg, 65.43 μmol , 72.3% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.92-7.86 (m, 2H), 7.28 (s, $J = 80.0$ Hz, 1H), 7.28-7.21 (m, 2H), 4.74 (d, $J = 3.5$ Hz, 2H), 4.24-4.18 (m, 1H), 3.85 (d, $J = 2.3$ Hz, 2H), 3.30 (d, $J = 5.6$ Hz, 2H), 3.13 (d, $J = 6.0$ Hz, 2H), 1.93 (t, $J = 6.9$ Hz, 2H), 1.88-1.80 (m, 2H), 1.78-1.72 (m, 1H), 1.59-1.51 (m, 2H), 1.47-1.37 (m, 2H), 1.30-1.25 (m, 1H), 1.25-1.19 (m, 1H), 1.13 (d, $J = 6.8$ Hz, 6H) ppm. MS: $m/z = 453.2$ (M+1).

Example 83: Synthesis of Compound 138



Step 1: 138-2

[00777] To a mixture of **138-1** (1 g, 5.88 mmol) in THF (20 mL) was added Borane-tetrahydrofuran complex (1 M, 17.63 mL) at 0 °C under the nitrogen atmosphere dropwise. The reaction mixture was stirred for 2 hr at 25 °C. Then, to the reaction mixture was added MeOH

(20 mL) at 0~25 °C dropwise. The reaction mixture was stirred at room temperature (~25 °C) for 0.5 hr and concentrated with a rotary evaporator to obtain crude **138-2** (900 mg, 5.76 mmol, 98.06% yield).

Step 2: 138-3

5 [00778] To a mixture of **138-2** (900 mg, 5.76 mmol), Triethylamine (1.75 g, 17.29 mmol, 2.41 mL) in DCM (20 mL) was added Methanesulfonic anhydride (1.51 g, 8.64 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated and purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 40%, v/v) to obtain **138-3** (1.25 g, 5.34 mmol, 92.59% yield).

10 *Step 3: 138-4*

[00779] To a solution of 4-bromobenzenethiol (2.52 g, 13.34 mmol), Cesium carbonate (5.22 g, 16.01 mmol) and Potassium iodide (442.87 mg, 2.67 mmol) in DMF (10 mL) was added **138-3** (1.25 g, 5.34 mmol) under the nitrogen atmosphere. The reaction mixture was heated at 55 °C for 3 hr. Ethyl acetate (100 mL) and H₂O (50 mL) were added, the organic layer was washed
15 with brine (50 mL × 4), dried over Na₂SO₄, filtered and concentrated to a crude, which was purified by column chromatography (ethyl acetate in petroleum ether, 0 ~ 15%) to give **138-4** (1.2 g, 3.67 mmol, 68.73% yield).

Step 4: 138-5

[00780] To a mixture of **138-4** (1.2 g, 3.67 mmol) and m-CPBA (2.23 g, 11.00 mmol, 85%
20 purity) in DCM (20 mL) was stirred at 20 °C for 2 hr. Na₂SO₃ (5 g) was added to the mixture and stirred for 20 minutes. Then, to the solution was added DCM (100 mL) and water (100 mL). The organic layer was washed with aqueous NaHCO₃ (50 mL × 3), brine (50 mL × 3), dried over Na₂SO₄, filtered, concentrated to give a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 40%) to give **138-5** (920 mg, 2.56 mmol, 69.84% yield).

25 *Step 5: 138-6*

[00781] A 30 mL microwave reaction tube was charged with **138-5** (920 mg, 2.56 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (780.40 mg, 3.07 mmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (187.39 mg, 256.10 μmol) and Potassium Acetate (754.01 mg, 7.68 mmol) in Dioxane (10 mL). After O₂ was purged
30 by bubbling N₂ into the reaction solution, the tube was sealed and heated at 120 °C for 0.5 hr in a Biotage microwave reactor. The reaction was cooled to room temperature, filtered and

concentrated under reduced pressure to give **138-6** (1.5 g, crude). The crude product was used into the next step directly without further purification.

Step 6: 138-7

[00782] To a mixture of crude **138-6** (1.5 g, 3.69 mmol) and Acetate acid (3.69 mmol, 0.4 mL) in THF (3 mL) was added Hydrogen peroxide (440.0 mg, 3.88 mmol, 0.4 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 65%) to give **138-7** (600 mg, 2.02 mmol, 54.84% yield).

Step 7: 138-8

[00783] To a mixture of **138-7** (600 mg, 2.02 mmol), **Intermediate A** (651.45 mg, 2.43 mmol) in Acetonitrile (5 mL) was added Cesium carbonate (1.32 g, 4.05 mmol) at 20 °C. The reaction solution was stirred for 1 hr at 95 °C. Then, the mixture was filtered and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 45%, v/v) to obtain **138-8** (430 mg, 889.26 µmol, 43.92% yield).

Step 8: 138-9

[00784] To a mixture of **138-8** (430 mg, 889.26 µmol) in Water (6 mL) and THF (6 mL) was added Lithium hydroxide monohydrate (373.13 mg, 8.89 mmol) at 20 °C. The reaction solution was heated to 55 °C and stirred for 8 hr. Then, pH of the mixture was adjusted to ~5 with 1 M HCl. The reaction mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over sodium sulfate, filtered and concentrated to give **138-9** (350 mg, 745.44 µmol, 83.83% yield).

Step 9: 138-10

[00785] To a mixture of cyclobutanamine (63.62 mg, 894.52 µmol, 76.37 µL), **138-9** (350 mg, 745.44 µmol) in DCM (10 mL) was added HATU (340.13 mg, 894.52 µmol) and Triethylamine (226.29 mg, 2.24 mmol, 311.7 µL) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The reaction mixture was concentrated to give a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 100%, v/v) to obtain **138-10** (300 mg, 574.02 µmol, 77.0% yield).

Step 10: Compound 138

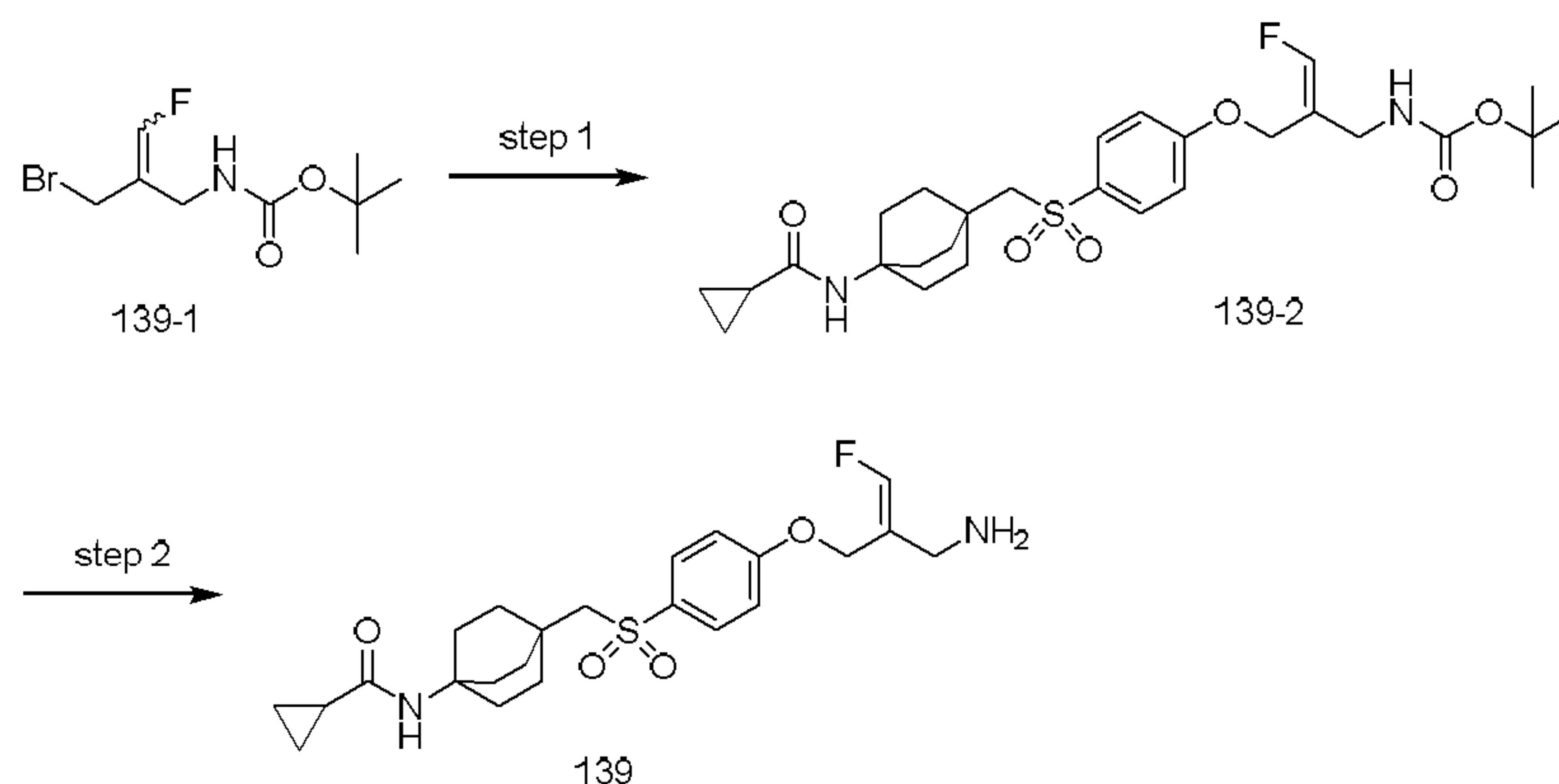
[00786] A mixture of **138-10** (300 mg, 574.02 μmol) and Hydrochloric acid/dioxane (4 M, 1 mL) was stirred for 1 hr at 20 °C. The mixture was concentrated, slurried in CH_3CN (6 mL) and filtered. The cake was dissolved in water and freeze-dried to give **Compound 138** (147.9 mg, 322.24 μmol , 56.14% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.92-7.85 (m, 2H), 7.28 (d, $J = 84.0$ Hz, 1H), 7.27-7.20 (m, 2H), 4.73 (dd, $J = 3.6, 1.0$ Hz, 2H), 4.30-4.20 (m, 1H), 3.84 (d, $J = 2.3$ Hz, 2H), 3.49 (s, 2H), 2.25-2.15 (m, 2H), 2.04-1.93 (m, 8H), 1.75-1.62 (m, 2H) ppm. MS: $m/z = 423.3$ (M+1).

[00787] The compounds of Formula (I') or (I) in Table 16 below were made according to **Example 83** of *Compound 138* (using **139-1** instead of **intermediate A**)

10 **Table 16**

Cmpd No.	^1H NMR and/or LC/MS data
140	^1H NMR (400 MHz, Methanol- d_4) δ 8.54 (s, 1H), 7.88 (d, $J = 8.9$ Hz, 2H), 7.23 (d, $J = 8.9$ Hz, 2H), 7.11 (d, $J = 84.0$ Hz, 1H), 4.90 (s, 2H), 4.30-4.26 (m, 1H), 3.64 (d, $J = 3.0$ Hz, 2H), 3.10 (s, 2H), 2.29-2.20 (m, 2H), 2.04-1.93 (m, 2H), 1.84-1.66 (m, 14H) ppm. MS: $m/z = 465.3$ (M+1).
141	^1H NMR (400 MHz, Methanol- d_4) δ 8.55 (s, 1H), 7.88 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 84.0$ Hz, 1H), 6.41 (s, 1H), 4.90 (s, 2H), 3.63 (d, $J = 3.0$ Hz, 2H), 3.09 (s, 2H), 1.78-1.74 (m, 12H), 1.32 (s, 9H) ppm. MS: $m/z = 467.3$ (M+1).

Example 84: Synthesis of Compound 139



Step 1: **139-2**

[00788] To a mixture of **76-3** (60 mg, 165.08 μmol), **139-1** (57.54 mg, 214.60 μmol , Z/E = 1/1, synthesized according to methods known in the art, such as the methods described in WO 2013/163675 A1) in Acetonitrile (10 mL) was added Cesium carbonate (161.36 mg, 495.24 μmol) at 25 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered and the filtrate was concentrated with a rotary evaporator to obtain a crude, which was purified by column chromatography (petroleum ether: ethyl acetate = 1: 2) to obtain **139-2** (32 mg, 58.11 μmol , 35.2% yield).

Step 2: Compound 139

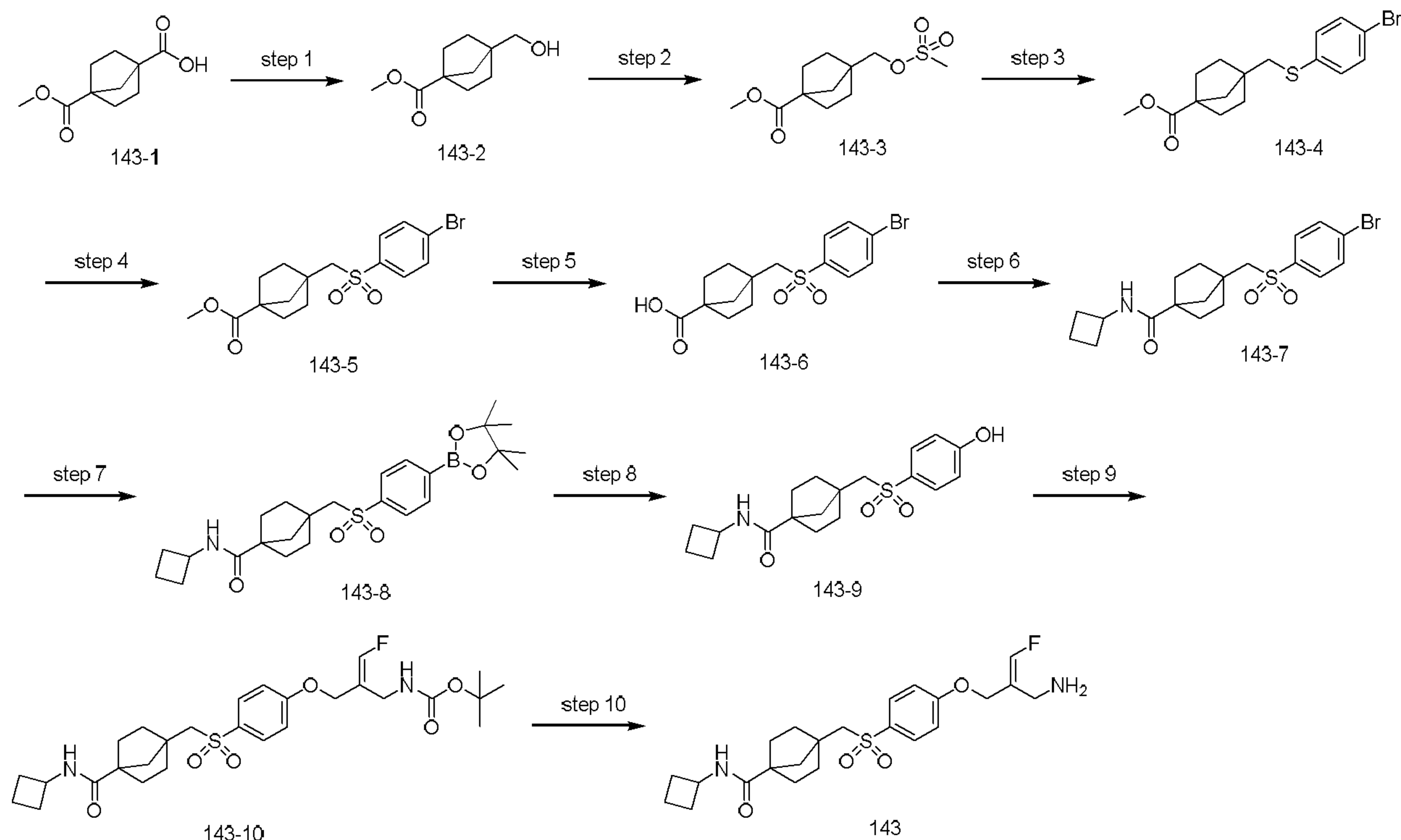
[00789] To a mixture of **139-2** (32 mg, 58.11 μmol) in dichloromethane (10 mL) was added HCl/Dioxane (4 M, 1 mL) at 25 °C and stirred for 2 hr. Then, the solution was concentrated to obtain a crude, which was purified by prep-HPLC(column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile; gradient: 5 - 75% B; GT: 18 min; flow rate: 15 mL/min) to obtain **Compound 139** (15.3 mg, 33.96 μmol , 58.44% yield, HCOOH salt). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.52 (s, 1H), 7.93-7.85 (m, 2H), 7.29-7.20 (m, 2H), 7.12 (d, *J* = 80.0 Hz, 1H), 4.93 (s, 2H), 3.68 (d, *J* = 3.1 Hz, 2H), 3.08 (s, 2H), 1.98-1.87 (m, 6H), 1.84-1.74 (m, 6H), 1.53 (td, *J* = 8.1, 4.0 Hz, 1H), 0.75 (dt, *J* = 4.7, 3.0 Hz, 2H), 0.70 – 0.63 (m, 2H) ppm. MS: *m/z* = 451.2 (M+1).

[00790] The compounds of Formula (I') or (I) in Table 17 below were made according to **Example 84 of Compound 139**

Table 17

Cmpd No.	¹ H NMR and/or LC/MS data
142	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.51 (s, 1H), 7.92-7.85 (m, 2H), 7.26-7.20 (m, 2H), 7.12 (d, <i>J</i> = 80.0 Hz, 1H), 6.33 (s, 1H), 4.92 (d, <i>J</i> = 2.9 Hz, 2H), 3.68 (d, <i>J</i> = 2.9 Hz, 2H), 3.09 (s, 2H), 1.93-1.88 (m, 6H), 1.81-1.74 (m, 6H), 1.14 (s, 9H) ppm. MS: <i>m/z</i> = 467.3 (M+1).

Example 85: Synthesis of Compound 143



Step 1: 143-2

[00791] To a mixture of **143-1** (480 mg, 2.42 mmol) in THF (10 mL) was added Borane-tetrahydrofuran complex (1 M, 3.63 mL) at 0 °C under the nitrogen atmosphere dropwise. The reaction mixture was stirred for 2 hr at 25 °C. Then, to the reaction mixture was added MeOH (20 mL) at 0~25 °C dropwise. The reaction mixture was stirred at room temperature (~25 °C) for 0.5 hr and concentrated with a rotary evaporator to obtain crude **143-2** (450 mg).

Step 2: 143-3

[00792] To a mixture of crude **143-2** (450 mg, 2.44 mmol), Triethylamine (741.49 mg, 7.33 mmol, 1.02 mL) in DCM (15 mL) was added Methanesulfonic anhydride (638.24 mg, 3.66 mmol) at 0 °C. The reaction solution was stirred for 2 hr at 25 °C. Then, the solution was concentrated with a rotary evaporator to obtain **143-3** (660 mg, crude).

Step 3: 143-4

[00793] To a solution of 4-bromobenzenethiol (951.41 mg, 5.03 mmol), Cesium carbonate (2.05 g, 6.29 mmol) and Potassium iodide (208.83 mg, 1.26 mmol) in DMF (10 mL) was added crude **143-3** (660 mg, 2.52 mmol) under the nitrogen atmosphere. The reaction mixture was heated at 65 °C for 4 hr. Ethyl acetate (50 mL) and H₂O (50 mL) were added, the organic layer was washed with brine (50 mL × 4), dried over Na₂SO₄, filtered and concentrated to a residue,

which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 8%, v/v) to give **143-4** (540 mg, 1.52 mmol, 60.41% yield).

Step 4: 143-5

[00794] To a mixture of **143-4** (540 mg, 1.52 mmol) and m-CPBA (925.72 mg, 4.56 mmol, 85% purity) in DCM (20 mL) was stirred at 20 °C for 2 hr. Na₂SO₃ (5 g) was added to the mixture and stirred for 20 minutes. Then, to the solution was added DCM (50 mL) and water (50 mL). The organic layer was washed with aqueous NaHCO₃ (50 mL × 3), brine (50 mL × 3), dried over Na₂SO₄, filtered, concentrated to give crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 20%, v/v) to give **143-5** (530 mg, 1.37 mmol, 90.04% yield).

Step 5: 143-6

[00795] To a mixture of **143-5** (530 mg, 1.37 mmol) in THF (20 mL) and water (20 mL) was added Lithium hydroxide monohydrate (574.22 mg, 13.68 mmol) at 20 °C. The reaction solution was heated at 55 °C for 8 hr. Then, pH of the mixture was adjusted to ~5 with 1 M HCl. The reaction mixture was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 2), dried over sodium sulfate, filtered and concentrated to give **143-6** (500 mg, 1.34 mmol, 97.88% yield).

Step 6: 143-7

[00796] A mixture of **143-6** (200 mg, 535.82 μmol), diisopropylethylamine (138.50 mg, 1.07 mmol, 186.66 μL), HATU (244.48 mg, 642.98 μmol), cyclobutanamine (57.16 mg, 803.73 μmol, 68.62 μL) and DCM (20 mL) was stirred at 20 °C for 16 hr. Then, the mixture was concentrated with a rotary evaporator to obtain a crude, which was purified by silica gel chromatography (ethyl acetate in petroleum ether: 0 ~ 60%, v/v) to give **143-7** (200 mg, 469.08 μmol, 87.54% yield).

Step 7: 143-8

[00797] A mixture of **143-7** (200 mg, 469.08 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (142.94 mg, 562.90 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (34.32 mg, 46.91 μmol) and Potassium Acetate (138.11 mg, 1.41 mmol) in Dioxane (5 mL) was heated at 80 °C for 2 hr under the nitrogen atmosphere. The reaction was cooled to room temperature, filtered and concentrated to give **143-8** (240 mg, crude).

Step 8: 143-9

[00798] To a mixture of **143-8** (240 mg, 506.94 μmol) and Acetate acid (608.32 μmol , 0.2 mL) in THF (5 mL) was added Hydrogen peroxide (220.0 mg, 1.94 mmol, 0.2 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated to obtain a crude, which was purified by column chromatography (MeOH in DCM: 0 ~ 15%, v/v) to obtain **143-9** (150 mg, 412.69 μmol , 81.41% yield).

Step 9: 143-10

[00799] To a mixture of **143-9** (150 mg, 412.69 μmol), **Intermediate A** (119.50 mg, 445.70 μmol) in acetonitrile (8 mL) was added potassium carbonate (114.08 mg, 825.38 μmol) at 20 °C. The reaction solution was stirred for 1 hr at 70 °C. Then, the mixture was filtered and the filtrate was concentrated to obtain a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 70%, v/v) to give **143-10** (170 mg, 308.71 μmol , 74.80% yield).

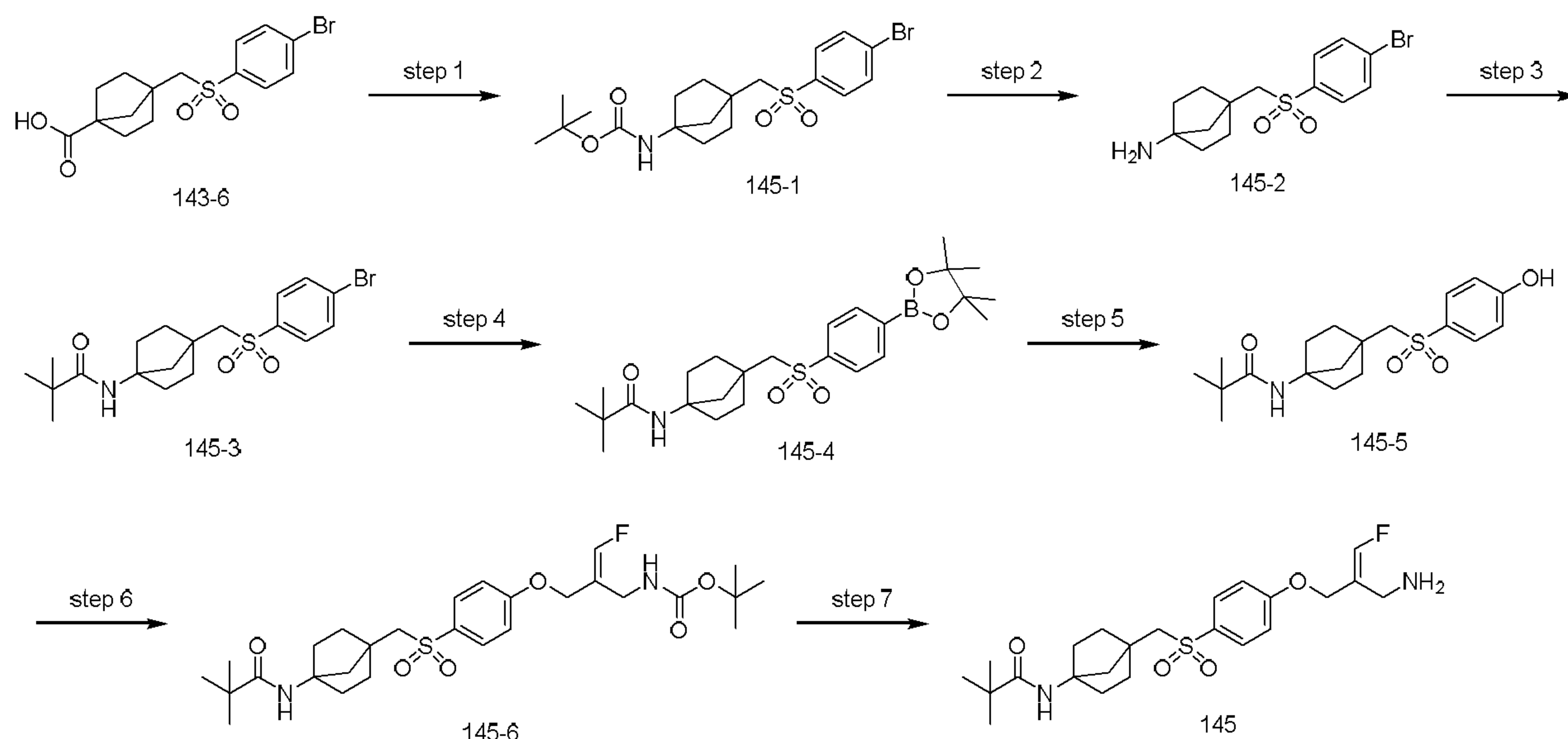
Step 10: Compound 143

[00800] To a solution of **143-10** (170 mg, 308.71 μmol) in DCM (5 mL) was added HCl/dioxane (4 M, 2 mL) at 20 °C and stirred for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (3 mL) for 15 minutes and filtered. The filter cake was dried under the reduced pressure by oil pump for 8 hr at 45 °C to give **Compound 143** (150 mg, 307.99 μmol , 99.77% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.94-7.84 (m, 2H), 7.27 (d, J = 80.0 Hz, 1H), 7.28-7.20 (m, 2H), 4.74 (d, J = 3.5 Hz, 2H), 4.30 (t, J = 8.3 Hz, 1H), 3.84 (d, J = 2.3 Hz, 2H), 3.51 (s, 2H), 2.29-2.17 (m, 2H), 2.08-1.93 (m, 2H), 1.88-1.57 (m, 12H) ppm. MS: m/z = 451.2 (M+1).

[00801] The compounds of Formula (I') or (I) in Table 18 below were made according to **Example 85 of Compound 143**

Table 18

Cmpd No.	^1H NMR and/or LC/MS data
144	^1H NMR (400 MHz, Methanol- d_4) δ 7.91-7.85 (m, 2H), 7.27 (d, J = 80.0 Hz, 1H), 7.26-7.20 (m, 2H), 4.77-4.71 (m, 2H), 3.95-3.89 (m, 1H), 3.87-3.82 (m, 2H), 3.27 (d, J = 6.4 Hz, 2H), 2.22 (d, J = 8.6 Hz, 2H), 1.74-1.48 (m, 8H), 1.11 (d, J = 6.6 Hz, 6H) ppm. MS: m/z = 427.3 (M+H). (Cis and trans mixture)

Example 86: Synthesis of Compound 145**Step 1: 145-1**

[00802] To a solution of **143-6** (300 mg, 803.73 μmol) in toluene (5 mL) and t-BuOH (0.2 mL) was added Triethylamine (105.73 mg, 1.04 mmol, 145.63 μL) and DPPA (254.11 mg, 1.04 mmol, 198.52 μL) at 20 °C under the nitrogen atmosphere. The reaction solution was heated to 70 °C and stirred for 3 hr. The reaction mixture was concentrated to give a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 20%, v/v) to obtain **145-1** (200 mg, 450.06 μmol , 56.0% yield). MS: m/z = 388.2 ($M+1-56$).

Step 2: 145-2

[00803] To a mixture of **145-1** (200 mg, 450.06 μmol) in DCM (10 mL) was added HCl/dioxane (4 M, 4 mL) at 20 °C and stirred for 1 hr. The reaction mixture was concentrated to give **145-2** (180 mg, crude, HCl salt). MS: m/z = 344.2 ($M+1$).

Step 3: 145-3

[00804] To a mixture of **145-2** (180 mg, 472.78 μmol , HCl salt) and Triethylamine (143.52 mg, 1.42 mmol, 197.69 μL) in DCM (10 mL) was added 2,2-dimethylpropanoyl chloride (114.01 mg, 945.56 μmol , 115.75 μL) at 25 °C. The reaction solution was stirred for 2 hr at 25 °C. The mixture was concentrated and purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 45%, v/v) to obtain **145-3** (170 mg, 396.84 μmol , 83.94% yield).

Step 4: 145-4

[00805] A mixture of **145-3** (170 mg, 396.84 μmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (120.93 mg, 476.21 μmol), bis(diphenylphosphino)ferrocene]dichloropalladium(II) (29.04 mg, 39.68 μmol) and Potassium acetate (116.84 mg, 1.19 mmol) in Dioxane (8 mL) was heated at 80 °C for 2 hr under the nitrogen atmosphere. The reaction was cooled to room temperature, filtered and concentrated to give **145-4** (200 mg, crude).

Step 5: 145-5

[00806] To a mixture of **145-4** (200 mg, 420.66 μmol) and Acetate acid (504.79 μmol , 0.2 mL) in THF (5 mL) was added Hydrogen peroxide (220.0 mg, 1.94 mmol, 0.2 mL, 30% purity) at 20 °C. The reaction solution was stirred for 0.5 hr at 20 °C. Then, the solution was concentrated to obtain a crude, which was purified by column chromatography (MeOH in DCM: 0 ~ 15%, v/v) to obtain **145-5** (110 mg, 300.97 μmol , 71.55% yield). MS: m/z = 366.2 (M+1).

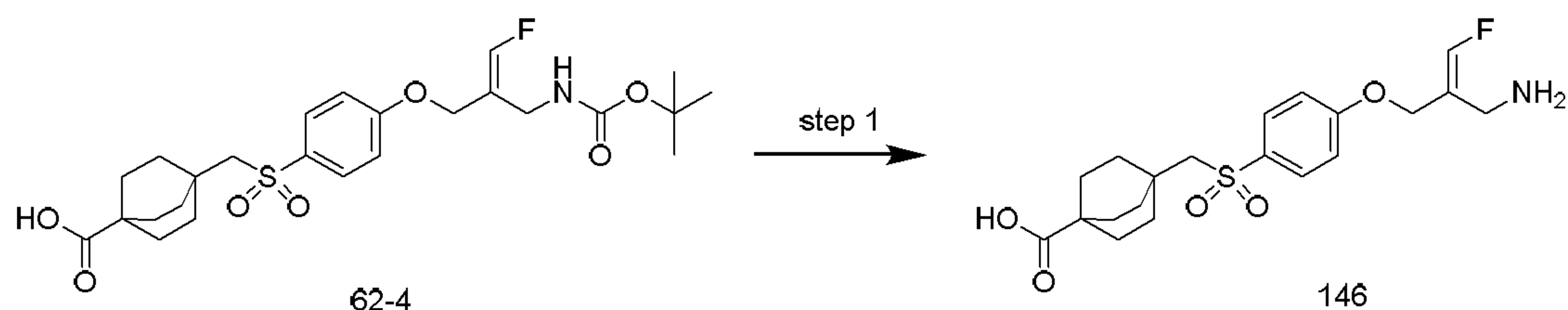
Step 6: 145-6

[00807] To a mixture of **145-5** (110 mg, 300.97 μmol), **Intermediate A** (87.15 mg, 325.05 μmol) in Acetonitrile (8 mL) was added potassium carbonate (83.19 mg, 601.94 μmol) at 20 °C. The reaction solution was stirred for 1 hr at 90 °C. Then, the mixture was filtered and the filtrate was concentrated to obtain a crude, which was purified by column chromatography (ethyl acetate in petroleum ether: 0 ~ 70%, v/v) to give **145-6** (20 mg, 36.19 μmol , 12.02% yield).

Step 7: Compound 145

[00808] To a mixture of **145-6** (20 mg, 36.19 μmol) in DCM (5 mL) was added HCl/dioxane (4 M, 266.67 μL) at 20 °C and stirred for 1 hr. The reaction mixture was filtered. The filter cake was slurried with acetonitrile (3 mL) for 15 minutes and filtered. The filter cake was dried under the reduced pressure by oil pump for 8 hr at 45 °C to give **Compound 145** (2.1 mg, 4.29 μmol , 11.87% yield, HCl salt). ^1H NMR (400 MHz, Methanol- d_4) δ 7.93-7.86 (m, 2H), 7.27 (d, J = 80.0 Hz, 1H), 7.26 (s, 1H), 7.25-7.20 (m, 2H), 4.73 (dd, J = 3.6, 1.1 Hz, 2H), 3.84 (d, J = 2.2 Hz, 2H), 3.48 (s, 2H), 1.86-1.73 (m, 8H), 1.66-1.58 (m, 2H), 1.15 (s, 9H) ppm. MS: m/z = 453.3 (M+1).

Example 87: Synthesis of Compound 146



Step 1: Compound 146

[00809] To a solution of **62-4** (150 mg, 293.20 μmol) in DCM (5 mL) was added HCl/Dioxane (1 mL, 4 M) at 25 °C and stirred for 18 hr. Then, the solution was concentrated to obtain a crude, which was purified by *prep*-HPLC (column: XBridge@ Prep C18 5 μm 19 $\times$ 150 mm; A: 0.2% HCO₂H water, B: acetonitrile; gradient: 5 - 60% B; GT: 18 min; flow rate: 15 mL/min) to obtain **Compound 146** (33 mg, 80.20 μmol , 27.35% yield, HCOOH salt). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.16-7.09 (m, 2H), 7.14 (d, *J* = 84.0 Hz, 1H), 4.61 (d, *J* = 3.5 Hz, 2H), 3.07 (s, 2H), 2.61 (s, 2H) 2.30 (s, 2H), 1.93 (q, *J* = 7.2, 6.6 Hz, 4H), 1.55 (d, *J* = 3.9 Hz, 8H) ppm. MS: *m/z* = 412.3 (M+1).

Example 88: SSAO Activity Assay

[00810] Amine oxidase activity of recombinant hSSAO, hMAO-A, and hMAO-B isoforms are measured using the MAO-Glo assay kit (Promega, V1402). Ten nL test compounds (with DMSO as vehicle, 0.1% v/v for hSSAO, hMAO-A and hMAO-B) were added into assay plates by Echo, and pre-incubated with 5 μL of enzyme for 30 mins at room temperature before the addition of 5 μL of luminogenic substrate. The substrate concentration is 40 μM for human recombinant SSAO, 40 μM for human recombinant MAO-A, and 4 μM for human recombinant MAO-B. The hSSAO and hMAO-A assays were conducted in the MAO-A reaction buffer in the kit, and the MAO-B assay was conducted in the MAO-B reaction buffer. Oxidation of the substrate was conducted for 1 hr, before the addition of detecting reagent according the manufacture's protocol. The IC₅₀ value of the tested compounds was calculated by fitting the dose response curve using a 4-parameter non-linear regression routine. As shown in Table 19, the compounds exhibit potent hSSAO inhibition ("A" means >0 nM and $\leq$ 20 nM; "B" means >20 nM and $\leq$ 100 nM; "C" means >100 nM and $\leq$ 500 nM, "D" means > 500 nM).

Table 19: SSAO activity of compounds of the application

Compound No.	SSAO Activity (IC ₅₀ , nM)
BI 1467335 (PXS-4728A)	A
1	A
2	B
3 or 4	B
4 or 3	B
5	A

6	B
7	A
8	B
9	A
10	B
11	B
12	B
13	B
14	B
15	A
16	B
17	B
18	A
19	A
20	A
21 or 22	B
22 or 21	B
23 or 24	B
24 or 23	A
25	B
26	B
27	B
28	A
29	B
30	A
31	B
32	B
33	B
34	B
35	B
36	B
37	A
38	A
39	A
40	B
41	B
42	B

43	C
44	B
45	B
46	B
47	C
48	B
49	B
50	B
51	B
52	B
53	B
54	B
55	B
56	B
57	B
58	C
59	B
60	B
61	A
62	B
63	B
64	A
65	A
66	A
67	A
68	A
69	A
70	B
71	A
72	A
73	B
74	B
75	A
76	A
77	A
78	B
79	A

80	A
81	A
82	A
83	A
84	A
85	B
86	A
87	A
88	A
89	C
90	A
91	A
92	A
93 or 94	D
94 or 93	B
95	C
96	A
97	B
98	B
99	B
100	B
101	B
102	A
103	B
104 or 105	B
105 or 104	B
106	B
107	A
108	B
109 or 110	B
110 or 109	B
111	B
112 or 113	B
113 or 112	A
114	B
115	B
116	B

117	C
118	B
119	B
120	B
121	B
122	B
123	B
124	B
125	B
126	C
127	C
128	C
129	B
130	B
131	B
132	B
133	C
134	C
135	B
136 or 137	B
137 or 136	B
138	B
139	A
140	A
141	B
142	A
143	B
144	B
145	B
146	B

Example 89: Brain Kpuu Assay

[00811] Brain Kpuu assay is composed of Blood-Brain-Barrier (BBB) assay and protein binding assay, which are conducted in ICR mice. Protein binding assays were performed in 96-
5 well plates, using equilibrium dialysis against brain lysate and plasma to calculate $f_{u(\text{brain})}$ and $f_{u(\text{plasma})}$, respectively. BBB assays were conducted in mice at 1mg/kg IV dosage. Plasma and

brain samples were collected at 5 minutes after dosing to analyze compounds concentration (C_{plasma} and C_{brain}). The K_{puu} value of the tested compounds was calculated by the equation:

$$K_{puu} = \frac{C_{brain}}{C_{plasma}} \times \frac{f_{u(brain)}}{f_{u(plasma)}} \quad (1)$$

5 [00812] As shown in Table 20, the compounds of the present application are selective for hSSAO over either hMAO-A or hMAO-B (“A” means <10 μM; “B” means ≥10 and ≤30 μM; “C” means >30 μM). In addition, the results in Table 21 demonstrate that the compounds are poorly brain penetrable.

Table 20: MAO-A and MAO-B activity of representative compounds of the application

Compound No.	MAO-A Activity (IC ₅₀ , μM)	MAO-B Activity (IC ₅₀ , μM)
BI 1467335 (PXS-4728A)	C	A
1	C	A
2	C	A
3 or 4	C	B
4 or 3	C	B
5	C	A
6	A	A
7	A	A
8	B	A
9	A	A
10	C	A
11	C	A
12	B	A

13	B	B
14	B	B
15	A	A
16	C	C
17	C	B
18	C	B
19	B	A
20	B	B
21 or 22	B	A
22 or 21	B	A
23 or 24	C	A
24 or 23	C	A
25	C	A
26	C	A
27	C	C
28	C	B
29	C	C
30	C	B
31	C	A
32	C	C

33	C	A
34	C	A
35	C	B
36	C	A
37	C	C
38	A	A
39	A	A
40	B	A
41	C	C
42	C	C
43	B	B
44	C	C
45	C	A
46	C	C
47	C	C
48	C	C
49	C	C
50	C	C
51	C	C
52	C	A

53	C	C
54	C	C
55	C	B
56	C	B
57	B	A
58	C	C
59	C	C
60	C	C
61	C	B
62	C	B
63	C	C
64	C	B
65	C	B
66	C	B
67	C	C
68	C	C
69	C	B
70	C	B
71	C	B
72	C	C

73	C	C
74	C	C
75	C	B
76	C	B
77	C	C
78	C	C
79	C	C
80	C	B
81	C	C
82	C	C
83	C	B
84	C	B
85	C	B
86	C	A
87	C	A
88	C	A
89	C	B
90	C	B
91	C	B
92	C	B

93 or 94	C	C
94 or 93	C	C
95	C	C
96	C	B
97	C	C
98	C	B
99	B	C
100	B	C
101	C	A
102	C	A
103	C	A
104 or 105	C	C
105 or 104	C	C
106	C	C
107	C	A
108	C	A
109 or 110	C	A
110 or 109	C	A
111	C	B
112 or 113	C	C

113 or 112	C	C
114	C	C
115	C	C
116	C	C
117	C	C
118	A	A
119	B	C
120	C	C
121	C	A
122	C	A
123	C	C
124	C	C
125	C	A
126	C	B
127	C	A
128	C	C
129	C	B
130	C	C
131	C	C
132	C	A

133	B	A
134	B	A
135	C	C
136 or 137	C	C
137 or 136	C	C
138	C	A
139	C	A
140	C	C
141	C	C
142	C	C
143	C	A
144	C	A
145	A	B
146	C	C

Table 21: Brain Kpuu value (t = 5 min) of representative compounds of the application

Compound No.	Kpuu (mouse, t = 5 min)
BI 1467335 (PXS-4728A)	0.23
44	0.025
62	0.034
65	0.018

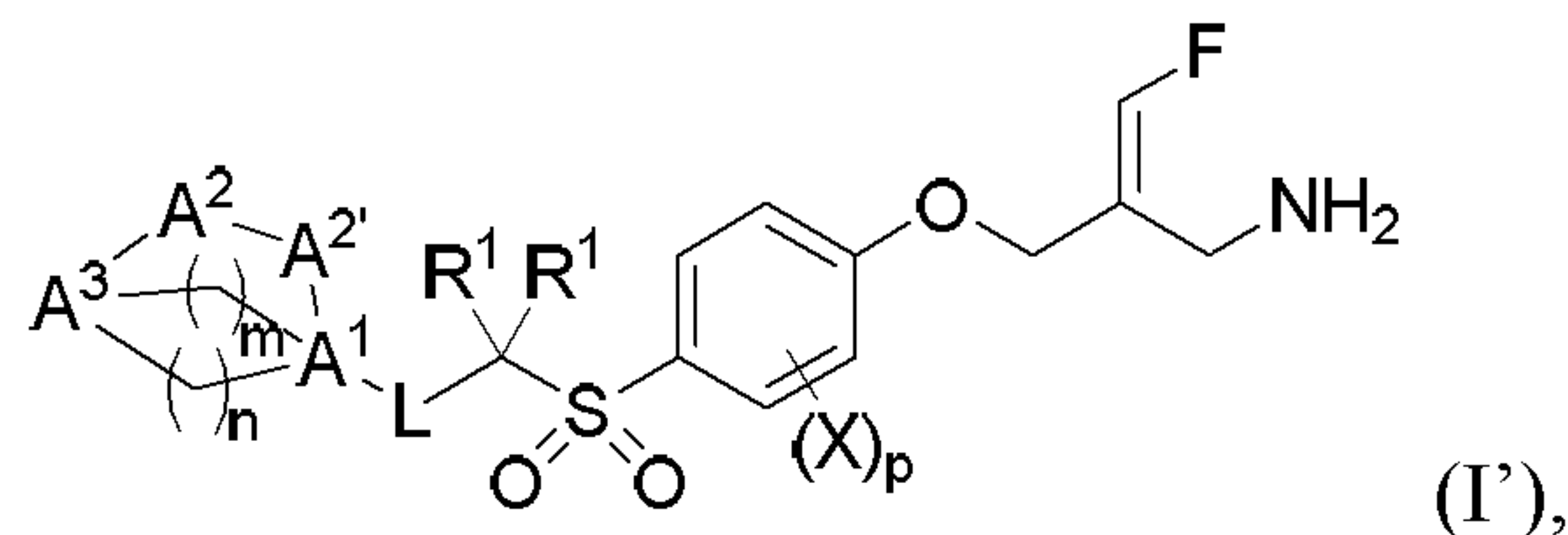
70	0.010
91	0.077

EQUIVALENTS

[00813] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

1. A compound of Formula (I'):



(I'),

or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof,

5 wherein:

each X is independently Cl or F;

p is 0, 1, 2, or 3;

L is absent, -O-, (C₁-C₄) alkylene, substituted (C₁-C₄) alkylene, -O-(C₁-C₄) alkylene, substituted -O-(C₁-C₄) alkylene, (C₁-C₄) alkylene-O-, or substituted (C₁-C₄) alkylene-O-,

10 wherein the substituted (C₁-C₄) alkylene, substituted -O-(C₁-C₄) alkylene, or substituted (C₁-C₄) alkylene-O- is substituted with one or more L¹;

each L¹ is independently (C₁-C₄) alkyl, F, or CF₃; or two L¹, together with the atom to which they are attached, form a 3- to 5-membered cycloalkyl ring;

each R¹ is independently H, F, methyl, ethyl, or CF₃;

15 R² is (C₁-C₄) alkyl substituted with one or more (C₁-C₄) alkoxy, (C₁-C₄) alkoxy, NR³C(O)R⁴, C(O)NR³R⁴, phenyl, (C₃-C₈) cycloalkyl, heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O, or heteroaryl comprising one or two 5- to 6-membered rings and 1 to 3 heteroatoms selected from N and O, wherein the phenyl, cycloalkyl, heterocyclyl, or heteroaryl is optionally substituted with one or more R⁵;

20 R³ is H, methyl, or ethyl;

R⁴ is (C₁-C₄) alkyl or (C₃-C₁₀) cycloalkyl optionally substituted with one or more R⁸; or

R³ and R⁴, together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R⁵;

25 each R⁵ is independently (C₁-C₄) alkyl, (C₁-C₄) alkoxy, hydroxy, cyano, oxo, C(O)R⁷, C(O)NR⁷R^{7'}, NR³C(O)R⁷, NR³S(O)₂R⁴, S(O)₂R⁴, (C₁-C₄) alkyl substituted with one or more hydroxy or R⁶, (C₃-C₁₀) cycloalkyl optionally substituted with one or more hydroxy or R⁶, or heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected

from N and O and optionally substituted with one or more hydroxy or R^6 ; or two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated or 5- or 6-membered aromatic ring optionally comprising 1 or 2 heteroatoms selected from N and O;

each R^6 is independently $NR^3C(O)R^7$ or $C(O)NR^3R^7$;

5 each R^7 is independently

OH, (C_1-C_4) alkoxy, (C_1-C_6) alkyl optionally substituted with one or more (C_1-C_4) alkoxy, CF_3 , F, or (C_3-C_{10}) cycloalkyl,

(C_3-C_{10}) cycloalkyl optionally substituted with one or more R^8 , or phenyl optionally substituted with one or more R^8 ;

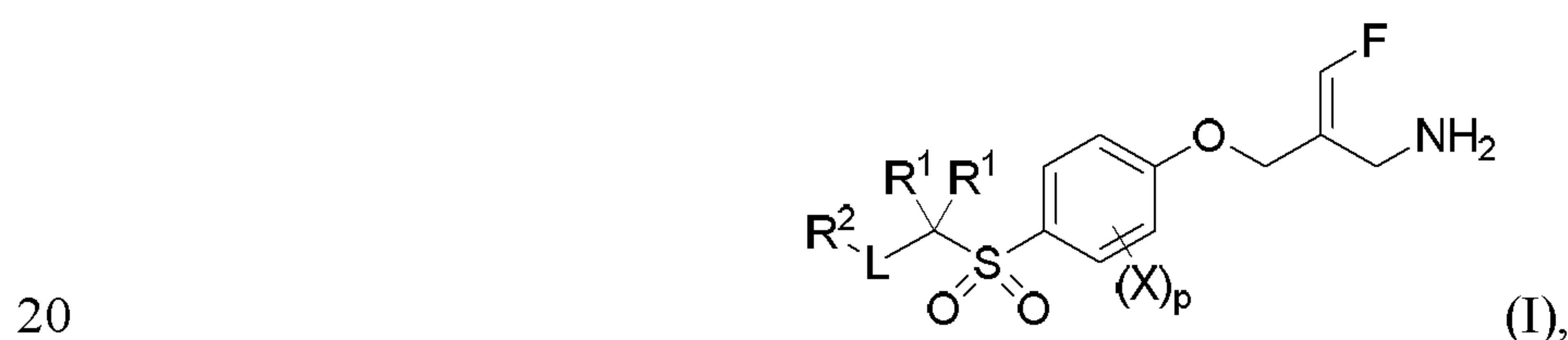
10 each $R^{7'}$ is independently H, methyl, or ethyl; or

R^7 and $R^{7'}$, together with the atom to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 ; or

15 R^3 and R^7 , together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 ; and

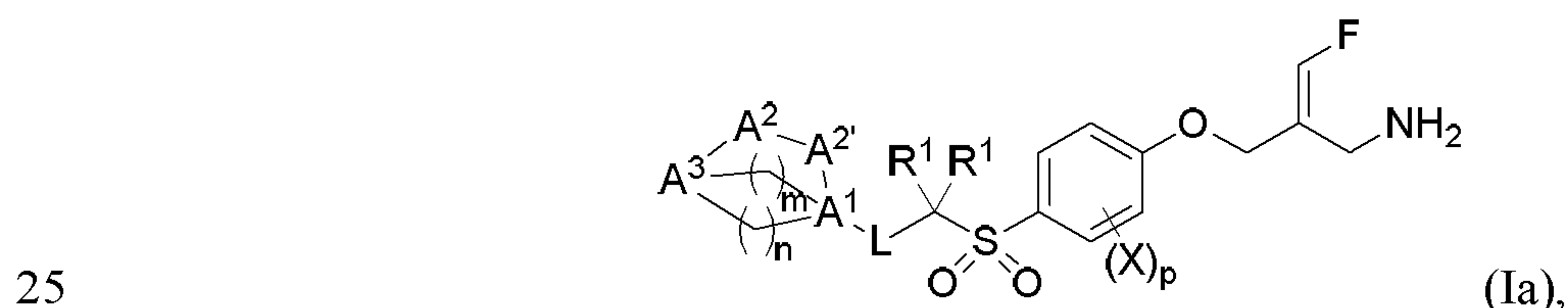
each R^8 is independently (C_1-C_4) alkyl, (C_1-C_4) alkoxy, CF_3 , OH, or F.

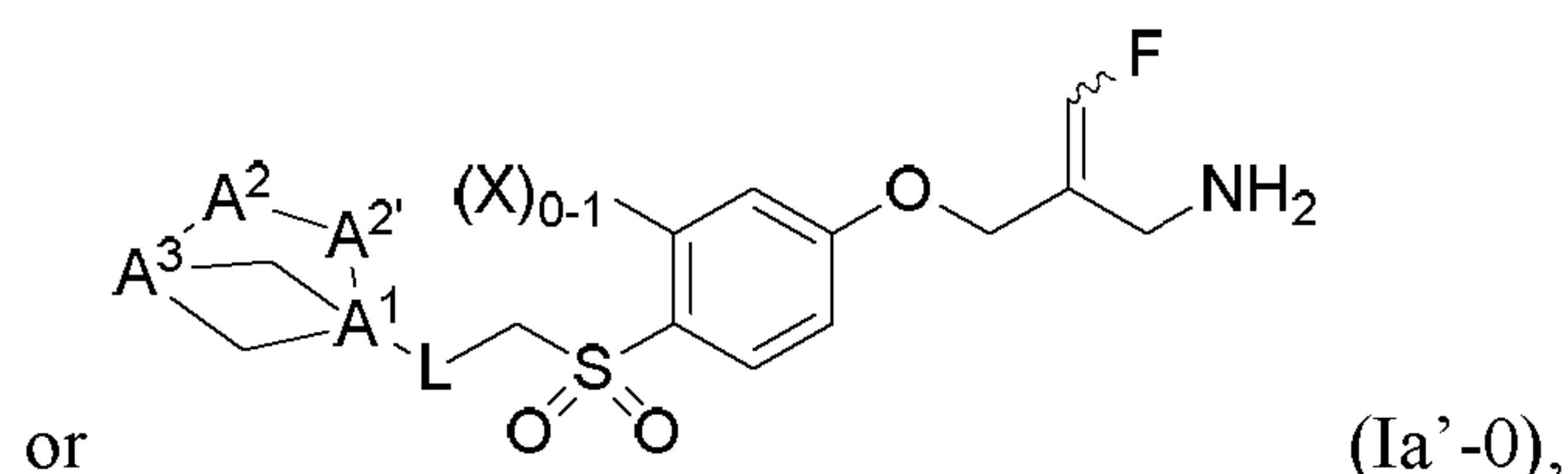
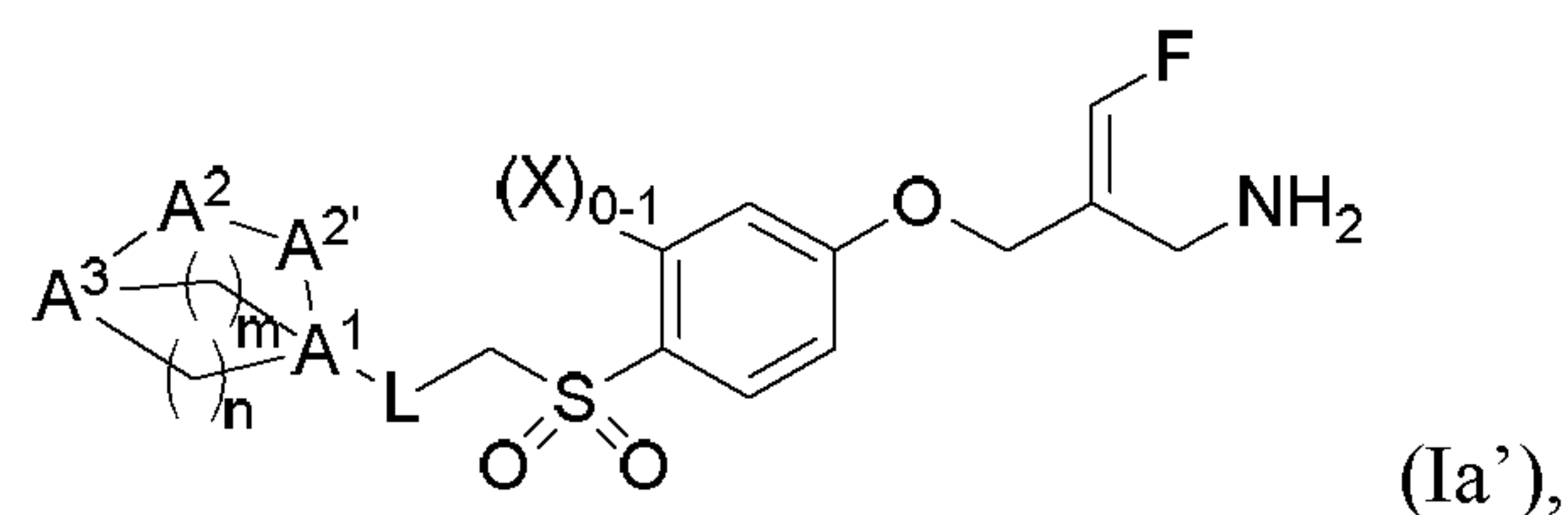
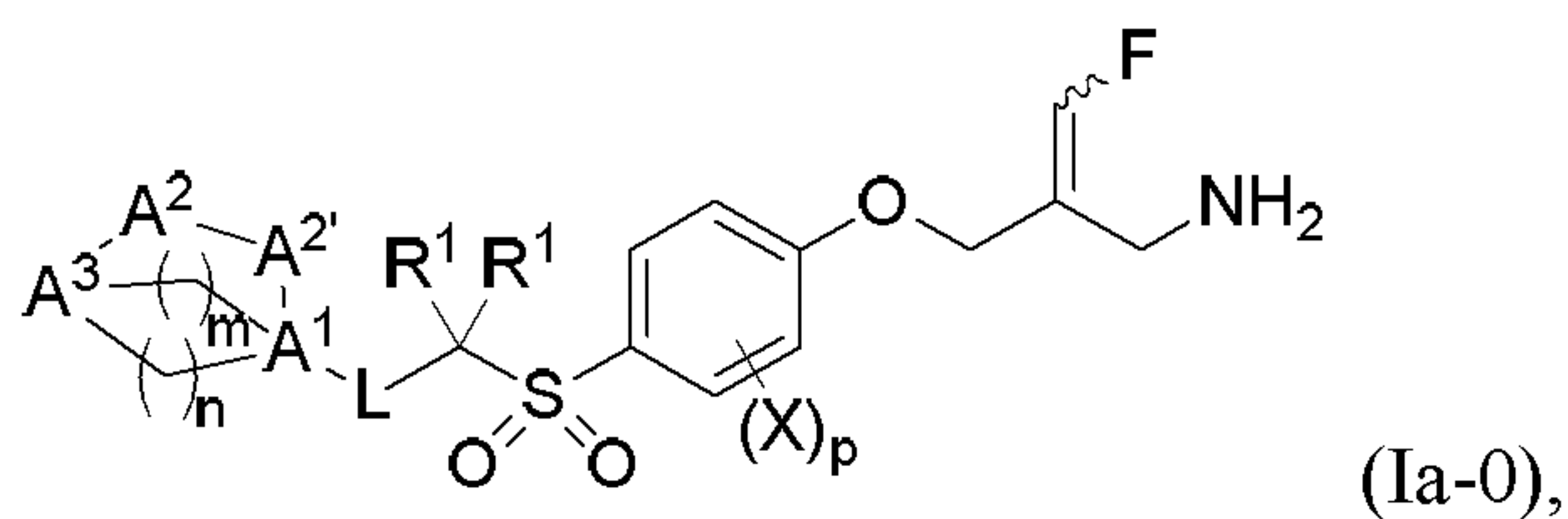
2. The compound of claim 1, wherein the compound is of Formula (I):



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

3. The compound of claim 1, wherein the compound is of Formula (Ia), (Ia-0), (Ia'), or (Ia'-0):





or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof,

5 wherein:

A^1 is N or $CR^{5'}$;

$R^{5'}$ is H, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy, or cyano;

A^2 and $A^{2'}$ are each independently absent, CH_2 , CHR^5 , $C(R^5)_2$, NH, NR^5 , or O, provided that at least one of A^2 and $A^{2'}$ is not absent and that $A^2-A^{2'}$ is not O-O, O-NH, O- NR^5 , NH-O,

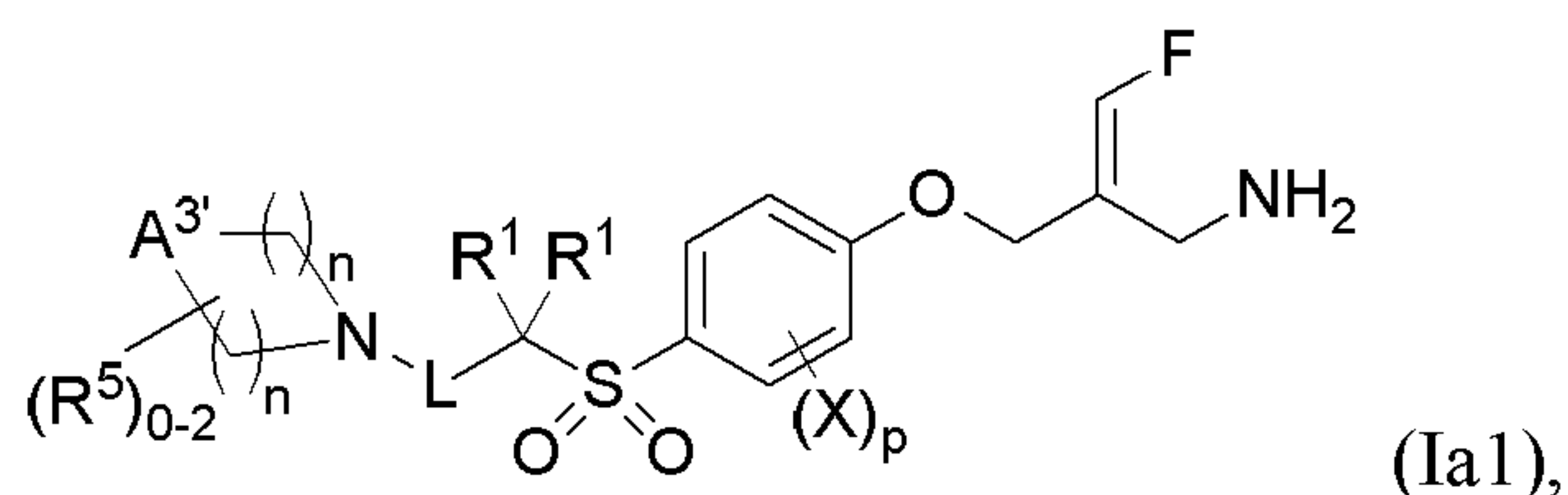
10 NH-NH, NH- NR^5 , NR^5 -O, NR^5 -NH, or NR^5 - NR^5 ;

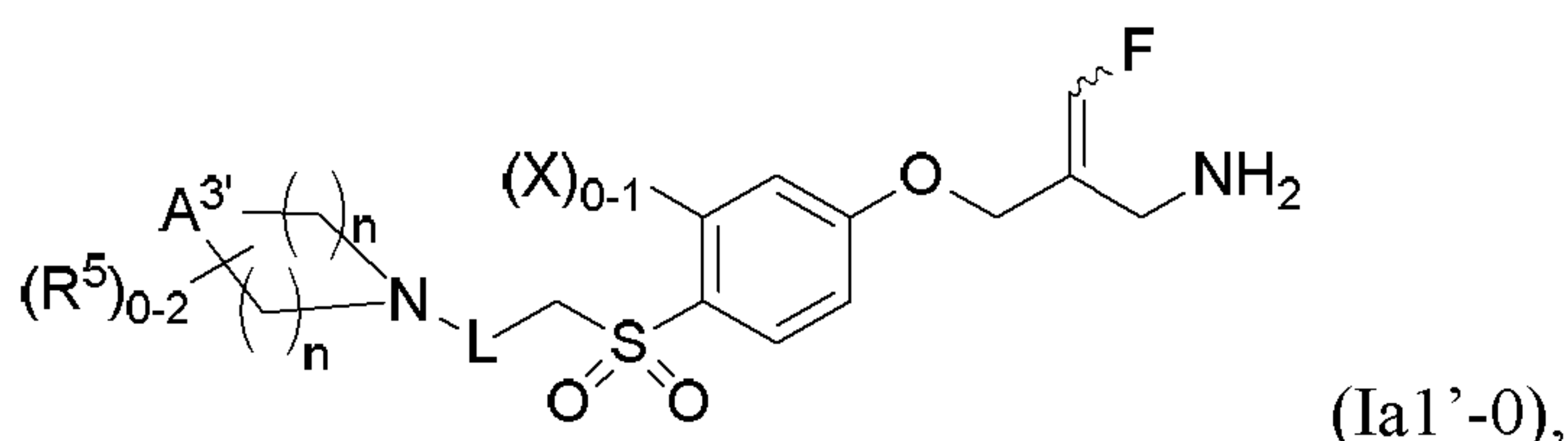
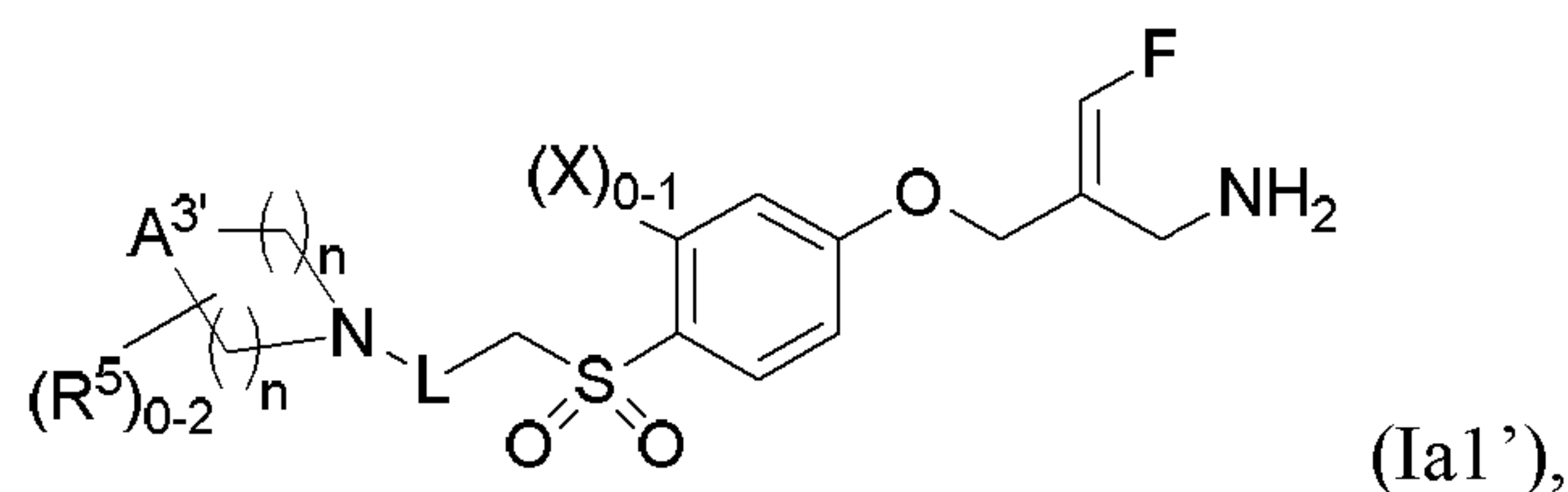
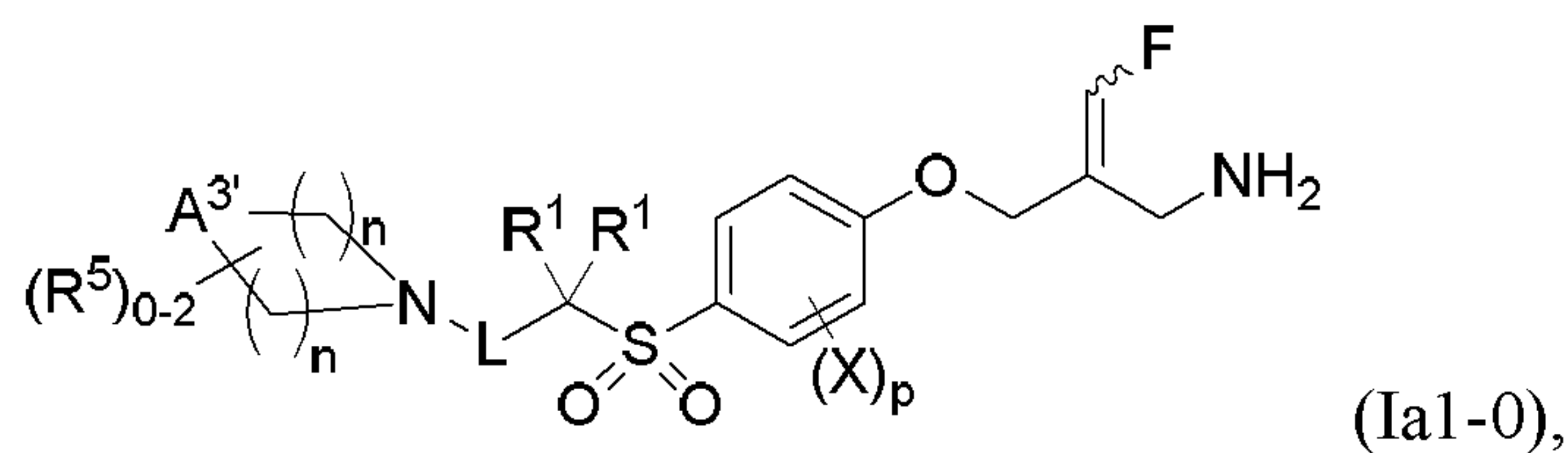
A^3 is CH_2 , CHR^5 , $C(R^5)_2$, NH, NR^5 , or O when m is 0, or CH or CR^5 when m is 1 or 2, provided that A^2-A^3 is not O-O, O-NH, O- NR^5 , NH-O, NH-NH, NH- NR^5 , NR^5 -O, NR^5 -NH, or NR^5 - NR^5 ;

m is 0, 1, or 2; and

15 n is 1 or 2.

4. The compound of claim 3, wherein the compound is of Formula (Ia1), (Ia1-0), (Ia1'), or (Ia1'-0):

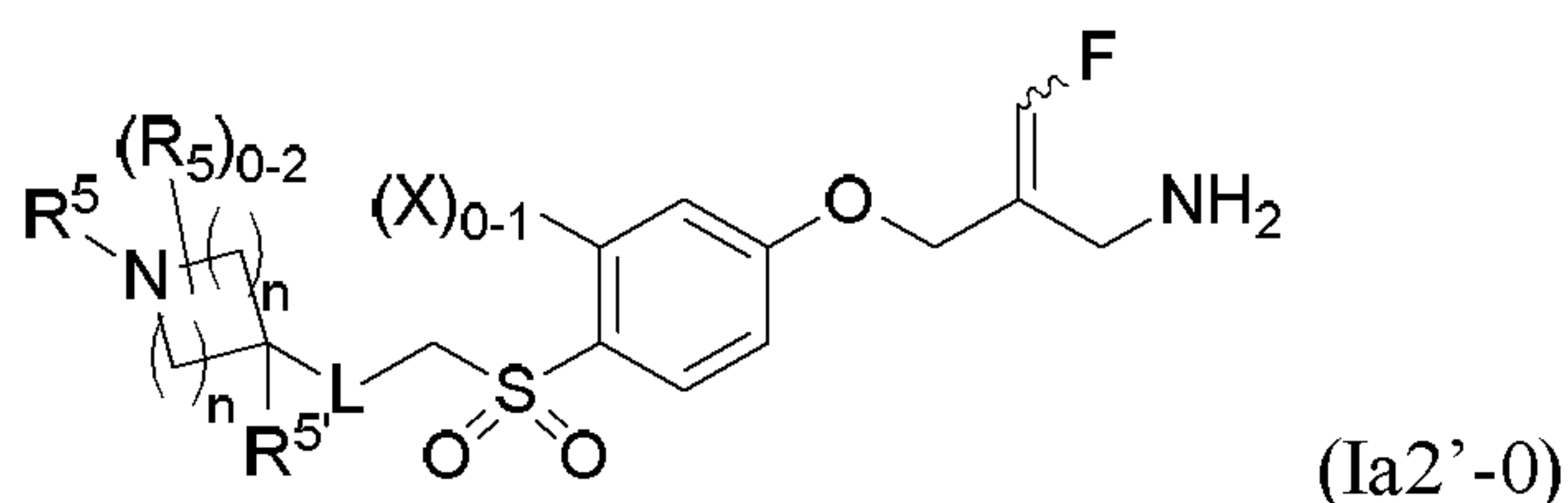
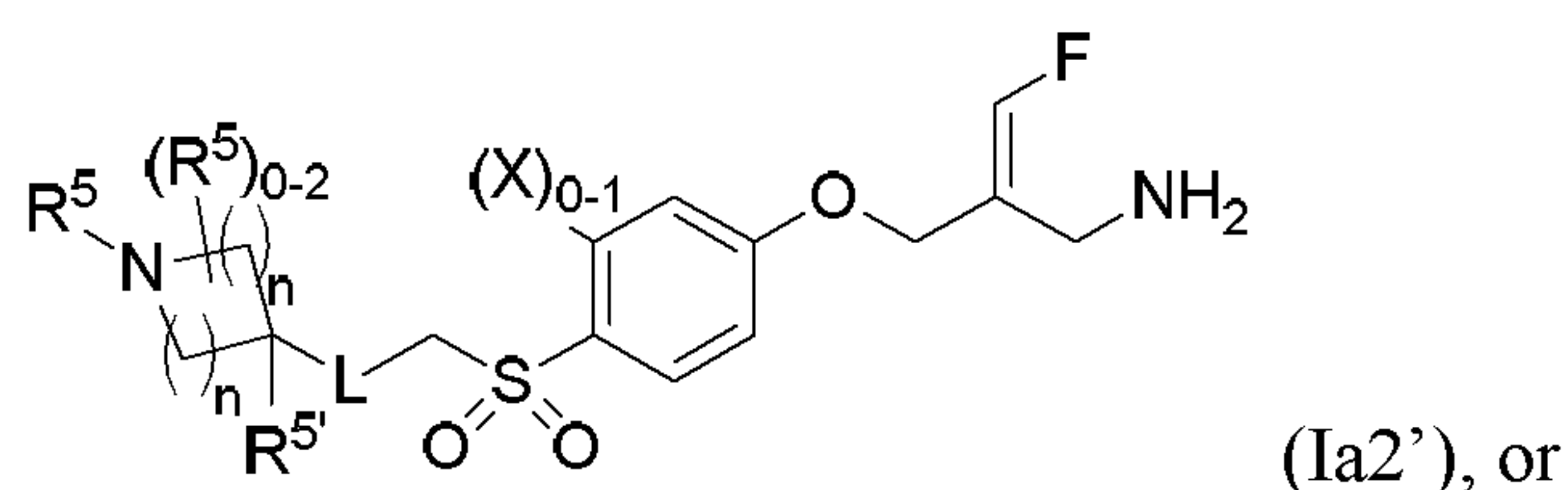
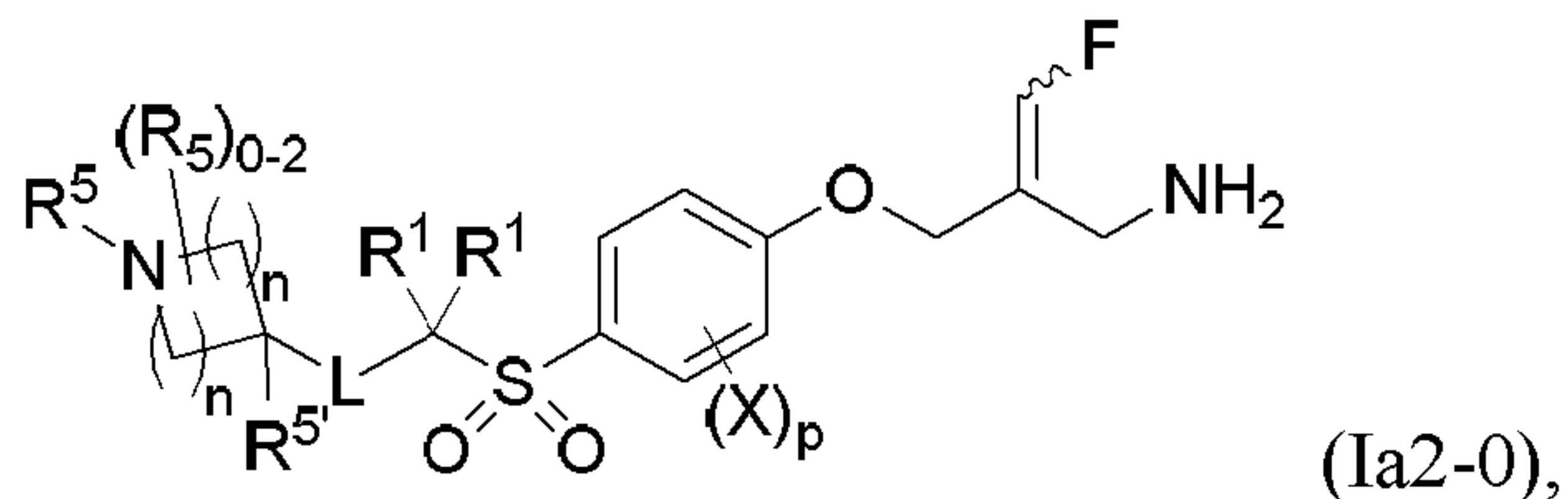
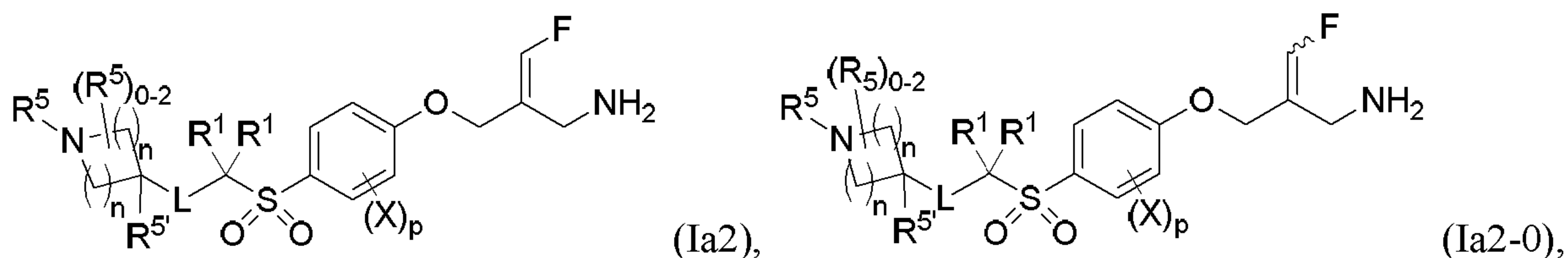




or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof,

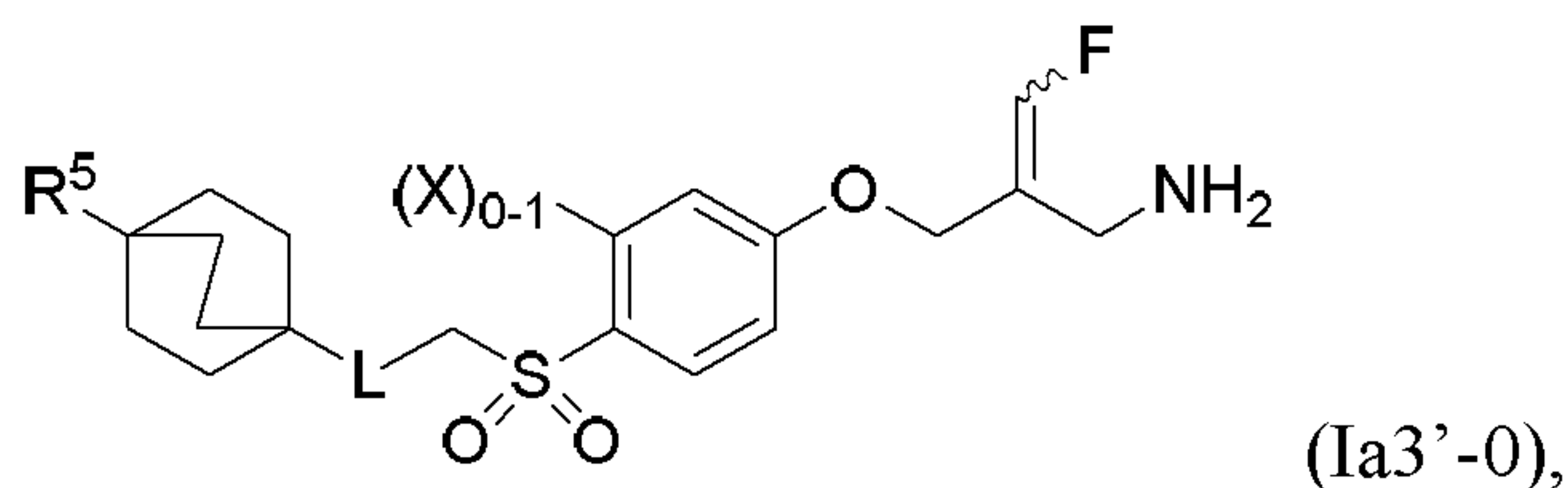
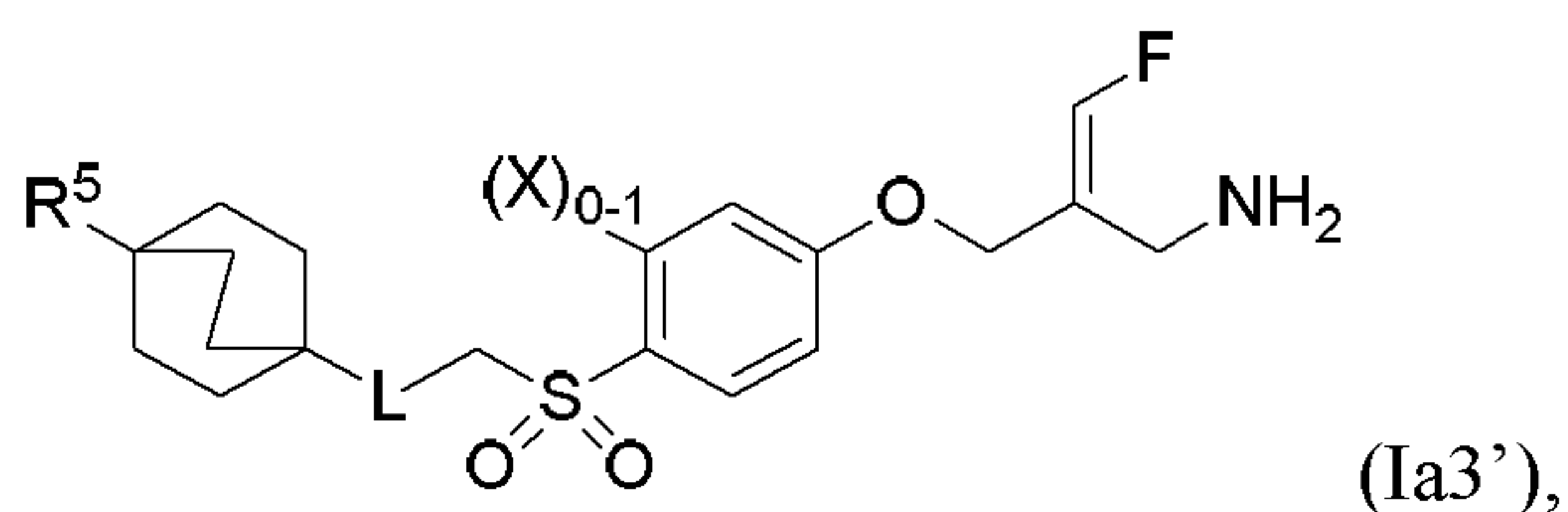
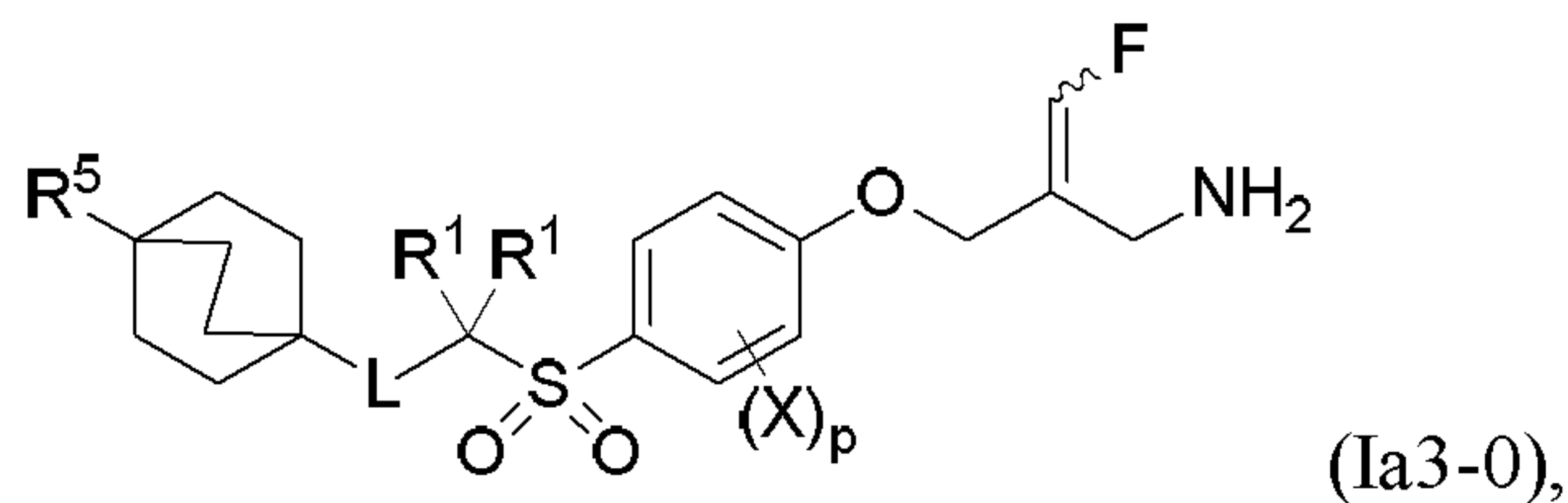
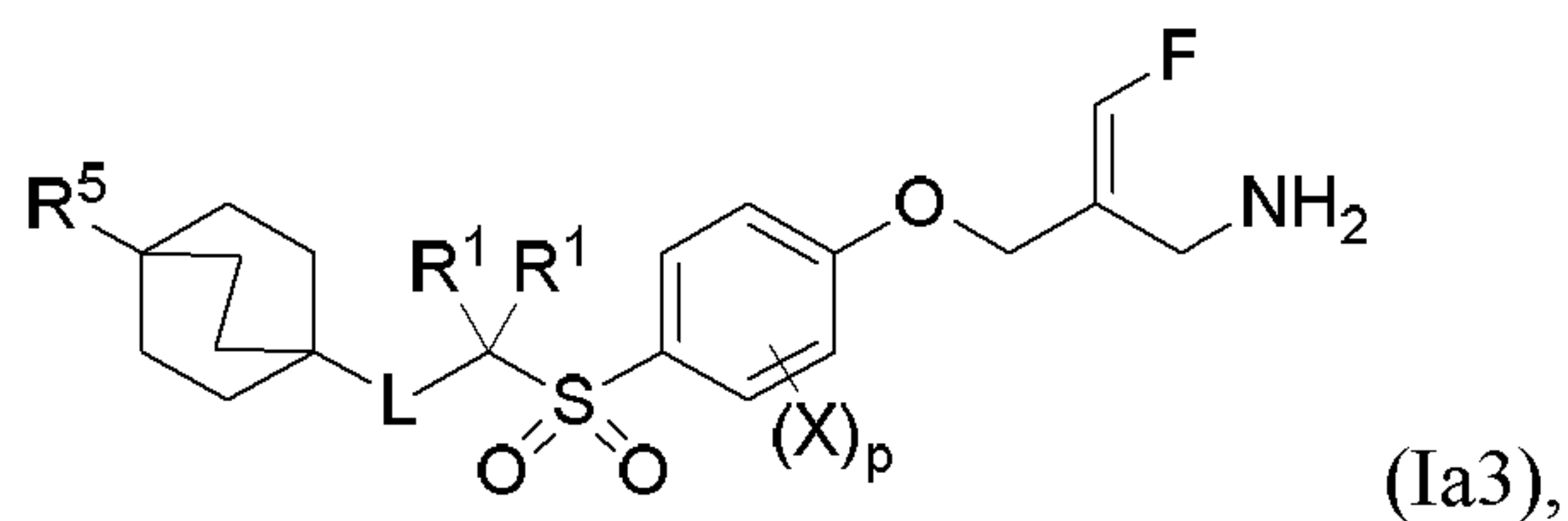
5 wherein A^{3'} is CH₂, CHR⁵, C(R⁵)₂, NH, NR⁵, or O.

5. The compound of claim 3, wherein the compound is of Formula (Ia2), (Ia2-0), (Ia2'), or (Ia2'-0):



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

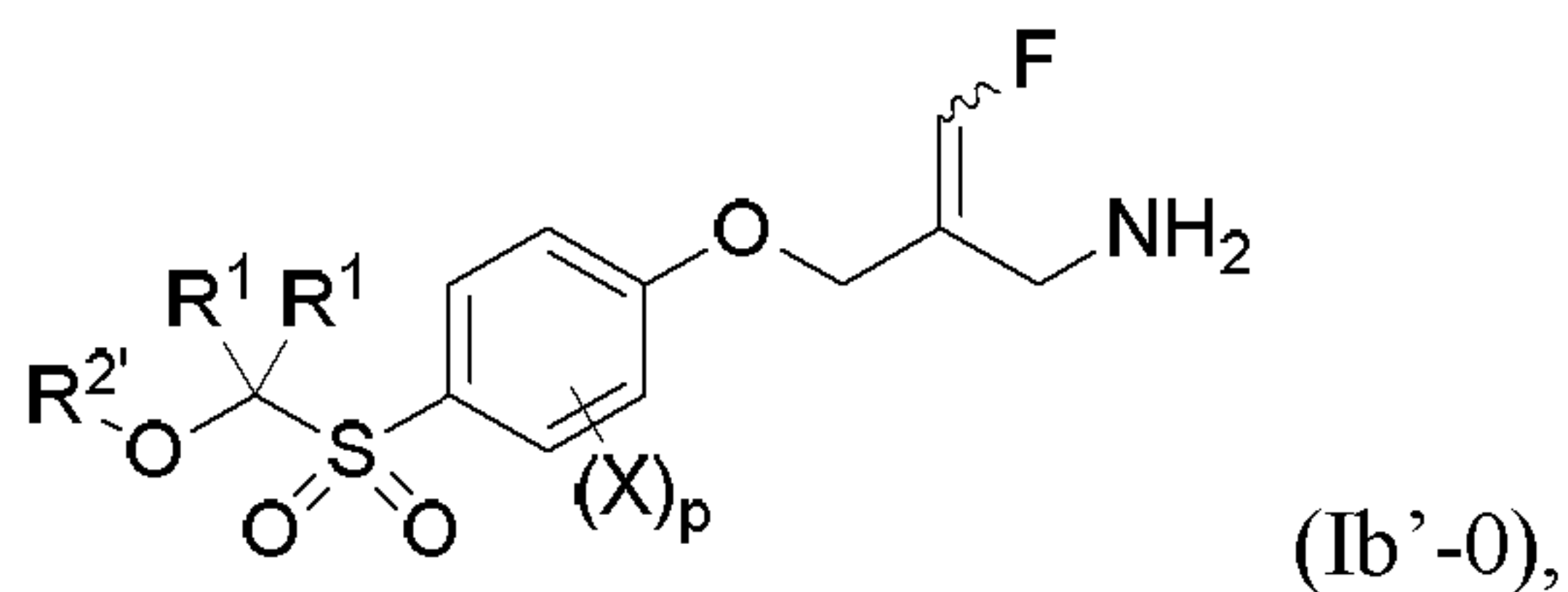
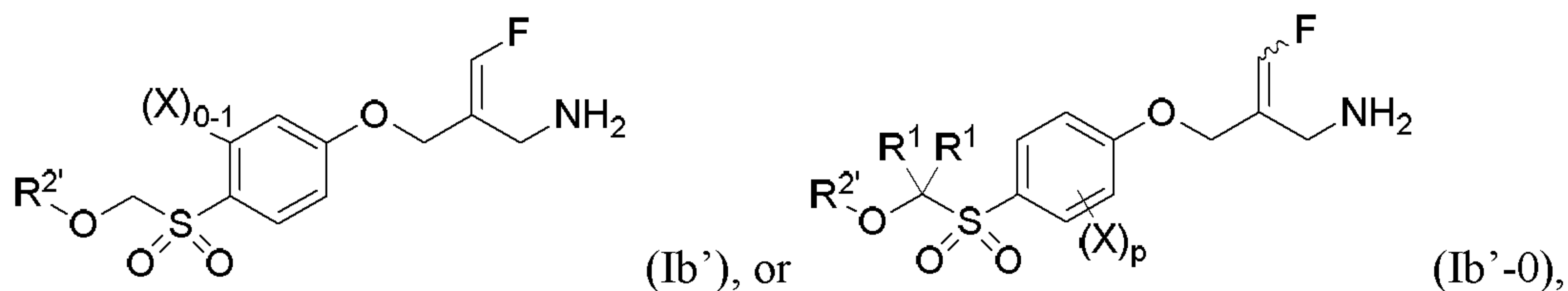
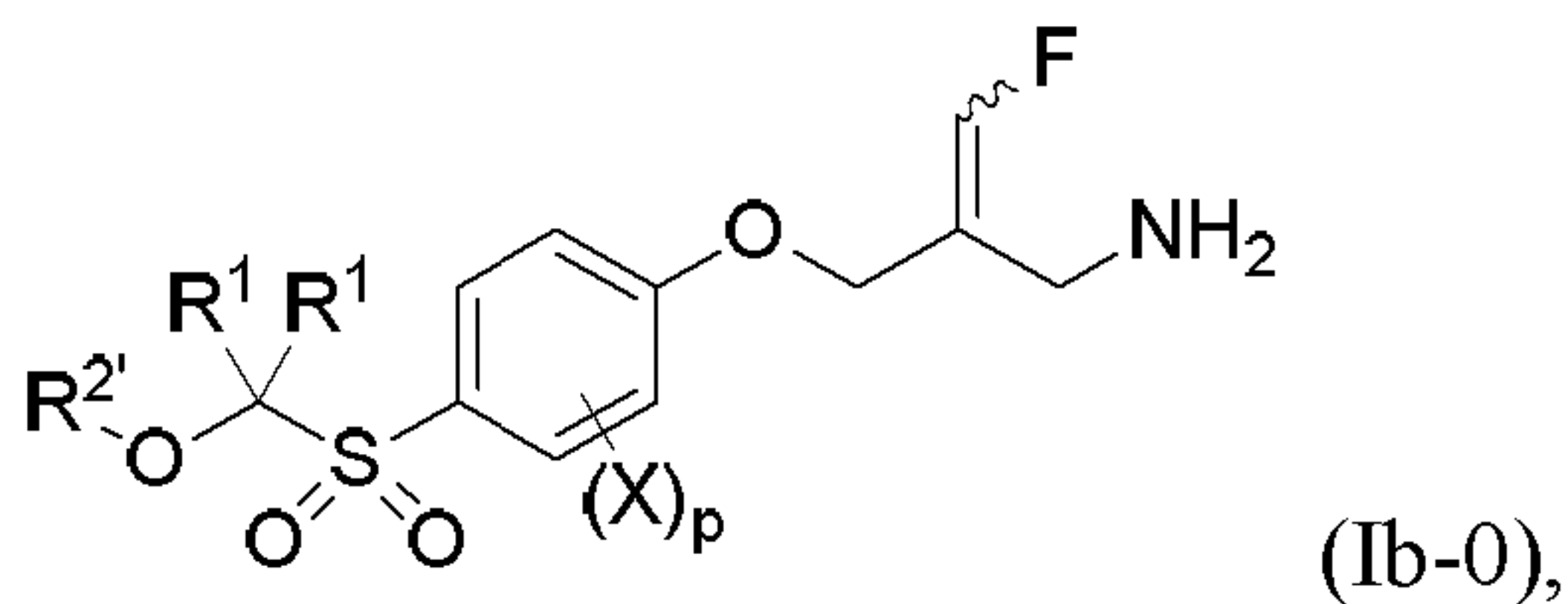
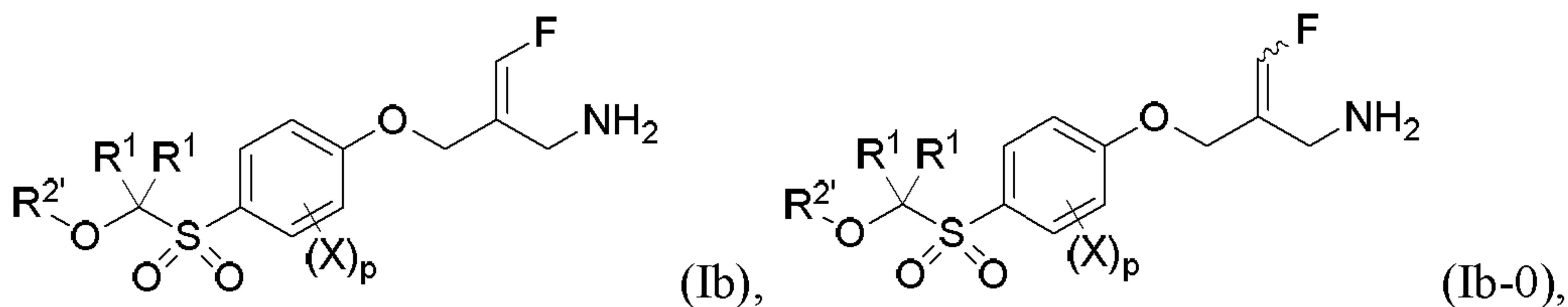
6. The compound of claim 3, wherein the compound is of Formula (Ia3), (Ia3-0), (Ia3'), (Ia3'-0):



or

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

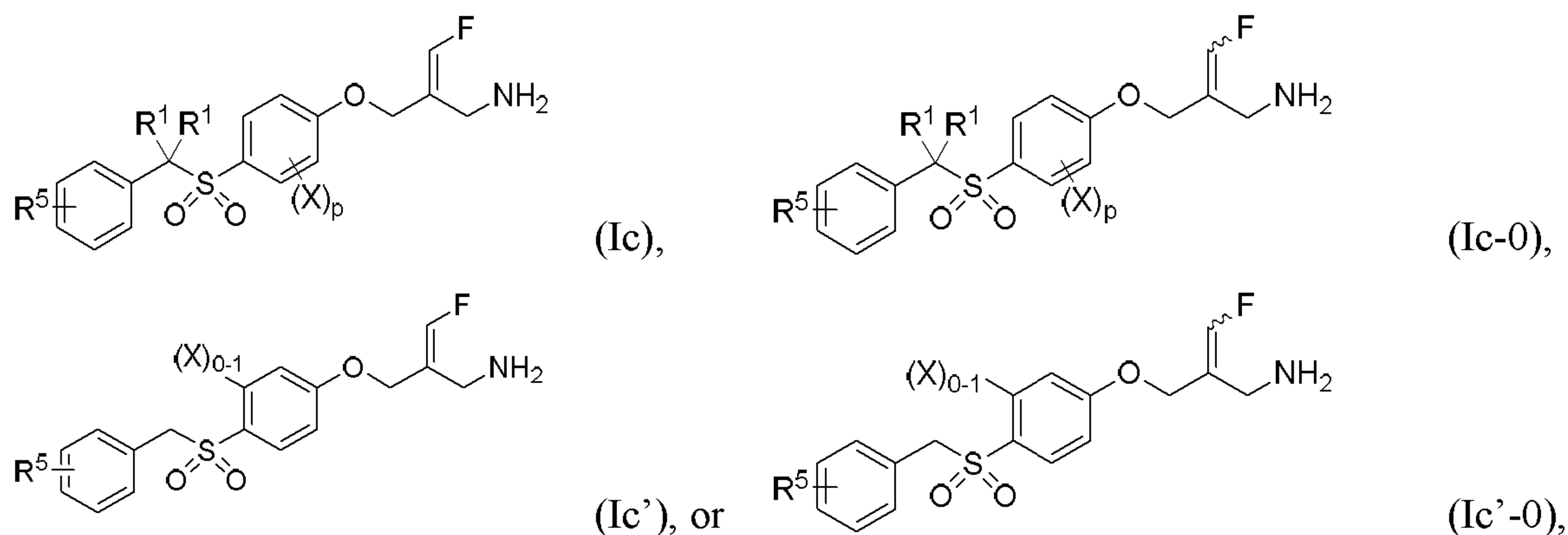
7. The compound of claim 1, wherein the compound is of Formula (Ib), (Ib-0), (Ib'), or (Ib'-0):



and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof, wherein R^{2'} is (C₁-C₄) alkyl substituted with one or more (C₁-C₄) alkoxy, (C₁-C₄) alkoxy,

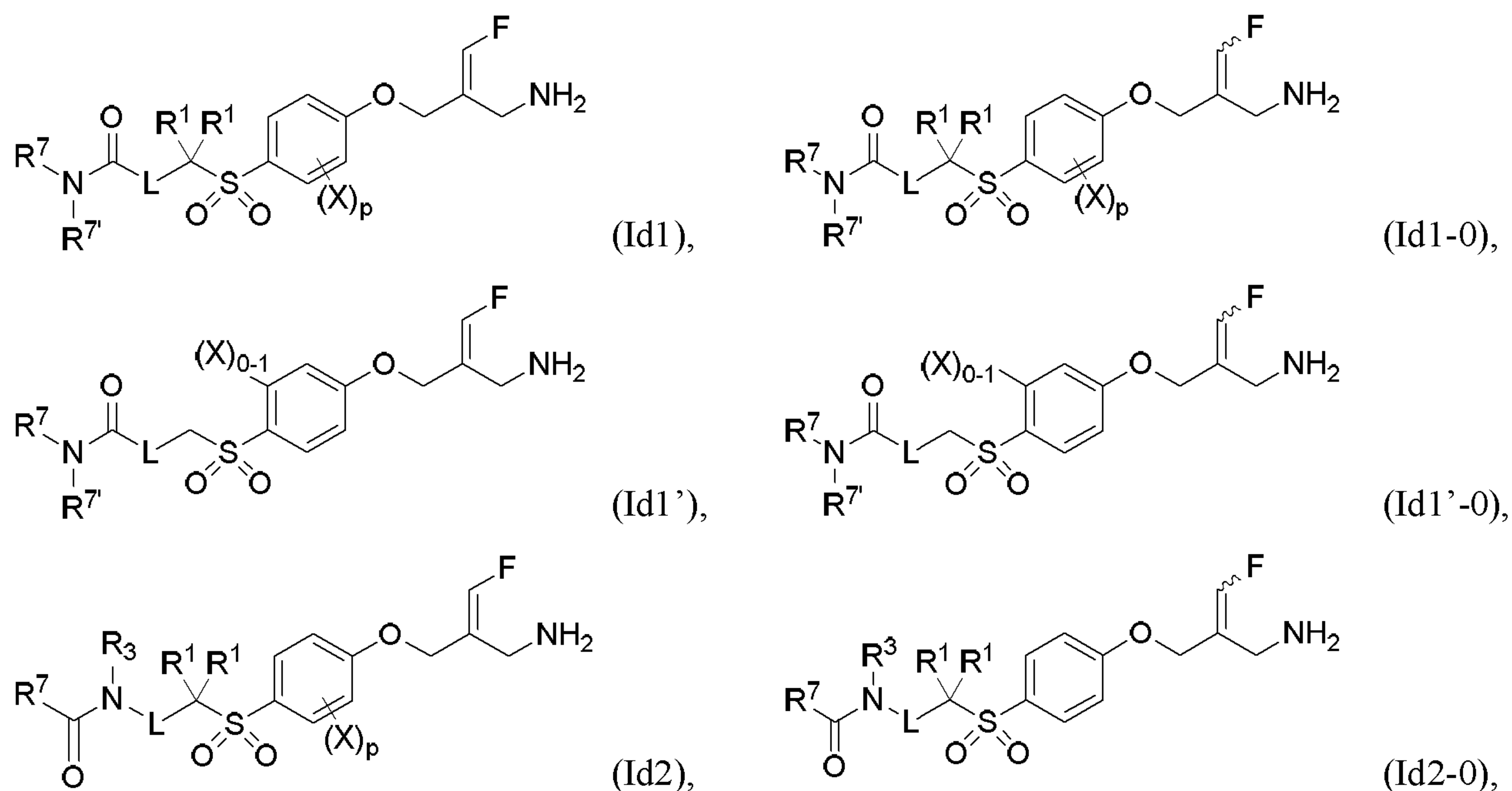
$\text{NR}^3\text{C}(\text{O})\text{R}^4$, $\text{C}(\text{O})\text{NR}^3\text{R}^4$, or heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O, wherein the heterocyclyl is optionally substituted with one or more R^5 .

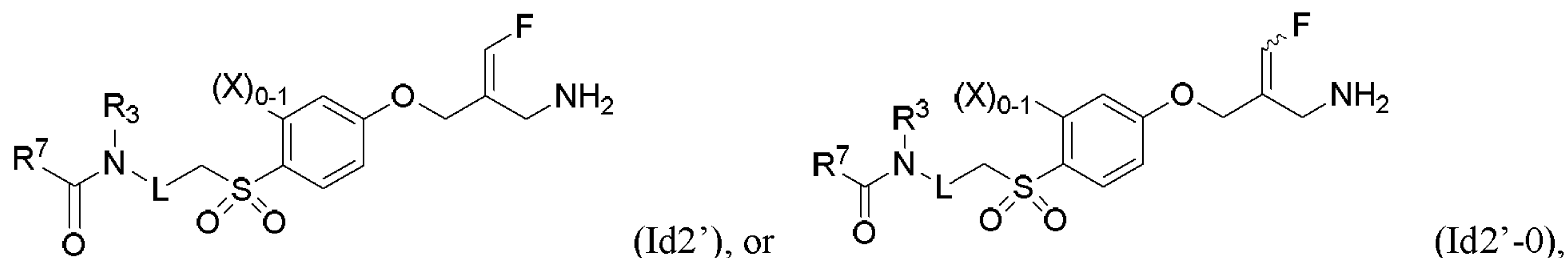
- 5 8. The compound of claim 1, wherein the compound is of Formula (Ic), (Ic-0), (Ic'), or (Ic'-0):



and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

9. The compound of claim 1, wherein the compound is of Formula (Id1), (Id1-0), (Id1'), (Id1'-0), (Id2), (Id2-0), (Id2'), or (Id2'-0):





and pharmaceutically acceptable salts, solvates, prodrugs, stereoisomers, and tautomers thereof.

10. The compound of any one of the preceding claims, wherein L is absent, -O-, (C₁-C₄) alkylene, substituted (C₁-C₄) alkylene, (C₁-C₄) alkylene-O-, or substituted (C₁-C₄) alkylene-O-.

5

11. The compound of any one of the preceding claims, wherein L is absent, -O-, (C₁-C₂) alkylene, substituted (C₁-C₂) alkylene, (C₁-C₂) alkylene-O-, or substituted (C₁-C₂) alkylene-O-.

12. The compound of any one of the preceding claims, wherein L is absent or -O-.

10

13. The compound of any one of claims 1-12, wherein each L¹ is independently (C₁-C₄) alkyl, F, or CF₃.

14. The compound of any one of claims 1-13, wherein each L¹ is independently methyl or ethyl.

15

15. The compound of any one of claims 1-12, wherein two L¹, together with the atom to which they are attached, form a cyclopropyl, cyclobutyl, or cyclopentyl ring.

16. The compound of any one of claims 1-15, wherein each R¹ is H.

20

17. The compound of any one of claims 1-15, wherein each R¹ is independently F, methyl, ethyl, or CF₃.

18. The compound of any one of claims 1-17, wherein R² is (C₁-C₄) alkyl substituted with one or more (C₁-C₄) alkoxy.

25

19. The compound of any one of claims 1-17, wherein R^2 is (C_1-C_4) alkoxy.

20. The compound of any one of claims 1-17, wherein R^2 is $NR^3C(O)R^4$ or $C(O)NR^3R^4$.

5

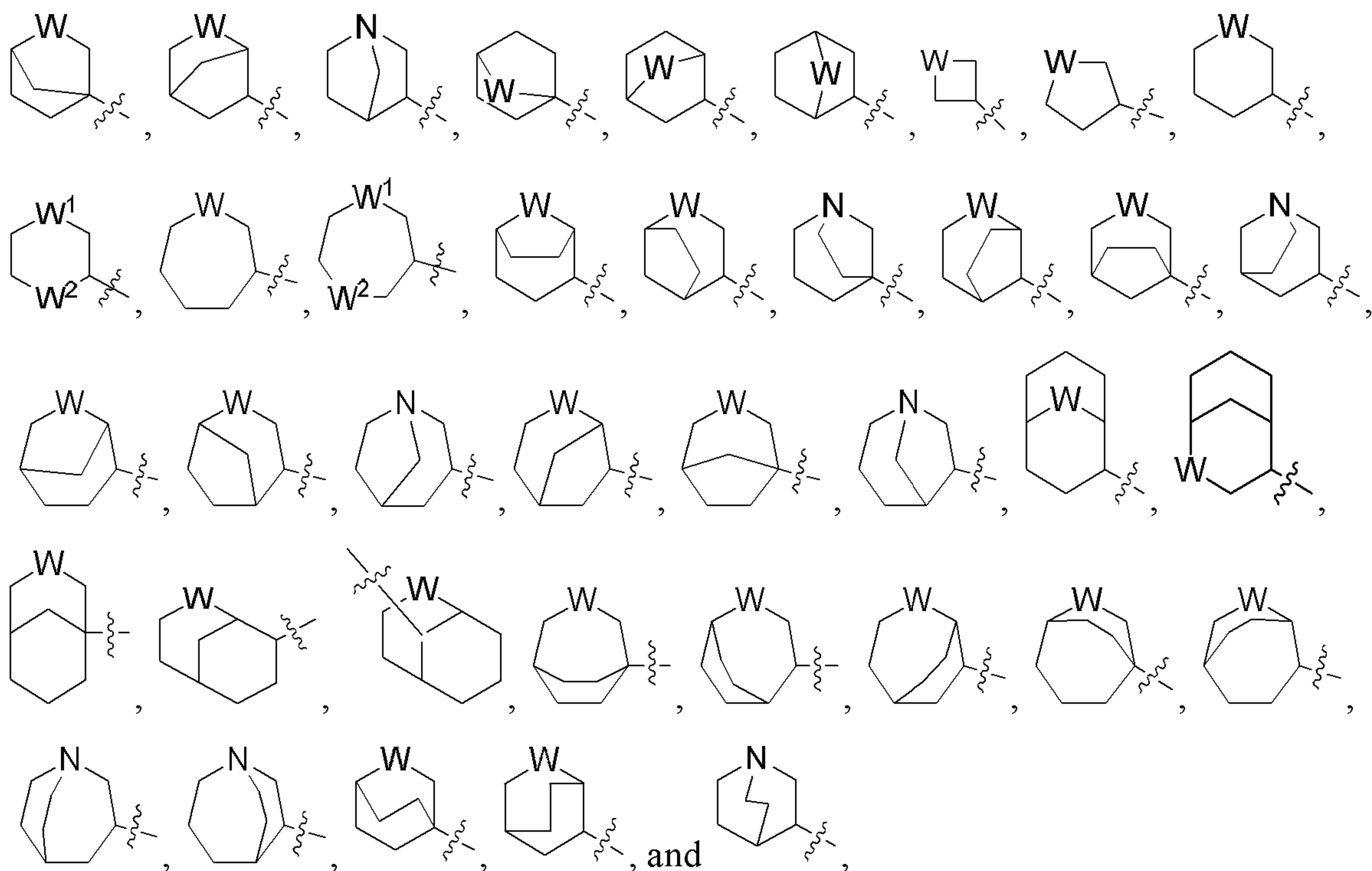
21. The compound of any one of claims 1-17, wherein R^2 is phenyl optionally substituted with one or more R^5 .

22. The compound of any one of claims 1-17, wherein R^2 is (C_3-C_8) cycloalkyl optionally substituted with one or more R^5 .

10

23. The compound of any one of claims 1-17, wherein R^2 is heterocyclyl optionally substituted with one or more R^5 .

15 24. The compound of any one of claims 1-17 and 23, wherein R^2 is a heterocyclyl selected from:



wherein W, W¹ and W² are each independently CH₂, CHR⁵, C(R⁵)₂, O, S, NH, or NR⁵, each optionally substituted with one or more R⁵.

25. The compound of any one of claims 1-17, wherein R² is heteroaryl optionally substituted with one or more R⁵.

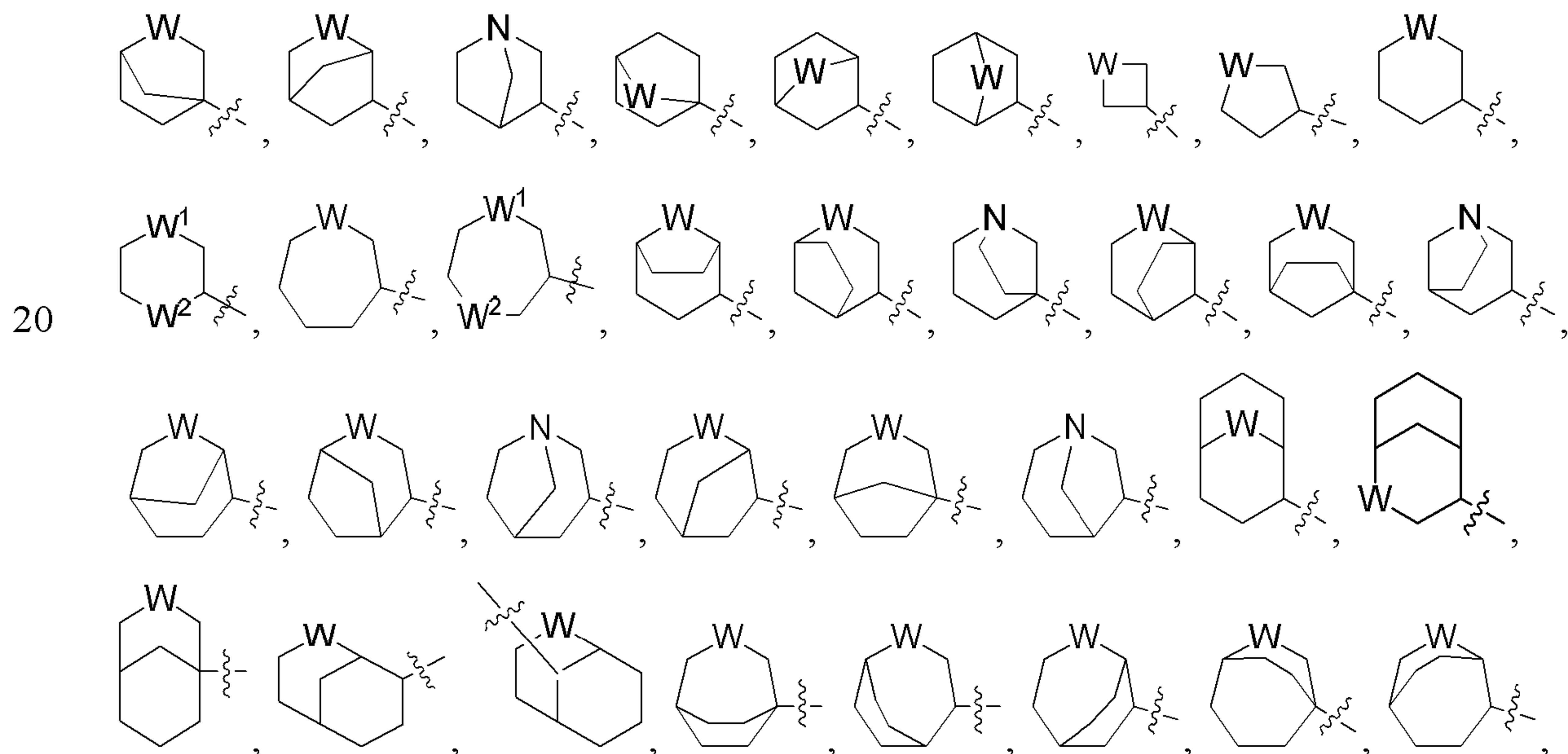
26. The compound of any one of claims 1-17, wherein R^{2'} is (C₁–C₄) alkyl substituted with one or more (C₁–C₄) alkoxy.

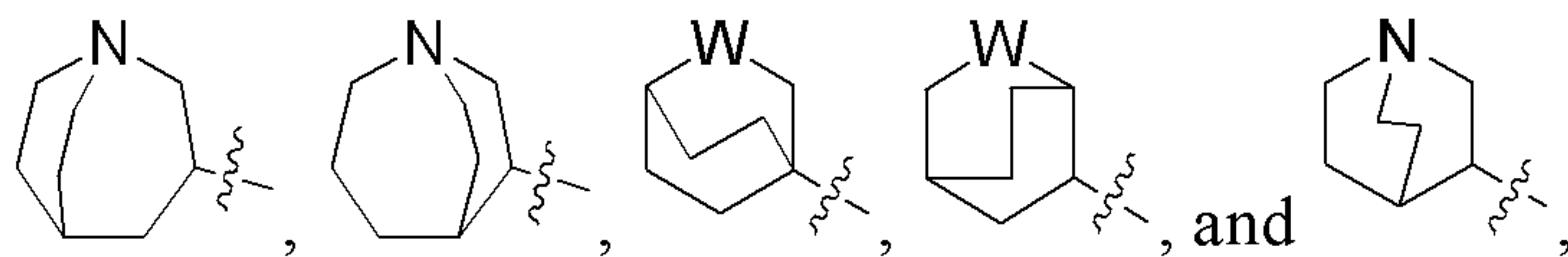
10 27. The compound of any one of claims 1-17, wherein R^{2'} is (C₁–C₄) alkoxy.

28. The compound of any one of claims 1-17, wherein R^{2'} is NR³C(O)R⁴ or C(O)NR³R⁴.

15 29. The compound of any one of claims 1-17, wherein R^{2'} is heterocyclyl optionally substituted with one or more R⁵.

30. The compound of any one of claims 1-17 and 29, wherein R^{2'} is a heterocyclyl selected from:





wherein W, W¹ and W² are each independently CH₂, CHR⁵, C(R⁵)₂, O, S, NH, or NR⁵, each optionally substituted with one or more R⁵.

- 5 31. The compound of any one of claims 1-30, wherein R³ is H.
32. The compound of any one of claims 1-31, wherein R⁴ is methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, or *t*-butyl.
- 10 33. The compound of any one of claims 1-31, wherein R⁴ is (C₃–C₁₀) cycloalkyl optionally substituted with one or more R⁸.
34. The compound of any one of claims 1-30, wherein R³ and R⁴, together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional

15 heteroatom selected from N and O and optionally substituted with one or more R⁵.
35. The compound of any one of claims 1-34, wherein at least one R⁵ is (C₁–C₄) alkyl, (C₁–C₄) alkoxy, hydroxy, cyano, oxo, C(O)R⁷, C(O)NR⁷R^{7'}, NR³C(O)R⁷, NR³S(O)₂R⁴, S(O)₂R⁴, or (C₁–C₄) alkyl substituted with one or more hydroxy or R⁶.

20
36. The compound of any one of claims 1-35, wherein at least one R⁵ is (C₁–C₄) alkyl, (C₁–C₄) alkoxy, hydroxy, cyano, oxo, or (C₁–C₄) alkyl substituted with one or more hydroxy or R⁶.
37. The compound of any one of claims 1-36, wherein at least one R⁵ is methyl, methoxy,

25 hydroxy, or cyano.
38. The compound of any one of claims 1-34, wherein at least one R⁵ is C(O)R⁷, C(O)NR⁷R^{7'}, NR³C(O)R⁷, NR³S(O)₂R⁴, or S(O)₂R⁴.

39. The compound of any one of claims 1-35 and 38, wherein at least one R^5 is $C(O)R^7$, $C(O)NR^7R^7$, or $NR^3C(O)R^7$.

40. The compound of any one of claims 1-34, wherein at least one R^5 is (C_3-C_{10}) cycloalkyl optionally substituted with one or more hydroxy or R^6 , or heterocyclyl comprising one or two 3- to 6-membering rings and 1 to 3 heteroatoms selected from N and O and optionally substituted with one or more hydroxy or R^6 .

41. The compound of any one of claims 1-34, wherein at least two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated or 5- or 6-membered aromatic ring optionally comprising 1 or 2 heteroatoms selected from N and O.

42. The compound of any one of claims 1-34, wherein at least two R^5 , together with the atom or atoms to which they are attached, form a phenyl ring.

43. The compound of any one of claims 1-34, wherein at least two R^5 , together with the atom or atoms to which they are attached, form a 3- to 5-membered saturated ring optionally comprising 1 or 2 heteroatoms selected from N and O.

44. The compound of any one of claims 1-43, wherein $R^{5'}$ is H.

45. The compound of any one of claims 1-43, wherein $R^{5'}$ is (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy, or cyano.

46. The compound of any one of claims 1-45, wherein at least one R^6 is $NR^3C(O)R^7$.

47. The compound of any one of claims 1-45, wherein at least one R^6 is $C(O)NR^3R^7$.

48. The compound of any one of claims 1-47, wherein at least one R^7 is (C_1-C_4) alkoxy, (C_1-C_6) alkyl optionally substituted with one or more (C_1-C_4) alkoxy, CF_3 , F, or (C_3-C_{10}) cycloalkyl.

49. The compound of any one of claims 1-47, wherein at least one R^7 is methyl or ethyl.
50. The compound of any one of claims 1-47, wherein at least one R^7 is (C_3-C_{10}) cycloalkyl optionally substituted with one or more R^8 .
51. The compound of any one of claims 1-47, wherein at least one R^7 is phenyl optionally substituted with one or more R^8 .
52. The compound of any one of claims 1-47, wherein R^7 and $R^{7'}$, together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .
53. The compound of any one of claims 1-30, 32, and 36-47, wherein R^3 and R^7 , together with atom(s) to which they are attached, form a 3- to 6-membered ring optionally comprising one additional heteroatom selected from N and O and optionally substituted with one or more R^8 .
54. The compound of any one of claims 1-53, wherein at least one R^8 is (C_1-C_4) alkyl or (C_1-C_4) alkoxy.
55. The compound of any one of claims 1-54, wherein p is 0 or 1.
56. The compound of any one of claims 1-55, wherein p is 0.
57. The compound of any one of claims 1-55, wherein p is 1.
58. The compound of any one of claims 1-57, wherein X is F.
59. The compound of any one of claims 1-57, wherein X is Cl.
60. The compound of any one of claims 1-59, wherein m is 0, 1, or 2.

61. The compound of any one of claims 1-60, wherein m is 0.
62. The compound of any one of claims 1-60, wherein m is 1.
- 5 63. The compound of any one of claims 1-60, wherein m is 2.
64. The compound of any one of claims 1-63, wherein n is 1 or 2.
65. The compound of any one of claims 1-64, wherein n is 1.
- 10 66. The compound of any one of claims 1-64, wherein n is 2.
67. The compound of claim 1, selected from Table 1.
- 15 68. A pharmaceutical composition comprising a compound of any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable diluent, excipient or carrier.
- 20 69. A method of modulating SSAO, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof.
70. A method of treating a SSAO-mediated disorder, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof.
- 25 71. A compound according to any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating a SSAO-mediated disorder or modulating SSAO.

72. Use of a compound according to any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in treating a SSAO-mediated disorder or modulating SSAO.

5 73. A compound according to any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, for use in the manufacture of a medicament for treating a SSAO-mediated disorder or modulating SSAO.

10 74. Use of a compound according to any one of claims 1-67, or a pharmaceutically acceptable salt, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a SSAO-mediated disorder or modulating SSAO.

15 75. The method according to claim 70, compound for use according to claim 71 or 73, or use according to claim 72 or 74, wherein the SSAO-mediated disorder is inflammation, liver inflammation, neuroinflammation, fibrosis, liver fibrosis, lung fibrosis, renal fibrosis, liver disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, cardiovascular disease, atherosclerosis, stroke or a complications thereof, myocardial infarction, kidney disease, autoimmune disease, metabolic disease, or pain.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2020/124381

A. CLASSIFICATION OF SUBJECT MATTER

C07D 309/04(2006.01)i; C07D 319/12(2006.01)i; C07D 309/10(2006.01)i; C07D 309/08(2006.01)i; C07C 317/14(2006.01)i; C07D 307/10(2006.01)i; C07D 309/12(2006.01)i; C07D 211/46(2006.01)i; C07D 309/06(2006.01)i; C07D 205/04(2006.01)i; C07D 275/02(2006.01)i; C07D 207/06(2006.01)i; C07D 401/04(2006.01)i; C07D 295/08(2006.01)i; A61K 31/10(2006.01)i; A61P 3/00(2006.01)i; A61P 9/00(2006.01)i; A61P 29/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; C07C; A61K; A61P

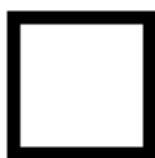
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, EPODOC, WPI, STN: ECCOGENE, SSAO, semicarbazide sensitive amine oxidase, halo, allyl, amine, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2019024924 A1 (SUNSHINE LAKE PHARMA CO., LTD.) 07 February 2019 (2019-02-07) see abstract, claims 1, 10-15	1-75
A	WO 2007120528 A2 (LA JOLLA PHARMACEUTICAL COMPANY, et al.) 25 October 2007 (2007-10-25) see abstract, paragraphs [0035], [0043]	1-75
A	WO 2013163675 A1 (PHARMAXIS LTD.) 07 November 2013 (2013-11-07) see abstract, claims 1, 5	1-75
PA	WO 2019241751 A1 (METACRINE, INC.) 19 December 2019 (2019-12-19) see claim 1	1-75
PA	WO 2020086747 A2 (METACRINE, INC.) 30 April 2020 (2020-04-30) see claim 1	1-75



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“E” earlier application or patent but published on or after the international filing date	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&” document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 December 2020

Date of mailing of the international search report

31 December 2020

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **69-70, 72, 75**
because they relate to subject matter not required to be searched by this Authority, namely:
[1] Claims 69-70, 72, 75 relate to method/ use for treating diseases, but the search has been carried out based on use of the said compounds in manufacture of medicaments for treating corresponding diseases.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2020/124381

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2019024924	A1	07 February 2019	CN	110914234	A	24 March 2020
WO	2007120528	A2	25 October 2007	US	2007293548	A1	20 December 2007
				EP	2004166	A2	24 December 2008
				US	2011269811	A1	03 November 2011
				US	2009203764	A1	13 August 2009
				WO	2007120528	A3	24 July 2008
WO	2013163675	A1	07 November 2013	LT	2844637	T	10 May 2018
				EP	2844637	A4	09 December 2015
				KR	102089935	B1	18 March 2020
				HU	E038437	T2	29 October 2018
				HK	1245237	A1	24 August 2018
				US	10160723	B2	25 December 2018
				US	2019071396	A1	07 March 2019
				CA	2871793	A1	07 November 2013
				CA	3086105	A1	07 November 2013
				BR	112014027406	A2	27 June 2017
				HR	P20180953	T1	27 July 2018
				US	9302986	B2	05 April 2016
				JP	2017132767	A	03 August 2017
				AU	2013203655	A1	21 November 2013
				JP	2015521167	A	27 July 2015
				KR	20150014926	A	09 February 2015
				TR	201807453	T4	21 June 2018
				PT	2844637	T	17 April 2018
				EP	2844637	B1	28 March 2018
				SG	11201406948P	A	27 November 2014
				PL	2844637	T3	28 September 2018
				HK	1203477	A1	30 October 2015
				RS	57086	B1	29 June 2018
				CN	104520268	A	15 April 2015
				JP	6602802	B2	06 November 2019
				US	2018086698	A1	29 March 2018
				ES	2668300	T3	17 May 2018
				AU	2013255103	A1	06 November 2014
				DK	2844637	T5	13 August 2018
				US	2015158813	A1	11 June 2015
				MX	2014013294	A	08 May 2015
				EP	3438087	A1	06 February 2019
				CN	104520268	B	24 May 2017
				CN	107266332	B	24 July 2020
				AU	2013203655	B2	02 February 2017
				KR	20200030126	A	19 March 2020
				CN	107266332	A	20 October 2017
				NO	2842608	T3	21 July 2018
				ME	03063	B	20 January 2019
				DK	2844637	T3	23 April 2018
				JP	2020019810	A	06 February 2020
				US	9815782	B2	14 November 2017
				SI	2844637	T1	31 July 2018
				US	2016244406	A1	25 August 2016

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2020/124381

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
				EP	2844637	A1	11 March 2015
				MX	360634	B	12 November 2018
				JP	6182595	B2	16 August 2017
				AU	2013255103	B2	29 September 2016
				CY	1120334	T1	10 July 2019
WO	2019241751	A1	19 December 2019	None			
WO	2020086747	A2	30 April 2020	US	2020181104	A1	11 June 2020
				WO	2020086747	A3	23 July 2020